The use of pregabalin in the treatment of hot flashes

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PERIMENOPAUSAL WOMEN OFTEN CONSULT health care professionals for help in managing vasomotor symptoms such as hot flashes and night sweats. Similar symptoms are also associated with the use of certain drugs such as tamoxifen and leuprolide.^{1,2} Various therapies have been studied for the treatment of these symptoms, the most predominant being hormonal therapy (HT). Because of the risks and contraindications associated with HT, however, nonhormonal pharmacologic therapy has been explored for the treatment of hot flashes. Antidepressants (e.g., venlafaxine, paroxetine and fluoxetine), as well as clonidine, Bellergal (belladonna, ergotamine and phenobarbital) and gabapentin are medications that can be prescribed as alternatives to HT, as suggested by the Society of Obstetricians and Gynaecologists of Canada (SOGC).³

While antidepressants affect the release and reuptake of serotonin and/or norepinephrine,⁴⁻⁶ gabapentin and pregabalin are gamma-aminobutyric acid analogues,^{7,8} and their mechanism of action related to the reduction of hot flashes is currently unclear. Patients using gabapentin for neurologic conditions have been described in the literature as having a reduction in hot flashes.⁹

Although pregabalin is not listed by the SOGC as one of the options for treating hot flashes, preliminary data supporting its use for this indication are available.^{10,11} This investigational use of pregabalin stems from past evidence that shows the benefit of gabapentin,^{12,13} an agent of the same class, for the treatment of hot flashes.

Methods

A literature search was performed using MEDLINE, EMBASE, International Pharmaceutical Abstracts, Cochrane Central Register of Controlled Trials and an internal citation

database of pharmacy journals (AskSam-Drug Information) to identify studies examining the use of pregabalin in the treatment of menopausal symptoms. Keywords and medical subject headings included *hot flashes*, *hot flush*, *flushing*, *climacteric* or *menopause*, and *pregabalin*, *gamma-aminobutyric acid* or *Lyrica*. No limitations were set for the databases. Two studies were identified: 1 small pilot study and 1 larger randomized controlled trial. All pertinent articles were then searched in SCOPUS to ensure inclusiveness.

Pilot study

Presant and Kelly¹⁰ examined the efficacy of pregabalin for the treatment of vasomotor symptoms in patients with breast cancer ($n = 6$) taking anastrozole ($n = 5$) or tamoxifen ($n = 1$) and patients with prostate cancer ($n = 2$) taking leuprolide. Patients eligible for this 4-week, open-label, noncontrolled trial had some type of pain for which pregabalin could be used and hot flashes unresponsive to environmental changes. No minimum number or severity of hot flashes was required for enrolment in the study. Previous agents used to alleviate hot flashes were not mentioned. Ages varied from 53 to 81 years old, with a median age of 63 years. Pregabalin was titrated in 50 mg increments from 50 mg orally once daily to 50 mg 3 times daily if no response and no toxicity were reported. No specific schedule was given for its titration. After 4 weeks of treatment with pregabalin, patients were interviewed to assess the outcomes of hot flash frequency and severity. A validated tool to determine the severity of vasomotor symptoms was not used; instead, the severity of the patient's symptoms (mild = 1, moderate = 2, severe = 3) was multiplied by the number of hot flashes per day to yield a hot flash score. This was

estimated by the patient, and the information was elucidated via semi-structured interviews. Because of this, comparison of pregabalin's efficacy to other agents is difficult, as a standard, validated tool was not used.

Of the 8 patients, 6 obtained some relief from their vasomotor symptoms, ranging from slight (1) to good (1) to excellent (4). After treatment, the mean reductions in the number of hot flashes per day and the hot flash score were 53% and 65%, respectively. Adverse effects reported by patients included drowsiness ($n = 4$), altered mentation ($n = 2$) and dizziness, lethargy, constipation and flatulence ($n = 1$). These side effects were similar to those reported in clinical trials examining approved indications for pregabalin.⁸ Three patients discontinued pregabalin due to altered mentation ($n = 2$) and drowsiness ($n = 1$).

Due to the small number of patients examined, study design and short follow-up, results from this study should be cautiously interpreted.

Randomized controlled trial

Patients enrolled in this 7-week, multicentre, double-blind, placebo-controlled phase III trial were eligible if they had had at least 28 hot flashes per week for a minimum of 1 month before study entry.¹¹ Adult women ($n = 207$) were randomized to receive 1 of the 3 following treatments: placebo ($n = 69$), or target pregabalin dose of 75 mg twice daily ($n = 69$) or 150 mg twice daily ($n = 69$), titrated at weekly intervals. At the physician's discretion, pregabalin doses could be decreased or discontinued if patients developed adverse reactions. Baseline data were collected by completion of a validated hot flash diary, the Profile of Mood States (POMS) tool and the Hot Flash Related Daily Interference Scale (HFRDIS).^{*} Most subjects in each group were 50 years or older (77%-81%) and had experienced hot flashes for 9 or more months (88%). The number of patients reporting a positive breast

^{*}The POMS tool is a 65-item rating scale and measures mood disturbances in the following categories: fatigue, vigor, tension, depression, anger and confusion. A Total Mood Disturbance score can be calculated and reflects a patient's global distress.¹⁴ This tool can be used to determine effects of drugs on mood state.¹⁵ The HFRDIS is a 10-item rating scale and measures the degree to which hot flashes interfere with a patient's daily activities such as work, sleep, mood and concentration. It also measures the impact of hot flashes on their overall quality of life.¹⁶

cancer history varied in each group (35%-44%), with most cancer patients taking aromatase inhibitors, raloxifene or tamoxifen. The primary end point was the change-from-baseline hot flash score (combining severity and frequency of hot flashes) as assessed by patient diaries after 6 weeks of treatment between the high-dose pregabalin group and placebo. Secondary end points included 1) change-from-baseline hot flash score between the low-dose pregabalin group and placebo, 2) change-from-baseline in hot flash frequency between pregabalin arms and placebo and 3) change in mood (POMS score), HFRDIS scores and toxicities between pregabalin arms and placebo.

Both low- and high-dose pregabalin therapy achieved statistical significance in reducing hot flash scores compared with placebo at week 6. Low-dose pregabalin reduced the hot flash score by 64.9% (95% confidence interval [CI], -83.6 to -57.8, $p = 0.009$), while the reduction with high-dose therapy was 71% (95% CI, -78.2 to -60.6, $p = 0.007$) compared with placebo. Also, both low- and high-dose pregabalin achieved statistical significance in reducing hot flash frequency compared with placebo at week 6, with reductions of 58.5% (95% CI, -74.6 to -48.8, $p = 0.007$) and 61.1% (95% CI, -72.3 to -48.3, $p = 0.007$), respectively. Results from HFRDIS showed that patients in both pregabalin arms had improvements in mood compared with placebo ($p = 0.01$). No change in total POMS score was found for either pregabalin arm compared with placebo. Dizziness was more significant in both low-dose ($p = 0.04$) and high-dose ($p = 0.0006$) pregabalin groups compared with placebo. Also, increased cognitive troubles were reported in the high-dose pregabalin arm ($p = 0.01$) compared with placebo. Despite experiencing treatment-related adverse events, patients in both low-dose ($p < 0.0001$) and high-dose ($p < 0.0001$) pregabalin arms were satisfied with their hot flash control compared with placebo. Low-dose pregabalin was effective in reducing hot flash scores and frequency and produced fewer adverse effects than high-dose pregabalin compared with placebo. There was no direct comparison in outcomes between low- and high-dose pregabalin.

The results from this study show that pregabalin may be effective in controlling hot flashes. Inclusion of patients with a minimum

of 28 hot flashes per week may limit its applicability.

Discussion

Although a subanalysis of the randomized controlled trial has not been conducted examining women without a history of breast cancer, the overall results are encouraging for the general population. Given the limited data available for pregabalin, however, it would be advisable to select other, more established pharmacological measures first, such as HT.

HT is generally the mainstay of treatment for women presenting with symptoms of hot flashes. However, many adverse events have been associated with HT, including an increased risk for breast cancer, ischemic stroke, thromboembolism and cardiovascular events.^{17,18} The results from the Women's Health Initiative (WHI) study demonstrated a slightly increased risk of breast cancer with combined HT (progesterone and oestrogen), when used for 5 or more years. In patients with a first-degree relative with a history of breast cancer, the use of HT does not seem to further increase risk. However, the risks associated with HT use in women diagnosed with breast cancer are unknown.³ The risk of stroke and venous thromboembolism was also increased in the WHI study. Results from the Heart and Estrogen/Progestin Replacement Study (HERS) demonstrated an increased risk of a second cardiovascular event in those using HT, even in the first year of treatment. Given this information, the use of nonhormonal

therapy such as pregabalin may be favoured in women diagnosed with breast cancer; a history of cardiovascular disease, stroke or thromboembolism; or in those who deem the risk of HT to outweigh its potential benefits.

Despite discontinuation rates between placebo and pregabalin (regardless of dose) being similar in the larger trial, adverse effects associated with pregabalin such as altered mentation and drowsiness may lead to discontinuation of the drug, as shown in the pilot study. Because of this, it would be reasonable to start at 75 mg twice daily of pregabalin to minimize these adverse effects. Pregabalin may be more convenient than gabapentin, as it is taken twice daily rather than 3 times.

Conclusion

Pregabalin may be beneficial in reducing the frequency and severity of hot flashes. Adverse effects associated with this indication are similar to those found with other uses and include dizziness, somnolence and cognitive troubles. While limited data demonstrate a beneficial effect of pregabalin for the treatment of hot flashes, no studies have compared its efficacy with other pharmacologic options such as HT or other nonhormonal drugs such as antidepressants, clonidine, Bellergeral or gabapentin. Due to a lack of comparative studies examining the efficacy of pregabalin to standards of care, its place in therapy for the treatment of hot flashes associated with menopause or cancer treatment remains unclear. ■

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