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Impact of transdermal estrogen therapy on migraine control in postmenopausal women: a systematic review

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Introduction
Estrogen fluctuations during menopause are known risk factors for the worsening of migraine. Although hormone therapy controls climacteric symptoms, the oral route of administration frequently aggravates the painful condition due to first-pass hepatic metabolism, which generates serum fluctuations. In contrast, the transdermal route offers continuous systemic absorption and greater hormonal stability, preventing new triggers.

Objective
To investigate the effects of transdermal estrogen hormone replacement therapy on migraine in postmenopausal women compared to oral therapy.

Methods
A systematic review conducted in accordance with the PRISMA 2020 guidelines. The literature search was performed in the PubMed database. Clinical trials and observational studies evaluating the effects of hormone administration routes on headache/migraine were included. Data extraction was conducted individually using standardized forms. The following information was extracted: characteristics of the studied populations, type and route of hormone therapy administration, association with progestogens, frequency and intensity of headaches, migraine worsening, and the occurrence of adverse events. The methodological risk of bias assessment was performed independently by two reviewers, using the standardized tools of the Cochrane Collaboration: RoB 2 for randomized clinical trials and ROBINS-I for observational and non-randomized studies.

Results
Out of the 30 articles identified, 7 comprised the final synthesis after analysis (4 clinical trials and 3 observational studies), which presented a risk of bias ranging from "Low/Some concerns" (RoB 2) to "Serious" (ROBINS-I). The impact of hormone therapy varied according to the primary diagnosis: patients with episodic tension-type headache showed no significant changes, whereas those with migraine without aura demonstrated high sensitivity to the route of administration. Oral therapy significantly worsened the migraine profile, with a substantial increase in the frequency, duration of attacks, and analgesic consumption in the 1st and 3rd months of treatment. In contrast, the transdermal route kept migraine parameters stable. Observational studies reinforced the transdermal potential, showing a reduction in nonspecific climacteric headache attacks in 95.7% of cases after 6 months. Pharmacokinetically, the transdermal route avoids first-pass hepatic metabolism, ensuring continuous serum concentrations that prevent the exogenous triggers and cerebral vascular hyperreactivity observed during the acute fluctuations of the oral route.

Conclusion
The transdermal route of estrogen administration is a clinically superior and safer alternative to the oral route for postmenopausal women with migraine. By preserving hormonal stability and avoiding the hepatic first-pass effect, it maintains attacks stabilized and attenuates climacteric headaches, serving as the primary clinical recommendation.

Keywords:
Migraine
Postmenopause
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