

New therapy for the treatment of hot flushes

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Life expands or contracts according to its value.

Anais Nin (1903-1977)



During the menopausal transition and subsequent years, due to the secondary hypoestrogenism by ovocyte depletion, in the majority of patients a series of symptoms occur often limiting the daily activities and requiring treatment. Probably the most annoying symptom are the hot flushes, along with sweating and redness, with a dysphoric state difficult to control. Hormone replacement therapy with estrogens, and associated progestins if the patient retains her uterus, is the most effective treatment for this symptom.

However, hormone replacement therapy can not be used in some cases. Patients with breast or uterine cancer, have a contraindication to estrogen use, being hormone-sensitive tumors. In these women an additional fact occurs: adjuvant endocrine therapy with tamoxifen or with aromatase inhibitors, as well as premature ovarian failure after chemotherapy in a significant proportion of young patients with breast cancer exacerbate the symptoms of estrogen deprivation, making symptomatic management difficult and necessary.

Hot flushes generated by hypoestrogenism are caused by intermittent, hypothalamic activation of heat-dissipating effectors, including vasodilation, sweating, and increased heart rate, leading to a decrease in body temperature. The lack of estrogens causes changes in the levels of some neurotransmitters that generate a narrowing of the thermoregulation zone, with activation of the heat dissipation effectors in response to minimal stimuli.

Recently, in the arcuate nucleus of the hypothalamus, a subset of neurons coexpressing estrogen Kisspeptin, neurokinin B (NKB) and dynorphin receptors has been described. These neurons, called KNDy neurons, would play a fundamental role in the generation of hot flushes mediated by decreasing circulating estrogens. It has been observed in menopausal women hypertrophy of these neurons and an increase in the expression of NKB and kisspeptine, which are suppressed by the action of estrogen at the hypothalamic level in women during reproductive life. These neurons are projected to the preoptic regions that control the heat dissipation effectors. Specifically, NKB and its receptor (NK3R) have been implicated in hot flushes during menopause, since it has been observed that NKB infusion in patients of

reproductive age induces this phenomenon with the same characteristics as those occurring in menopausal patients.

The most effective measure for vasomotor symptoms is estrogen therapy, which has been substituted, in patients with contraindication to its use, with other therapies as serotonin reuptake inhibitors, clonidine, phytoestrogens, cimicifuga racemosa, among others. These treatments seek to stabilize the neurotransmitters at the hypothalamic level to broaden the thermoregulation zone. The effectiveness of these treatments is not the same as hormonal therapy, in addition with annoying side effects in some cases, for this reason persists the search for the ideal drug that relieves symptoms to the same extent as estrogen, to be used in this subgroup of patients.

Julia Prague and colleagues in May 2017 published in *The Lancet*, a Phase 2 randomized, double-blind, placebo-controlled study evaluating the use of a neurokinin receptor antagonist (NK3R), the MLE4901, for the control of hot flushes in menopausal patients. A cross-over study was performed with 40 mgr of MLE4901 twice daily in group 1 for 4 weeks compared to placebo in group 2, followed by a clearance period of 2 weeks and then 4 weeks of group 1 with placebo and group 2 with MLE4901. 45 menopausal patients with severe vasomotor symptoms were evaluated. The objective was to evaluate the total number of hot flushes during the 4 weeks of treatment with MLE4901 or placebo. Severity, discomfort or interference of hot flushes, the gonadotropin levels, pulsatility of luteinizing hormone and the number of hot flushes detected by a monitor skin conductance was also evaluated.

The results were encouraging, the use of MLE4901 significantly reduced the number of weekly hot flushes compared to placebo: 49.01 episodes with placebo (95% CI: 40.81-58.56) and 19.35 episodes with MLE4901 (15.99-23.42), $p < 0.0001$, with a 45% reduction in the number of heat waves. The treatment also reduced severity, associated discomfort and interference in the daily activities of vasomotor symptomatology. To perform an objective measure of the treatment effect, a skin conductance measurement was performed with a Bahr monitor, which also showed a decrease with the use of the NK3R antagonist. Compliance with treatment was adequate, despite dosing twice daily, and no serious adverse events were reported. A small group of participants had a transient elevation of transaminases, apparently without clinical significance.

Although studies with a larger number of patients and a longer observation period, which are ongoing, are needed, it appears that this new drug is an alternative for patients who are unable or unwilling to use hormone replacement therapy for the treatment of hot flushes. In addition to increasing the number of patients and the time of observation of the treatment, it is necessary to evaluate if the attenuation effects of the vasomotor symptoms are maintained over time, because in some non-hormonal treatments, a decrease in the effect with the time, that is, a rebound effect is produced by drug tolerance. It is also necessary to evaluate this treatment in patients with breast cancer and adjuvant endocrine therapy, especially the possible drug interaction and the improvement of the symptoms in the treatment with tamoxifen or aromatase inhibitors, in addition to the hypoestrogenism derived from the premature ovarian insufficiency, which are important inducers of thermoregulatory instability.

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Also, it is important to clarify whether transient elevation of transaminases is a side effect that limits its indication, especially with prolonged use of MLE4901.

It is necessary to await the results of the ongoing studies with this new drug; however, it is outlined as a very interesting and novel option for the treatment of vasomotor symptoms from estrogen deprivation in patients with hormonal contraindication. Adherence to treatment for ten years is essential in many patients treated for breast cancer in endocrine-adjuvant treatment, so the management of hot flushes will help ensure compliance. This new drug could be consolidated as an effective non-hormonal alternative capable of providing adequate quality of life in menopausal patients.

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