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Magnitude of placebo response identified in drug for treatment of hot flashes

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Hot flashes are one of the most concerning and most reported symptoms among menopausal women and breast cancer survivors. Currently, paroxetine is a FDA-approved non-hormonal drug used for the treatment

of hot flashes. In an article published this month in the journal *Frontiers in Psychiatry*, researchers at Baylor University tested the efficacy of paroxetine by conducting a systematic review and meta-analysis of six clinical trials, finding that the benefits of paroxetine in the treatment of hot flashes to be comparable to that of the placebo response.

The study included information from all available clinical trials of paroxetine for hot flashes and provides the most comprehensive view of the drug's benefits.

"This is the first meta-analysis to systematically review clinical trials of paroxetine versus placebo with the aim of determining the magnitude of the placebo response among included clinical trials," said Joshua Rhodes, Ph.D., research assistant and lead author. "It is also the most robust with the inclusion of both published and unpublished outcome data derived from the national clinical trial database."

In clinical trials of treatments for hot flashes, the drug or other intervention is usually compared to a placebo (such as a "sugar pill" or non-effective intervention). This helps to determine if a medication has actual effects or if the perceived benefits are due to other factors such as having a hope or expectancy of benefit. Since paroxetine is used by many women, it is very important to have information about the effects beyond taking a placebo pill. The Baylor study was conducted to examine the extent of such placebo factors in taking paroxetine for hot flashes.

The researchers coded and analyzed the six randomized clinical trials that included 1,486 women. The results demonstrated that the placebo response accounted for the majority of treatment responses for reductions in both hot flash frequency and severity:

- 79% of the mean treatment response for hot flash frequency is

accounted for by a placebo response, resulting in a mean true drug effect of 21% at most.
- Additionally, 68% of the mean treatment response for hot flash severity is accounted for by a placebo response, resulting in a maximum true drug effect of 32%.

"We sought to provide objective information for women about the actual active drug benefit of taking paroxetine for hot flashes," said Gary Elkins, Ph.D., professor of psychology and neuroscience and director of the Mind-Body Medicine Research Laboratory at Baylor. "Our intent is to provide information that is needed for women to make informed decisions about taking paroxetine and the benefit beyond the non-specific effects of placebo."

Paroxetine efficacy

The drug paroxetine mesylate, marketed under the trade name of Brisdelle, is an SSRI used to treat anxiety and depression with associated potential side effects, including headache, fatigue, nausea/vomiting and a specific warning for increased risk of suicidal ideation.

"Results indicated that most of the benefit of paroxetine in reducing hot flashes is due to a non-specific placebo response. The meta-analysis shows that the benefit is rather small and is mostly due to placebo effects rather than drug-specific effects," Elkins said. "Further, this antidepressant medication has undesirable side effects and may reduce the benefit of breast cancer preventive medications."

Although the results call into question the efficacy of paroxetine for hot flashes, more research is needed to reevaluate the use of paroxetine to treat postmenopausal hot flashes and and emphasize the importance of considering effective, alternative treatments, the researchers said.

Reliable treatment needed for hot flashes

Hot flashes are triggered by a decline in estrogen either during natural menopause or as a result of breast cancer treatments. Approximately 80% of menopausal women and about 96% of breast cancer survivors experience hot flashes to some degree. For those experiencing these symptoms, it can cause a marked decrease in quality of life, physical discomfort and sleep disturbances. Symptoms generally last about seven years on average but can continue for 20 or more years for some women, Elkins said.

Previously, hormone replacement therapy (HRT) was widely used to manage hot flashes. However, research has shown that HRT is associated with an increased risk of breast cancer and cardiovascular disease for some women. Because of this, women often search for alternative solutions for symptom relief.

Having as much accurate information as possible about HRT and alternatives such as paroxetine empowers women to make decisions about how best to manage hot flashes and symptoms associated with menopause, Elkins said. The Baylor study provides important information for health care providers and women with menopausal symptoms who desire to avoid HRT for hot flashes.

The findings emphasize the need for more research to determine alternative and integrative health interventions for hot flashes, e.g., hypnotherapy, mindfulness, medications, and to address women's health concerns.

More information: Joshua R. Rhodes et al, Magnitude of placebo response in clinical trials of paroxetine for vasomotor symptoms: a meta-analysis, *Frontiers in Psychiatry* (2023). DOI: 10.3389/fpsyt.2023.1204163

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