Acid reflux drugs may have negative side effects for breast cancer survivors

January 17 2020, by Emily Caldwell

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Acid reflux drugs that are sometimes recommended to ease stomach problems during cancer treatment may have an unintended side effect: impairment of breast cancer survivors' memory and concentration.

New Ohio State University research shows an association between breast cancer survivors' use of proton pump inhibitors (PPIs) and reports of problems with concentration and memory. On average, cognitive problems reported by PPI users were between 20 and 29 percent more severe than issues reported by non-PPI users. PPIs are sold under such brand names as Nexium, Prevacid and Prilosec.

The study, the first to look at PPI use in breast cancer survivors, used data from three previous Ohio State clinical trials examining fatigue, a yoga intervention and vaccine response in breast cancer patients and survivors. In each of those studies, participants had reported their use of prescribed and over-the-counter medications and rated any cognitive symptoms they had as part of routine data collection.

After controlling for a variety of factors that could affect cognition—such as depression or other illnesses, types of cancer treatment, age and education—the researchers found that PPI use predicted more severe concentration and memory symptoms as well as lower quality of life related to impaired cognition.

"The severity of the cognitive problems reported by PPI users in this study was comparable to what patients undergoing chemotherapy had reported in a large observational study," said Annelise Madison, lead author of the study and a graduate student in clinical psychology at Ohio State. "PPI non-users also reported problems, but were definitely getting better. Based on what we're seeing, we don't know if PPI users might not be able to fully recover cognitively after chemotherapy. It's an area for further investigation."

The study is published online in the *Journal of Cancer Survivorship*.

Madison pursued this study based on her knowledge of PPIs' known potential to bypass the blood-brain barrier and previous research

suggesting that off-label use of PPIs in cancer patients may increase tumors' responsiveness to chemotherapy and protect the digestive system from the ravages of chemo drugs.

"I thought there could be a cognitive effect from taking PPIs, particularly in this population, because breast cancer survivors are already at risk for cognitive decline," she said. "PPIs are over the counter and generally considered safe so there haven't been many long-term trials, especially looking at cognitive outcomes, because nobody was really thinking that would be a downstream effect."

As part of her graduate program, Madison works in the lab of Janice Kiecolt-Glaser, professor of psychiatry and psychology and director of the Institute for Behavioral Medicine Research at Ohio State. For this work, Madison conducted secondary analyses of three of Kiecolt-Glaser's earlier studies examining inflammation's connection to breast cancer treatment and survivorship.

Data from 551 women in those earlier studies, 88 of whom reported taking PPIs, were used in Madison's analysis. The women in the previous studies had provided self-reports of PPI use and cognitive symptoms multiple times over varied periods of time depending on the design of each study.

Women in the studies looking at fatigue in newly diagnosed patients and investigating yoga's effect on inflammation and fatigue in survivors had completed a questionnaire rating the severity of their memory and concentration problems on a scale of 0 to 10 over the previous five days. Madison's analysis found that on average, PPI users' concentration problems in the fatigue study were 20 percent more severe than those reported by non-PPI users. In the yoga study, PPI users' concentration problems were 29 percent more severe than those reported by non-PPI users. There were no differences in reported memory problems.

In the third study, which featured data from the placebo visit of a typhoid vaccine trial, reported memory problems were 28 percent more severe in PPI users than in non-users, with no differences in reports of concentration issues. Breast cancer survivors in this study completed an additional questionnaire measuring the functional implications of their cognitive impairment. PPI users' scores were lower than non-users' scores on this assessment, where PPI users reported a poorer quality of life, greater cognitive impairment and poorer cognitive abilities compared to non-users.

"The fact that this study found similar effects across three different sets of patients who are at different stages of cancer survivorship gives some weight to what we're seeing," said Kiecolt-Glaser, senior author of the paper and an investigator in Ohio State's Comprehensive Cancer Center. "Had it been in only a single study, it could have been a chance effect."

The U.S. Food and Drug Administration has approved PPIs for short-term use to treat common gastric acid conditions and longer-term use for gastric ulcers and disorders involving excessive acid secretion. Madison noted that the off-label maintenance use of PPIs in cancer patients can last a long time: Her analysis showed that at least two-thirds of the breast cancer survivors using PPIs had taken them for between six months and two years.

Madison stressed that the study shows a correlation between PPI use and cognitive problems in breast cancer survivors, and that a clinical trial controlling PPI doses and obtaining objective cognitive data would be required to identify any causal effect.

More information: Annelise A. Madison et al, Cognitive problems of breast cancer survivors on proton pump inhibitors, *Journal of Cancer Survivorship* (2020). DOI: 10.1007/s11764-019-00815-4

Provided by The Ohio State University