Antipsychotic drugs may increase risk of breast cancer

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Tracking medications provided to over a half million U.S. women, researchers at Washington University School of Medicine in St. Louis have found that many commonly prescribed older antipsychotic

medications, and some newer ones, are associated with a significant increase in risk of breast cancer. Antipsychotics are prescribed for a broad range of conditions, including depression, bipolar disorder, schizophrenia, dementia and autism spectrum disorders.

While earlier studies have uncovered links between antipsychotic drug use and breast cancer risk, this is the first study to compare newer antipsychotics to older drugs, and to look at how the drugs affect levels of a hormone called prolactin. Increased levels of prolactin have been associated with breast cancer.

Prolactin is an important hormone involved in puberty, pregnancy and breastfeeding. However, many antipsychotics elevate prolactin levels and can produce side effects such as menstrual cycle irregularities, abnormal breast milk production and abnormal breast tissue growth.

The findings will be published in the February issue of the *Journal of Clinical Psychopharmacology* but are available online.

"Many women with psychiatric illnesses such as schizophrenia and bipolar disorder will take antipsychotics for decades, and they are essential to keeping symptoms in check," said the paper's first author, Tahir Rahman, MD, associate professor of psychiatry. "But both older antipsychotic medicines and some newer drugs raise levels of prolactin and increase the risk of breast cancer, which is concerning. Our study confirms findings from a smaller European study that advised women and their doctors to first try drugs that don't affect prolactin levels. We agree with that advice and believe psychiatrists should start to monitor prolactin levels in their patients taking antipsychotics."

The researchers classified antipsychotic drugs into three categories, based on their established effects on prolactin. Category 1 included drugs associated with high prolactin levels, such as haloperidol,

paliperidone and risperidone. Category 2 drugs, which had mid-range effects on prolactin, included the drugs iloperidone, lurasidone and olanzapine. Category 3 included drugs with less of an effect on prolactin levels, such as aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, quetiapine and ziprasidone.

The researchers compared the effects of all three categories of antipsychotic drugs to anticonvulsant drugs and lithium, which also often are prescribed to treat psychiatric disorders. When compared with those drugs, the relative risk of breast cancer was 62% higher for women who took Category 1 drugs and 54% higher for those taking Category 2 drugs, whereas Category 3 antipsychotics were not associated with any increase in breast cancer risk.

"Certain drugs are known to elevate prolactin, and the women taking those drugs were more likely to have breast cancer," Rahman said. "But we didn't detect any increased risk in women taking antipsychotics that don't raise prolactin levels."

In mouse models, prolactin can contribute to a weakening of cellular systems that keep precancerous lesions from becoming breast cancer. In people, prolactin levels tend to be lower in women who have had more children at a younger age than in women who have fewer children or wait until they are older to do so.

In this study using data collected from 2012 through 2016, the research team performed a retrospective, observational study of breast cancer risk in women ages 18 through 64 who took antipsychotics. The data came from the IBM MarketScan and Multi-State Medicaid databases, which contain anonymized medical information on more than 170 million people.

Rahman and his colleagues used billing codes from the databases to learn

which patients were treated for breast cancer during a 12-month period. Next, they matched that information to patients taking antipsychotic drugs. Of the 540,737 women in the database taking antipsychotics, only 914 were identified as having breast cancer. But a significant number of those women were taking drugs known to increase prolactin.

"Antipsychotic medications can be lifesaving for patients who have psychotic episodes where they experience symptoms such as hallucinations and delusions," Rahman said. "In recent years, the drugs have been approved to treat other conditions, too, including depression and bipolar disorder. As those high-prolactin agents are used more widely, the number at risk could increase. We've been advising against using these high-prolactin agents in women who already have breast cancer, but we'd like to investigate whether keeping prolactin levels lower even might prevent some of these cancers."

In another recent study, his team analyzed blood samples from women who took the antipsychotic drug aripiprazole (Abilify) as an add-on treatment for depression. They found that their prolactin levels did not increase and that a few women who began the study with high prolactin levels experienced decreases in prolactin levels after 12 weeks of treatment.

Those findings—combined with preclinical evidence of the anticancer effects of some antipsychotics—have inspired Rahman and his colleagues to propose repurposing some antipsychotic drugs in the fight against breast cancer.

"We don't want to alarm patients taking antipsychotic drugs for life-threatening mental health problems, but we also think it is time for doctors to track prolactin levels and vigilantly monitor their patients who are being treated with antipsychotics," Rahman said.

More information: Tahir Rahman et al, Risk of Breast Cancer With Prolactin Elevating Antipsychotic Drugs, *Journal of Clinical Psychopharmacology* (2021). DOI: 10.1097/JCP.0000000000001513