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Antipsychotic Use and Risk of Breast Cancer in Women with Schizophrenia

SUMMARY

- Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.[1-4]
- Studies by **Kern et al (2024)**,[5] **Rahman et al (2022)**,[6] and **Taipale et al (2021)**[7] presented conflicting results on the risk of breast cancer associated with the use of prolactin (PRL) increasing antipsychotics.
    - **Kern et al (2024)**[5] did not find a statistically significant correlation between high PRL increasing antipsychotics and the risk of incident breast cancer, or risk of breast cancer over time when comparing high vs low PRL increasing antipsychotics
    - **Rahman et al (2022)**[6] found that women treated with high- or mid-PRL increasing drugs had a significantly increased risk of breast cancer compared to patients treated with anticonvulsants or lithium
    - **Taipale et al (2021)**[7] found that cumulative exposure of 1 to 4 years was not associated with an increased risk of breast cancer vs exposure of <1 year for PRL-increasing antipsychotics, but cumulative exposure for ≥5 years was associated with an increased risk.
- Human breast cancer is a multifactorial disease that develops as a result of interactions between genetic, environmental, and hormonal factors.[8-11] No clear relationship has been established between the use of antipsychotics and the risk of breast cancer, but many antipsychotics are known to elevate serum PRL levels.[12]
- PRL regulation is complex, involving many different neurochemicals and receptors. The 2 primary receptors involved in the release of PRL are the dopamine D_2 and serotonin $5HT_{2A}$ receptors.[13-16]
- Literature suggests that most of the atypical antipsychotics produce significantly less elevation in PRL than do conventional agents, most likely due to the lower dopamine D_2-binding affinities of the newer agents.[17]
- Paliperidone has a PRL-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of PRL than other antipsychotic drugs.[18]

CLINICAL DATA – ANTIPSYCHOTIC USE AND BREAST CANCER

Cohort Studies

Kern et al (2024)[5] conducted a retrospective, longitudinal, cohort study to evaluate the association between the risk of breast cancer and the use of PRL-increasing antipsychotics in patients diagnosed with schizophrenia, using data from the MarketScan Medicaid database, between January 1, 2006, and June 30, 2021.

Study Design/Methods

- Female patients included in the analysis were aged ≥18 years on the index date (defined as the first observed fill for an antipsychotic), with ≥365 days of prior observation period during which they were diagnosed with schizophrenia.
- The study comprised 2 potential exposure cohorts, including patients exposed to high and moderate PRL-increasing antipsychotics, and a comparator cohort, including patients exposed to non/low-PRL-increasing antipsychotics.
- Antipsychotics included under the high-, moderate-, and low/non-exposure groups were as follows[19]:

    - High: acetophenazine, chlorpromazine, chlorprothixene, fluphenazine, haloperidol, loxapine, molindone, paliperidone, perphenazine, risperidone, thioridazine, thiothixene, and trifluoperazine
    - Moderate: iloperidone, lurasidone, and olanzapine
    - Low/non: aripiprazole, asenapine, brexpiprazole, clozapine, lumateperone, quetiapine, and ziprasidone
- The outcome of interest was the incidence of new breast cancer diagnosis, which was defined by 2 algorithms: the Nattinger algorithm, validated against the gold-standard Surveillance, Epidemiology, and End Results (SEER) classification, and the Rahman algorithm, which is commonly used in breast cancer claims data, but has not been validated. Both algorithms used a combination of diagnosis codes, breast cancer-related procedures, and surgical interventions.
- Patient characteristics such as demographics, comorbid conditions, baseline and concomitant medications, procedures and measurements at baseline, and baseline healthcare utilization were fed into the propensity score model as covariates. Greater than 25,000 covariates were identified and balanced between the exposure cohorts for propensity score matching.
- Propensity score matching and stratification were used to control potential confounding factors. Additionally, hazard analysis was conducted using Cox proportional hazard models.
- The association between antipsychotic exposure and the outcome was evaluated using two different methods: the intent-to-treat (ITT) analysis (in which the end of the risk was equated to the end of the observation period) and the per-protocol/on-treatment analysis (in which the end of the risk was equated to the end of continuous exposure to the antipsychotic). The at-risk period started 180 days following the index date.

Results

Demographic characteristics

- The patient pool was racially diverse (Black, 45%; White, 41%), with a mean age of 48 years (age range, ≥18 to >85 years).
- Common comorbidities included depression, anxiety, bipolar disorder, diabetes, hypertension, hyperlipidemia, obesity, and osteoarthritis.
- Commonly observed medications at baseline included antidepressants, antiepileptics, anxiolytics, and datives.
- In the 4 ITT analyses, there were between 4256 and 6341 patients included in each group, and the average follow-up was approximately 4 years.

Risk of breast cancer

- No statistically significant association was observed between exposure to high PRL-increasing antipsychotics and the risk of incident breast cancer; the HR was close to the null hypothesis (1.0) (HR range: 0.96 [95% confidence interval (CI), 0.62-1.48] to 1.28 [95% CI, 0.40-4.07]) across the different analyses.
- Kaplan-Meier analysis indicated no significant difference in breast cancer risk over time between the patients exposed to high vs low/non-PRL-increasing antipsychotics.

Limitations

- The incidence of breast cancer was confirmed from administrative claims data, the accuracy of which was high in terms of validity, but lack of information on biomarkers, cancer grade, tumor staging, or other clinical outcomes.
- The lack of information on serum PRL levels limits accurate interpretation of the hypothesized link between the risk of breast cancer and exposure to high PRL-increasing antipsychotics.
- The mean follow-up of approximately 4 years may not be sufficient to identify the true risk of breast cancer.

- The study did not consider several confounding factors that may have influenced the increased risk of breast cancer, including socioeconomic factors (education, income), behavioral factors (diet, exercise, and drug and/or tobacco use), and other breast cancer risk factors (genetic mutations, family history, breast density, and menopause status).

Rahman et al (2022)[6] evaluated the risk of breast cancer in 540,737 women (aged 18 to 64 years) newly exposed to antipsychotics compared to anticonvulsants and/or lithium through a retrospective, observational cohort study using data from IBM® MarketScan Commercial and Multi-State Medicaid databases.

Study Design/Methods

- Women aged 18 to 64 years with an outpatient prescription claim for an antipsychotic, anticonvulsant, or lithium from January 1, 2007, to June 30, 2016, were included (index date = fill date of the study drug).
- Antipsychotic drugs were separated into 3 categories based on their propensity to elevate PRL:
    - Category 1 (high PRL): "typical" neuroleptics such as haloperidol, as well as, risperidone and paliperidone
    - Category 2 (mid PRL): iloperidone, lurasidone, and olanzapine
    - Category 3 (low PRL): aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, quetiapine, and ziprasidone
- Lithium and anticonvulsants were identified as comparator drugs because they are prescribed for patients with mental illness but are not known to raise PRL levels.
    - Exposure within the drug categories was measured using drug-specific defined daily dose (DDD), created by the World Health Organization's Collaborating Centre for Drug Statistics Methodology. The average DDD per day of observed treatment was defined as the cumulative DDD/total days of observed treatment period.

Results

Demographic characteristics

- At baseline, a total of 40% of women in the study population had a diagnosis of major depression, 12.4% had a diagnosis of bipolar disorder, and 2.6% were diagnosed with schizophrenia.
- A total of 914 (0.2%) women were diagnosed with invasive breast cancer during the study period, which consisted of a median duration of follow-up of approximately 4 years.
- Approximately 52% of the study population filled at least 1 prescription for a category 3 antipsychotic, 15% filled at least 1 prescription for a category 1 antipsychotic, and 49% filled an anticonvulsant agent during the study period.
- The median age of women diagnosed with breast cancer was significantly higher at 53 years vs 41 years for women not diagnosed with breast cancer ($P<0.0001$).
- Obesity, diabetes, hormone replacement therapy, and pre-existing benign breast disease were more common in women newly diagnosed with invasive breast cancer than in women who were not.

Risk of invasive breast cancer

- Women treated with antipsychotic drugs (categories 1 to 3) had a higher overall risk of breast cancer than women treated with anticonvulsants or lithium (HR, 1.40; 95% CI, 1.19-1.64).
- There were little differences shown in the risk of breast cancer associated with antipsychotic exposure after adjustment for known breast cancer risk factors, including obesity, diabetes, hormone-replacement therapy, alcohol abuse, and pre-existing benign breast disease.

- Antipsychotic categories 1 and 2 were associated with significantly increased risk of breast cancer compared to anticonvulsants or lithium: category 1 (HR, 1.50; 95% CI, 1.25-1.81) and category 2 (HR, 1.65; 95% CI, 1.25-2.18).
- Category 3 antipsychotics were not associated with significantly increased risk of breast cancer compared to anticonvulsants or lithium (HR, 1.10; 95% CI, 0.83-1.50).

Limitations

- The authors noted the median duration of follow-up at approximately 4 years in each group may be too short.
- The analysis did not include women 65 years and older.
- Twelve months of insurance enrollment without a study drug was required for enrollment, so it is possible women enrolled as "new users" had prior experience with study drugs.
- Unable to control for residual confounding due to parity, menopausal status, family history of breast cancer, alcohol, sedentary lifestyle, diet, obesity, and age at first birth; although, the adjustment for diagnosed mental health conditions may have reduced residual confounding of some of these comorbid conditions.
- Potential confounding due to the comparison of women taking antipsychotics to those taking anticonvulsants or lithium or due to clinician favor of one antipsychotic drug category (eg, illness severity, insurance coverage) may have occurred.
- Actual serum PRL levels may not be reflective of the 3 antipsychotic categories, and all patients may not have the same PRL response.

Taipale et al (2021)[7] analyzed the risk of breast cancer in 30,785 women diagnosed with schizophrenia between 1972 and 2014 in a nested-case control study using Finnish nationwide registers of hospital treatment, prescription drug purchases, and cancer diagnoses.

Study Design/Methods

- A total of 1069 patients with breast cancer were matched by age (mean age, 62.2 years) and duration of illness (mean duration: 23.7 years) with 5339 women without cancer.
- Women with any previous cancer diagnosis, receipt of organ transplant, mastectomy, or human immunodeficiency virus were excluded from the study.
- The association between cumulative exposure to PRL-increasing drugs and breast cancer was analyzed and adjusted for comorbid conditions and concomitant medications.

Results

- Compared with matched controls, cumulative exposures of 1 to 4 years (adjusted odds ratio [aOR]: 0.95; 95% CI: 0.73-1.25) or ≥5 years (aOR: 1.19; 95% CI: 0.90-1.58) to PRL-sparing antipsychotics (clozapine, quetiapine, aripiprazole) were not associated with an increased risk of breast cancer vs minimal exposure of less than 1 year.
- Cumulative exposure of 1 to 4 years was not associated with an increased risk of breast cancer compared with exposure of <1 year (aOR: 1.04; 95% CI: 0.79-1.36) for PRL-increasing antipsychotics (all other antipsychotics).
- Cumulative exposure for ≥5 years was associated with an increased risk (aOR: 1.56; 95% CI: 1.27-1.92; $P<0.0001$).
- The risk of developing lobular adenocarcinoma associated with long-term use of PRL-increasing antipsychotics (aOR: 2.36; 95% CI: 1.46-3.82) was higher than developing ductal adenocarcinoma (aOR: 1.42; 95% CI: 1.12-1.80).
- Paliperidone, a PRL-increasing antipsychotic was not included among the cases or controls in this study.

Limitations

A critical analysis of the study methodology identified several important limitations:

- PRL concentrations were not considered in the study, therefore, the authors are unable to establish causality between hyperprolactinemia due to PRL-increasing antipsychotics and increased risk of breast cancer.[7]
- Important breast cancer risk factors like body mass index, smoking, family history of breast cancer, lifestyle, and alcohol consumption were not captured in the study; information on hormone exposure and parity was incomplete, and information on lactation was missing.[7]
- In general, the use of ORs tends to overestimate the association as compared with relative risks. In addition, the data indicate the presence of residual confounding. It was noted for concomitant medication use that there was a substantial relative difference between controls and cases, with a consistently higher proportion of medication use in cases for each drug category, which indicates that the case population had an overall worse health status (ie, sicker) than controls. Sensitivity analyses are required to control for unmeasured confounding and other biases inherent in real-world data studies.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 30 January 2025.

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