BJPsych | The British Journal of Psychiatry (2025)
1–3. doi: 10.1192/bjp.2025.16

Guest Editorial

Real-world studies in psychiatry: insights into antipsychotic-associated breast cancer risk and their broader implications

Olivier Corbeil, Itziar Montalvo, Javier Labad and Jurjen J. Luykx

Summary

Real-world studies provide valuable insights into long-term outcomes across diverse populations. Here, we contextualise recent findings on the association between antipsychotic use and breast cancer risk in women with schizophrenia. We discuss clinical implications and the strengths and limitations of real-world studies in psychiatry. We conclude with future perspectives.

Keywords

Psychiatry; schizophrenia; real-world studies; breast cancer; antipsychotics.

Real-world studies are increasingly recognised for their value in capturing long-term outcomes and population-level trends that randomised controlled trials (RCTs) often cannot disentangle. By including the 80% of patients with schizophrenia who are not represented in RCTs,[1] such as those with comorbidities, real-world studies provide critical insights into clinical practice. Here, we use a South Korean population-based cohort study recently published in the *BJPsych*[2] as a case study to illustrate the strengths, limitations and potential future directions of real-world studies in psychiatry. The findings link long-term antipsychotic use to breast cancer risk in women with schizophrenia, providing an example of how real-world studies can inform clinical practice and generate hypotheses for further research.

The most salient findings of the Yang et al study

Yang and colleagues reported on the risk of breast cancer in women with schizophrenia using data from the South Korean National Health Information Database (NHID).[2] The authors detected a 1.25-fold (95% CI 1.19–1.31) increased risk of breast cancer in women with schizophrenia compared with the general population, and a 1.16-fold (95% CI 1.10–1.21) increased risk compared with women with other psychiatric disorders. Relative to women with schizophrenia who had used antipsychotics for <0.5 years, risks were higher in those who had used antipsychotics for 1–3 years (hazard ratio = 1.27, 95% CI 1.04–1.56) and ≥4 years (hazard ratio = 1.32, 95% CI 1.09–1.61), especially in those who had used first-generation antipsychotics for 3–4 years (hazard ratio = 1.45, 95% CI 1.12–1.88). No associations were found between breast cancer risk and second-generation antipsychotics. Although data on specific antipsychotics were unavailable, the authors hypothesised that hyperprolactinaemia, a common side-effect of first-generation antipsychotics, is a potential mechanism underlying the increased breast cancer risk.

Antipsychotic use and breast cancer risk: the broader context

The South Korean findings are consistent with previous studies suggesting an increased risk of breast cancer associated with long-term use of prolactin-increasing antipsychotics. Findings from two previous nested case–control studies using population registers hint that exposure to prolactin-increasing antipsychotics, but not prolactin-sparing antipsychotics, is associated with increased odds of breast cancer in women with schizophrenia[3] and with severe mental illness (SMI) generally.[4]

In the first of these two real-world studies, 1069 cases of breast cancer were identified in Finnish women with schizophrenia, uncovering a 1.56-fold (95% CI 1.27–1.92) increased odds of breast cancer with exposure to prolactin-increasing antipsychotics for >5 years compared with minimal exposure to such agents (<1 year).[3] The second study included 1642 cases of breast cancer among Swedish women with SMI, detecting increased odds of breast cancer in those with prior exposure to prolactin-increasing antipsychotics for 1–4 years (adjusted odds ratio aOR = 1.20, 95% CI 1.03–1.41) and for ≥5 years (aOR = 1.47, 95% CI 1.26–1.71) compared with minimal use (<1 year).[4]

Altogether, these studies and the findings by Yang et al[2–4] hint that hyperprolactinaemia induced by these medications contributes to the development of breast cancer.

Strengths and weaknesses of real-world studies in psychiatry

Although RCTs are the gold standard for establishing causality, their stringent exclusion criteria in schizophrenia studies, for example, often exclude participants with comorbidities commonly observed in people with the condition, limiting the generalisability of their findings to clinical practice.[1] Real-world studies address this gap by including diverse populations and capturing long-term outcomes, including rare or delayed adverse effects that often go undetected in RCTs. For instance, breast cancer risk has not been identified in RCTs of antipsychotic maintenance treatment, likely because of their duration, which in most cases does not exceed 52 weeks. Given that the latency period for drug–cancer associations is typically at least 1–5 years, detection of many such risks requires extended follow-up. For example, the excess risk of breast cancer associated with menopausal hormone therapy in women mostly emerges after 1–4 years of use, with progressively higher risks observed beyond 5 and 10 years.[5] Moreover, relatively rare adverse drug reactions are notoriously difficult to detect in RCTs. Importantly, the absence of reported adverse events in an RCT does not rule out their occurrence. In a trial with 300 participants and no observed events, the frequency of the adverse reaction could still be as high as 1 in 100.[6] Detecting events with an incidence of approximately 1.5 in 1000, similar to the breast cancer

https://doi.org/10.1192/bjp.2025.16 Published online by Cambridge University Press

incidence among women with schizophrenia reported by Yang et al,[2] would require a trial involving at least 2000 participants followed for 1 year to have a 95% chance of observing just one occurrence.

In the study by Yang and colleagues,[2] use of the Korean NHID allowed access to comprehensive data on healthcare utilisation, diagnoses and prescribed medications over an extended period (2007–2018). This facilitated the detection of small effect sizes after several years of use, which in RCTs and even meta-analyses of RCTs is challenging owing to the small study populations and relatively short follow-up. Moreover, in the Finnish and Swedish studies discussed above,[3,4] women with breast cancer were matched to other women without breast cancer of the same age, with the same primary psychiatric diagnosis and disease duration, reducing the likelihood of indication bias.

However, real-world studies also have limitations, particularly the lack of randomisation, which makes them more susceptible to confounding arising, for example, from unmeasured behavioural, genetic or environmental factors. Factors that may confound the association between antipsychotic use and risk of breast cancer are not captured in most population registry-based real-world studies, including genetic predisposition, prolactin serum concentrations, illness severity, treatment adherence, access to care, breast cancer screening and lifestyle.

In the South Korean study,[2] although age-matched control groups were included and statistical adjustments were done for proxies of comorbidity and socioeconomic status, residual confounding remains possible. For instance, the psychiatric control group, consisting of women with diagnoses other than psychotic disorders, also showed an increased risk of breast cancer compared with the general population. This suggests that there may be shared factors across psychiatric disorders contributing to the elevated risk, not limited to schizophrenia. Such findings underscore a common limitation of many real-world studies, where important variables that might influence both the risk and the outcome are often missing. In contrast, RCTs are designed to address this issue through randomisation, which helps ensure that confounders are equally distributed across all groups, providing greater confidence in causal inferences.

Moreover, certain methodological choices in real-world studies can introduce biases. For example, combining dopamine agonists with dopamine antagonists into a single group of prolactin-sparing antipsychotics hinders distinguishing between prolactin-lowering antipsychotics, such as aripiprazole, and prolactin-sparing antipsychotics. Selection bias may also occur. For instance, the use of clozapine may reflect a distinct clinical profile, with patients being more likely to be treatment adherent and undergo close monitoring than those receiving aripiprazole or prolactin-increasing antipsychotics. In addition, severely ill patients and/or those with poor insight and treatment adherence may be relatively more likely to be prescribed long-acting injectable antipsychotics, the majority of which are prolactin-increasing. Furthermore, antipsychotic use itself may reflect better access to healthcare services, including cancer screening.

Antipsychotics and breast cancer: is hyperprolactinaemia a risk factor?

Although data on prolactin serum concentrations were unavailable in the above-mentioned real-world studies examining the relationship between prolactin-increasing antipsychotics and breast cancer,[2–4] other studies suggest that hyperprolactinaemia contributes to increased breast cancer risk. In a meta-analysis of observational studies,[7] a positive association was found between elevated prolactin levels and breast cancer occurrence (relative risk = 1.26, 95% CI 1.15–1.37), particularly for oestrogen receptor-positive (ER+)/prolactin receptor-positive (PR+) tumours (relative risk = 1.49, 95% CI 1.23–1.75) and invasive cancers (relative risk = 1.42, 95% CI 1.24–1.60) and in postmenopausal women (relative risk 1.29, 95% CI 1.16–1.43).

A preclinical study explored the role of prolactin-Janus kinase 2 (JAK2)-signal transducer and activator of transcription 5 (STAT5) signalling in mammary tumorigenesis, as both factors promote cell differentiation and inhibit apoptosis.[8] In that study, risperidone and pimozide (both prolactin-increasing antipsychotics), but not aripiprazole, caused precancerous cells to activate STAT5 and inhibit apoptosis without affecting proliferation. The mechanism at play here may be that, on binding of prolactin to its receptor (PRLR), the JAK/STAT pathway is activated, which in turn prompts phosphorylation and activation of STAT5 and STAT4, promoting cellular processes such as growth, survival and differentiation. The binding of prolactin to PRLR also stimulates breast epithelial cell proliferation. Elevated levels of prolactin and increased PRLR signalling can thus enhance cell division, contributing to tumour growth.

Clinical implications of associations between antipsychotic use and breast cancer

Although the findings reported in the three above-mentioned real-world studies[2–4] do not confirm whether hyperprolactinaemia mediates the elevated risk of breast cancer associated with antipsychotic use, they highlight the need for greater attention to the long-term risk of breast cancer in women using antipsychotics, particularly first-generation agents. At the same time, when appraising the increased risks of breast cancer linked to antipsychotic use across studies, we note that the absolute risks are modest. For instance, in a psychiatric facility treating 100 women with schizophrenia, independent of antipsychotic use, approximately one additional case of breast cancer would be expected over 30 years compared with women in the general population based on the Yang et al findings.[2] A similar observation period of 3000 person-years would be needed to find one additional case among women who used first-generation antipsychotics for >3 years compared with those who used them for <6 months. Nonetheless, the most important implication of the study by Yang and colleagues is the need for clinicians to consider and monitor breast cancer risk, especially in middle-aged and older women with schizophrenia and those having used prolactin-increasing agents for several years. In addition, although parsing antipsychotic-associated breast cancer risk estimates in women with a history of (breast) cancer from those without such a history would require very large study populations, an intuitive implication of the Yang et al findings is that women with such a history should be closely monitored, with prolactin-sparing antipsychotics preferred for them when possible.

Future directions for research

Real-world studies are increasingly using advanced methods, such as propensity score matching and instrumental variable analysis, to mitigate some of the inherent biases and confounding issues. These approaches bolster the robustness of findings, adding to the value of real-world evidence to inform clinical decision-making. In the context of antipsychotic-associated breast cancer risk, future research would benefit from incorporating broader data sources, such as genetic information, patient-reported outcomes and prolactin serum levels. Incorporating such data into real-world data analyses may provide more nuanced insights into medication- and patient-specific

https://doi.org/10.1192/bjp.2025.16 Published online by Cambridge University Press

risks, enhance mechanistic understanding and shed light on the aetiological and pathophysiological pathways involved.

A key focus for future research should be to examine the differential contributions of specific antipsychotics to breast cancer risk by avoiding the lumping of combinations of antipsychotics with distinct mechanisms of action within the same exposure group. Clozapine, in particular, should be treated separately from other prolactin-sparing antipsychotics because of its indication for treatment-resistant schizophrenia and the close monitoring it requires. Additionally, if hyperprolactinaemia is confirmed to increase breast cancer risk (e.g. using Mendelian randomisation or mechanistic studies), aripiprazole, especially as monotherapy, would be expected to diminish breast cancer risk compared with other antipsychotics because of its prolactin-lowering effects. Although individual studies may lack sufficient statistical power because of small sample sizes, meta-analyses of individual patient data may allow for better powered analyses of antipsychotic-specific risks.

Another promising avenue for future research is the integration of real-world and RCT findings, which can help clinicians better weigh the benefits and risks of different treatment options, especially for vulnerable populations that are underrepresented in clinical trials.[1] A recent example is a study integrating data on effectiveness (derived from real-world studies) and efficacy (derived from RCTs) of antipsychotics, resulting in the largest study on these outcome measures for antipsychotics.[9] By applying such designs, similarities and differences in absolute and relative effect estimates between RCT and real-world settings may be disentangled.

Finally, intervention studies may examine the need and (cost-) effectiveness of personalised strategies, such as prioritising prolactin-sparing antipsychotics and implementing regular screening for high-risk patients.

In conclusion, as psychiatry slowly moves towards treatment strategies tailored to individual patient profiles, the need for real-world evidence is increasingly critical. Real-world studies can inform clinicians about the safety and effectiveness of interventions across diverse populations and help identify which patients are most likely to benefit from specific treatments. The association between antipsychotic use and breast cancer risk in women with schizophrenia exemplifies an adverse event that real-world studies can uncover, while RCTs may be underpowered to detect such rare adverse outcomes. To further advance evidence-based practices in psychiatry, future research should prioritise real-world studies that complement and, where possible, integrate RCT findings.

Olivier Corbeil, Faculty of Pharmacy, Laval University, Quebec City, Canada; and Department of Pharmacy, Quebec Mental Health University Institute, Quebec City, Canada; **Itziar Montalvo**, Department of Mental Health, Parc Taulí University Hospital, Parc Taulí Research and Innovation Institute (I3PT-CERCA), Barcelona, Spain; Department of Psychiatry and Legal Medicine, Autonomous University of Barcelona, Barcelona, Spain; and Centre for Biomedical Research in Mental Health (CIBERSAM), Madrid, Spain; **Javier Labad**, Centre for Biomedical Research in Mental Health (CIBERSAM), Madrid, Spain; and Department of Mental Health and Addictions, Maresme Health Consortium, Barcelona, Spain; **Jurjen J. Luykx**, Department of Psychiatry, Amsterdam University Medical Center, Amsterdam, The Netherlands; GGZ inGeest Mental Health Care, Amsterdam, The Netherlands; Amsterdam Neuroscience Mood, Anxiety, Psychosis, Stress & Sleep (MAPSS) programme and Amsterdam Public Health (Mental Health Program) Research Institute, Amsterdam University Medical Center, Amsterdam, The Netherlands; and Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands

Correspondence: Jurjen J. Luykx. Email: j.j.luykx@amsterdamumc.nl

First received 4 Oct 2024, final revision 19 Dec 2024, accepted 1 Jan 2025

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

All authors made substantial contributions to the conceptualisation, drafting and revision of this editorial. O.C. and J.J.L. led the initial drafting of the manuscript. I.M. and J.L. provided input on the interpretation of the findings and critically reviewed the manuscript. All authors approved the final version for submission.

Funding

This study received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

References

1 Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, Radua J, Efthimiou O, Vinkers CH, et al. Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. *JAMA Psychiatry* 2022; **79**: 210–8.

2 Yang JS, Kang S, Kim K, Tsai AC, Cho C-H, Jung SJ. Breast cancer risk among women with schizophrenia and association with duration of antipsychotic use: population-based cohort study in South Korea. *Br J Psychiatry* [Epub ahead of print] 31 Oct 2024. Available from: https://doi.org/10.1192/bjp.2024.170.

3 Taipale H, Solmi M, Lähteenvuo M, Tanskanen A, Correll CU, Tiihonen J. Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland. *Lancet Psychiatry* 2021; **8**: 883–91.

4 Solmi M, Lähteenvuo M, Tanskanen A, Corbeil O, Mittendorfer-Rutz E, Correll CU, et al. Antipsychotic use and risk of breast cancer in women with severe mental illness: replication of a nationwide nested case-control database study. *Schizophr Bull* 2024; **50**: 1471–81.

5 Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* 2019; **394**: 1159–68.

6 Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol* 2007; **7**: 32.

7 Aranha AF, Dos Anjos LG, Turri JAO, Simões RS, Maciel GAR, Baracat EC, et al. Impact of the prolactin levels in breast cancer: a systematic review and meta-analysis. *Gynecol Endocrinol* 2022; **38**: 385–90.

8 Johnston AN, Bu W, Hein S, Garcia S, Camacho L, Xue L, et al. Hyperprolactinemia-inducing antipsychotics increase breast cancer risk by activating JAK-STAT5 in precancerous lesions. *Breast Cancer Res* 2018; **20**: 42.

9 Efthimiou O, Taipale H, Radua J, Schneider-Thoma J, Pinzón-Espinosa J, Ortuño M, et al. Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. *Lancet Psychiatry* 2024; **11**: 102–11.

https://doi.org/10.1192/bjp.2025.16 Published online by Cambridge University Press