Medicines Adverse Reactions Committee

Meeting date	4/12/2025	Agenda item	3.2.2
Title	**Antipsychotic induced hyperprolactinemia and the risk of breast cancer**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Chlorpromazine	Largactil*	Clinect NZ Pty Limited
Haloperidol	Haldol*	Clinect NZ Pty Limited
	Serenace*	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Periciazine	Neulactil*	Clinect NZ Pty Limited
Prochlorperazine	Nausafix*	Teva Pharma (New Zealand) Limited
	Prochlorperazine maleate Buccal*	Max Health
	Stemetil*	Clinect NZ Pty Limited
Zuclopenthixol	Clopixol*	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Amisulpride	Sulprix*	Viatris Limited
Aripiprazole	Abilify Abilify Maintena*	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
	Aripiprazole Lupin	Lupin NZ Limited
	Aripiprazole Sandoz*	Sandoz New Zealand Limited
Clozapine	Clozaril*	Viatris Limited
	Clopine*	Douglas Pharmaceuticals Limited
	Versacloz*	Douglas Pharmaceuticals Limited
Olanzapine	Zypine*	Viatris Limited
	Zyprexa*	Pharmaco (NZ) Ltd
Quetiapine	Quetapel*	Viatris Limited
Risperidone	Risperdal*	Janssen-Cilag (New Zealand) Ltd
	Risperidone (Teva)*	Teva Pharma (New Zealand) Limited
	Risperon*	Viatris Limited
Paliperidone	Invega*	Janssen-Cilag (New Zealand) Ltd
Ziprasidone	Zusdone*	Douglas Pharmaceuticals Limited

PHARMAC funding	Currently funded brands marked with *
International action	US FDA – epidemiological studies show inconsistent results
Prescriber Update	Hyperprolactinaemia with Antipsychotics (May 2001)
Classification	Prescription medicine

Usage data	See section 2.5 – Usage

Advice sought	**The Committee is asked to advise:**
	• On the strength of the evidence for an association between the use of antipsychotics and the risk of breast cancer, and whether there is evidence of a link between breast cancer and
	  o First generation vs second generation antipsychotics
	  o Antipsychotics that increase prolactin vs those that do not
	  o Any other factors (eg, dose, duration).
	• Whether regulatory action is required (eg, updates to the data sheets)?
	• Whether further communication is required, other than in MARC's remarks?

Table of Contents

1 PURPOSE

[redacted]

The purpose of this report is to review the latest evidence on the potential association between antipsychotic use and the risk of breast cancer and whether regulatory action is required.

2 BACKGROUND

2.1 Typical vs atypical antipsychotics

Antipsychotics are broadly classified as typical (first generation antipsychotic, FGA) or atypical (second generation antipsychotic, SGA).

FGAs act predominately by blocking dopamine D2 receptors in the brain. They are not selective for any of the four dopamine pathways and can cause a range of adverse effects, particularly extrapyramidal symptoms and elevated prolactin [1]. Approved FGAs include chlorpromazine, haloperidol, periciazine, prochlorperazine, and zuclopenthixol.

SGAs can generally be distinguished by their binding to additional receptors, and that their serotonin 5HT2 receptor binding exceeds their affinity for dopamine D2 receptors. They have a lower risk of causing extrapyramidal side effects and hyperprolactinemia compared to FGAs [2]. Approved SGAs include amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone and ziprasidone.

2.2 Role of dopamine and hyperprolactinemia

Prolactin is a hormone that contributes to many physiological functions, including milk production and the development of mammary glands within breast tissues.

Prolactin is primarily synthesised by lactotrophs in the anterior pituitary gland. Dopamine acts on lactotrophic cells through D2 receptors, inhibiting prolactin synthesis. In the absence of pregnancy (ie, high oestrogen) or lactation in sexually mature females, prolactin is constitutively inhibited by dopamine [3].

Antipsychotics that interfere with dopamine-receptor binding can therefore increase prolactin secretion. The specific mechanism involves non-selective D2 dopamine-receptor inhibition in multiple dopaminergic pathways, including the tuberoinfundibular tract, resulting in disinhibition of prolactin release [3]. The extent of dopamine D2 receptor antagonism correlates positively with the elevation of prolactin levels [4].

Hyperprolactinemia is defined as a serum prolactin concentrations greater than 20 ng/ml in men and 25 ng/ml in women. Hyperprolactinemia is most frequently observed with use of FGAs and certain SGAs (ie,

risperidone, paliperidone and amisulpride). Clozapine, aripiprazole and quetiapine have the smallest effect on prolactin secretion (Table 1) [4].

Table 1: Antipsychotics as well as their generation and propensity to increase prolactin [5]

Comments:

Grouping of antipsychotics as prolactin increasing or sparing can differ based on reference sources. For the purpose of this report, all FGAs (eg, chlorpromazine, haloperidol, pericyazine, prochlorperazine, levomepromazine, flupentixol, and zuclopenthixol) and the SGAs: risperidone, paliperidone and amisulpride will be considered prolactin-increasing antipsychotics. This list based on UpToDate 'Medicines that cause hyperprolactinaemia' [5] and Health New Zealand Waitaha Canterbury 'Which antipsychotic is right for me?' leaflet.

2.3 Hyperprolactinemia and breast cancer

In mice studies, prolactin-inducing antipsychotics have shown to increase breast cancer risk by activating the JAK-STAT5 pathway in precancerous lesions. This activation leads to suppression of apoptosis, thereby promoting the progression of precancerous cells to cancerous ones [4].

Another study investigated the effects of olanzapine in rats. Olanzapine induced significant mammary gland development and histopathological hyperplasia, which was dose- and time-dependent and was associated with increased prolactin receptor expression in the mammary gland [4].

The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unclear [6]. Several large prospective studies, in which blood was collected prior to breast cancer diagnosis, have observed positive associations between prolactin and risk [4].

One suggested mechanism is that antipsychotics primarily increase the risk of breast cancer through dopamine inhibition. This inhibition reduces the suppressive effect of dopamine on prolactin secretion, leading to hyperprolactinemia [7].

2.4 Breast cancer

Breast cancer is the most common cause of cancer in women in New Zealand and the third most common cancer overall. Breast cancer affects one in nine New Zealand women over their lifetime [8]. It is more common in people aged >50 years, although 25-30% of cases occur in younger people with 6% in women under the

age of 40, and can affect all genders. Māori women experience higher rates of breast cancer, and Māori and Pasifika women more commonly get breast cancer at a younger age [9]. Male breast cancer accounts for about 1% of all breast cancer cases. In New Zealand, approximately 25 men are diagnosed with breast cancer every year [10].

Risk factors for breast cancer include increasing age, alcohol consumption, obesity, physical inactivity, family history of breast and/or ovarian cancer, early menstruation, higher levels of oestrogen, increasing age of pregnancy, late menopause, use of hormone therapy, and radiation exposure [9].

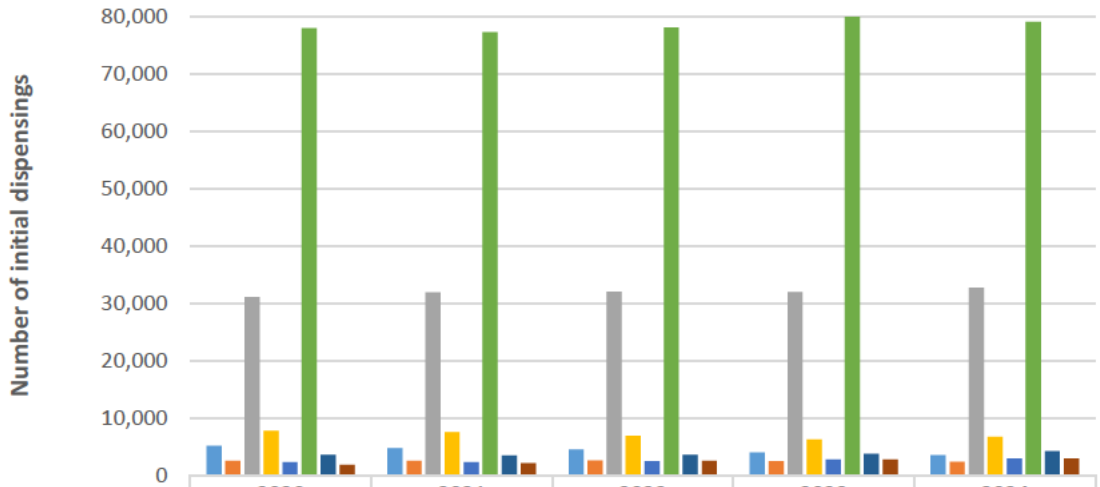
Women with schizophrenia have a higher prevalence of breast cancer risk factors (unhealthy lifestyle behaviours, obesity, diabetes) and may be more prone to developing breast cancer compared to the general population. Further, breast cancer may be underdiagnosed in women with schizophrenia because of a decreased odds of undergoing screening compared with the general population [11].

2.5 Usage

Figures 1 and 2 show FGA and SGA usage by number of (a) initial dispensings and (b) number of people who received a dispensing from 2020 to 2024.

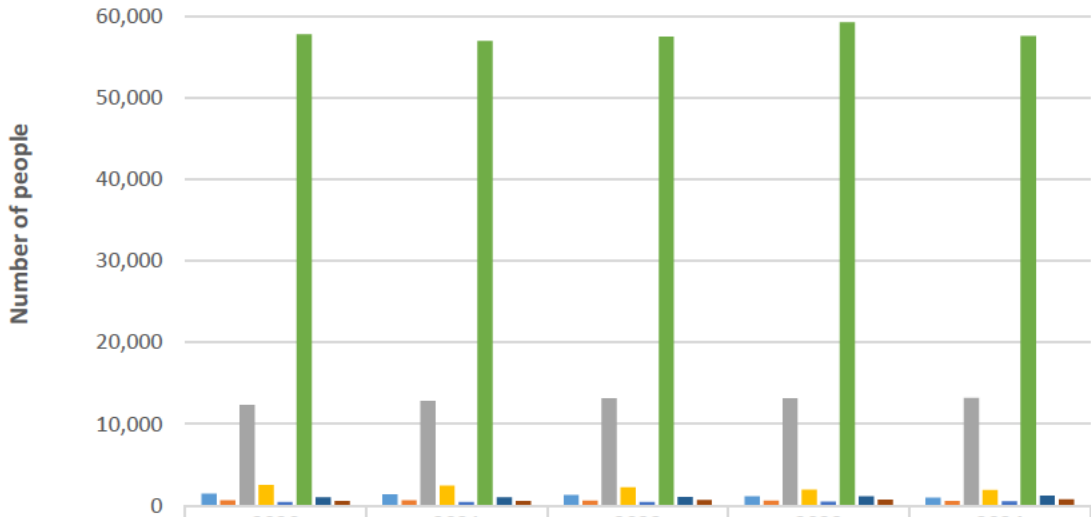
Figure 1: Usage of first-generation antipsychotics in New Zealand from 2020 to 2024

(a) Number of initial dispensings[a]



	2020	2021	2022	2023	2024
Chlorpromazine	5,101	4,725	4,529	3,962	3,497
Flupenthixol decanoate	2,510	2,505	2,563	2,439	2,347
Haloperidol	31,133	31,887	32,019	31,957	32,727
Levomepromazine	7,728	7,505	6,833	6,246	6,669
Pericyazine	2,263	2,283	2,422	2,742	2,887
Prochlorperazine	78,011	77,309	78,125	80,200	79,148
Zuclopenthixol decanoate	3,572	3,451	3,582	3,744	4,151
Zuclopenthixol hydrochloride	1,818	2,124	2,506	2,749	2,963

(b) Number of people[b]



	2020	2021	2022	2023	2024
Chlorpromazine	1,470	1,370	1,313	1,125	988
Flupenthixol decanoate	663	661	637	628	601
Haloperidol	12,348	12,850	13,172	13,142	13,208
Levomepromazine	2,548	2,431	2,256	1,948	1,912
Pericyazine	426	418	441	475	517
Prochlorperazine	57,791	56,960	57,481	59,251	57,576
Zuclopenthixol decanoate	1,009	1,038	1,047	1,128	1,203
Zuclopenthixol hydrochloride	536	589	704	766	779

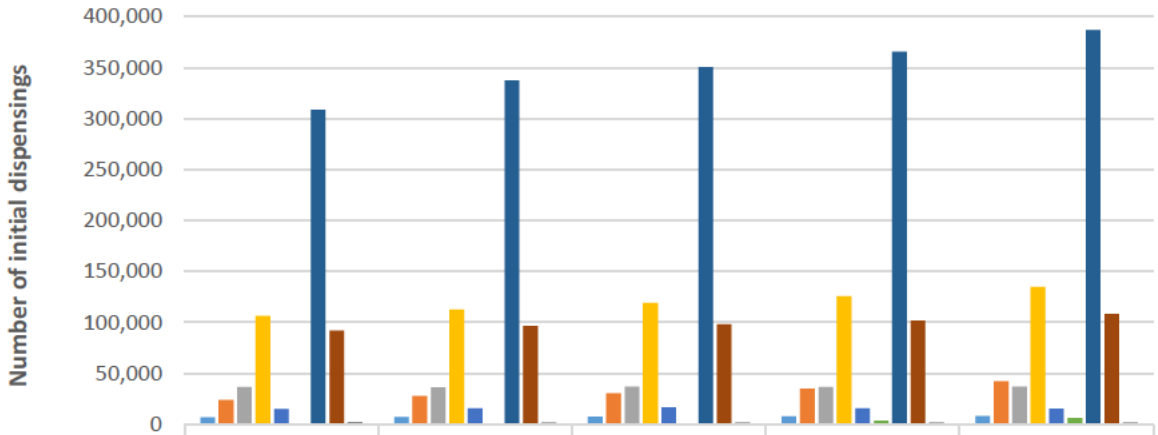
Comment:

Usage of prochlorperazine and haloperidol is higher than for other FGA. This may be due to their multiple short-term use for indications such as nausea and vomiting rather than as an antipsychotic for schizophrenia.

Injectable prochlorperazine is relatively low, with the minimum and maximum usage per year between 2020-2024 being 173 to 217 number of initial dispensings (or 140 to 159 number of people).

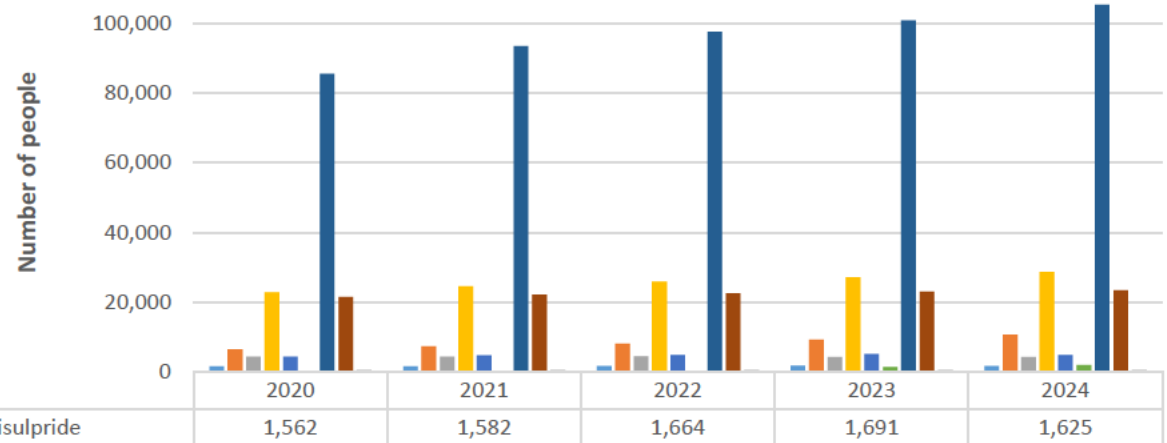
Figure 2: Usage of second-generation antipsychotics in New Zealand from 2020 to 2024

(a) Number of initial dispensings[a]



	2020	2021	2022	2023	2024
Amisulpride	7,120	7,360	7,907	8,175	8,406
Aripiprazole	24,159	27,843	30,672	35,176	42,336
Clozapine	36,690	36,435	37,055	36,636	36,962
Olanzapine	106,390	112,696	119,337	125,985	135,085
Paliperidone	15,274	16,057	16,975	15,981	15,646
Paliperidone palmitate			82	3,697	6,239
Quetiapine	308,658	337,455	350,339	365,590	387,063
Risperidone	92,095	96,813	98,334	102,001	108,514
Ziprasidone	2,145	1,984	1,942	1,939	1,797

(b) Number of people[b]



	2020	2021	2022	2023	2024
Amisulpride	1,562	1,582	1,664	1,691	1,625
Aripiprazole	6,399	7,346	8,065	9,193	10,668
Clozapine	4,335	4,328	4,352	4,221	4,204
Olanzapine	22,813	24,513	25,953	27,121	28,640
Paliperidone	4,310	4,629	4,795	5,103	4,755
Paliperidone palmitate			78	1,375	1,950
Quetiapine	85,607	93,553	97,728	100,871	105,412
Risperidone	21,501	22,188	22,551	23,006	23,478
Ziprasidone	435	449	451	441	414

Notes:

(a) Dispensings: Number of times the pharmaceutical product is dispensed from a pharmacy to the named person on all occasions including repeats (except for administrative dispensings such as owed balances) during the year.
(b) People: Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year (includes people who only received a repeat dispensing during the year.

Source: Te Whatu Ora Health New Zealand Pharmaceutical Data web tool: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (Accessed 6 November 2025).

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search was conducted, using the terms 'antipsychotic' and 'breast cancer'. A summary of recent publications (<10 years old) is provided below. They are presented in two sections (1) Systematic reviews and meta-analyses and (2) observational studies. Articles not publicly available are attached as annexes.

SYSTEMATIC REVIEWS AND META-ANALYSES

3.1.1 Bird et al 2025 – Antipsychotic-induced hyperprolactinemia: Toxicologic mechanism and the increased breast cancer risk [4]

Aim: In 2023 and 2024, 5 studies were published examining the association of antipsychotic use and breast cancer. However, given the close approximation of their publication, none of the more recent studies were able to consider all published data. The aim of this paper was to review the literature including these new studies and generate a summary statistic for a possible association between antipsychotic use and breast cancer.

Methods: The PRISMA checklist was used to conduct this review. A search of English-language articles published in peer-reviewed journals in PubMed from 1950 until 1 November 2024 was undertaken. Studies that contained data regarding the use of antipsychotics as well as quantitative data on breast cancer occurrence, the absolute number of patients, or risk ratios between the evaluated groups were included.

For each study included in this analysis, the reported Odds Ratio (OR), Hazard Ratio (HR), or Relative Risk (RR) of developing breast cancer following exposure to antipsychotic medicines, along with the 95% confidence intervals for these measures, were extracted. Pooled OR for the risk of breast cancer was estimated (1) from all studies reporting any antipsychotic use, (2) studies reporting antipsychotic use for 4 years or more, and (3) studies that reported use of prolactin-inducing antipsychotics.

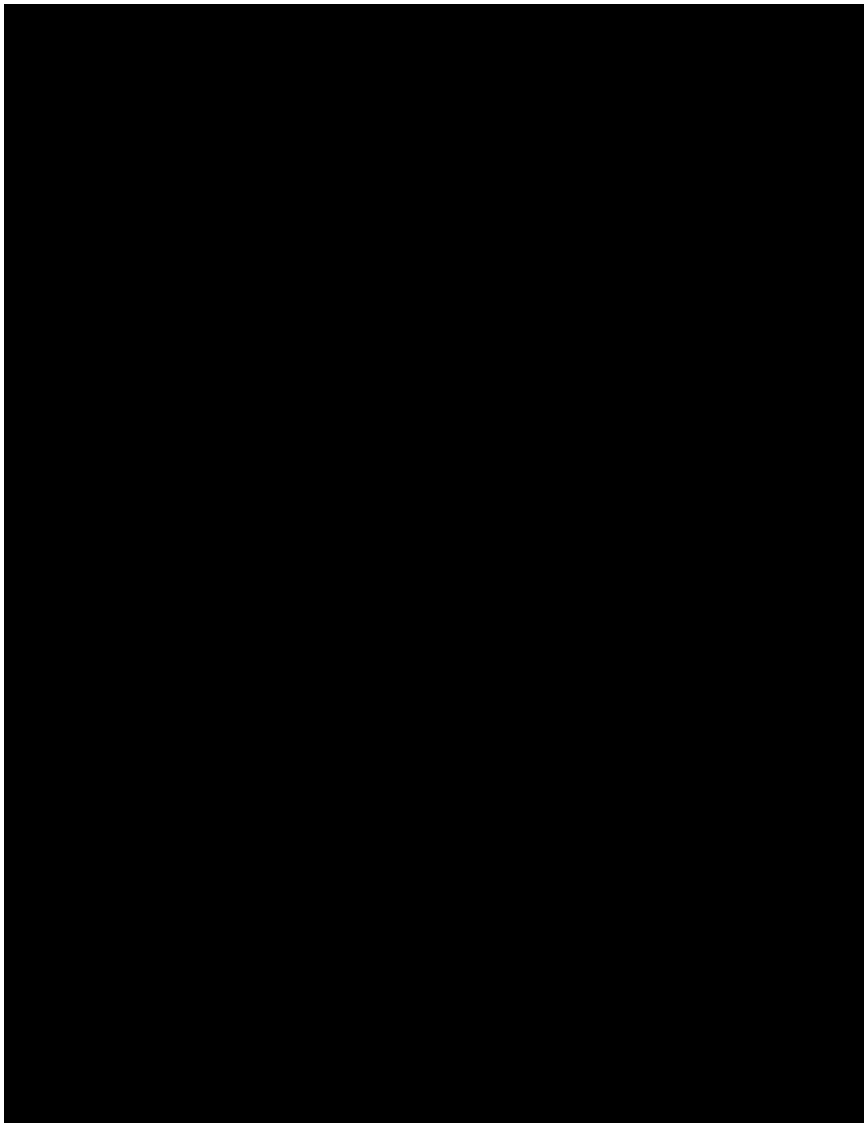
The Newcastle Ottawa scale (NOS) was used to assess quality of studies. Studies were then categorised based upon selection, comparability and results. Scores ≥ 8 were considered as high quality; score between 4 and 7 were considered as moderate quality; and a score ≤ 3 were considered as low quality.

Heterogeneity between studies was assessed using Cochran's Q test and the I^2 statistic. The studies were pooled using the inverse variance method, a random effects meta-analysis was performed, and the resulting risks and confidence intervals were reported.

Results: 15 studies met the inclusion criteria for the review. The year of publication ranged from 2000 to 2024. All but two studies were considered high quality.

Pooled OR for the overall risk of breast cancer in users of any antipsychotic at any dose and for any duration was OR: 1.19 (95 % CI 1.10–1.30) (Figure 3). There was statistically significant heterogeneity across all of the studies ($Q = 67.71$, $p < .0001$, $I^2 = 79\%$).

Figure 3: Risk of breast cancer with any antipsychotic use of any duration, from the 15 included studies.



Only a few studies reported use of antipsychotics for at least 4 years, giving a pooled OR of 1.26 (95% CI, 1.12 to 1.43) (Figure 4).

Figure 4: Risk of breast cancer in those studies that examined antipsychotic use for 4 or more years.

Only two studies examined the risk of high-prolactin inducing antipsychotics and the risk of breast cancer. There was a statistically significant association with these antipsychotics and breast cancer risk OR: 1.59 (95% CI 1.37 to 1.85).

Discussion and conclusions:

This review demonstrated an overall 19% increased risk of breast cancer in women taking antipsychotics. This increased risk was evident when combining all antipsychotics and when looking specifically at those medicines which increase prolactin to the greatest degree. While few studies examined or reported any sort of dose-response, a summary of those studies revealed a 26% increased risk of breast cancer with antipsychotic use for 4 or more years.

The authors acknowledge that observational studies are likely to carry unidentified and unmeasured confounders. Additionally, studies included in this review had heterogenous methodologies such as duration of exposure, follow-up and differences in doses used.

3.1.2 Gao et al 2022 – Antipsychotic exposure is an independent risk factor for breast cancer: a systematic review of epidemiological evidence [12]

Aim: To complete a systematic review and meta-analysis of the literature to determine the relationship between antipsychotics use and risk of breast cancer, and to explore the differences between first- and second-generation antipsychotics and the role of prolactin.

Methods: The authors followed PRISMA guidelines in conducting this review. Online databases (Embase, Scopus, PubMed, Cochrane) for observational studies investigating the effects of antipsychotics and breast cancer were searched. Studies were excluded if they had an imprecise conclusion, patients with primary hyperprolactinemia, metastatic cancers not related to psychotropics, patients with multiple immune mediated disease or non-population based statistical models. Meta-analysis was performed using R version 4.1.2. The odds ratio (OR) and its 95% confidence interval (CI) were used to evaluate the proportion of breast cancer in different groups.

Results: There were 12 studies included in the systemic review and 11 of these studies included in the meta-analysis (retrospective cohort study n=6, case-control study n=4, prospective cohort study n=1). The 11 studies included 1,499,001 participants.

Figure 5 shows the odds of breast cancer in participants exposed to antipsychotics vs those not exposed to antipsychotics, n= 1,401,265. Participants exposed to antipsychotics were at a higher risk of breast cancer than those not exposed to antipsychotics (OR=1.23; 95% CI, 1.04–1.47), with significant heterogeneity (I^2 =89%, p < 0.01).

Figure 5: Odds ratio of breast cancer in participants exposed to antipsychotics vs unexposed

Figure 6 shows participants exposed to typical antipsychotics vs those exposed to atypical antipsychotics, n= 97,736. There was no significant difference in breast cancer prevalence found in the two groups (OR= 1.23; 95% CI, 0.93–1.63), with significant heterogeneity (I^2= 85%, p < 0.01).

Figure 6: Odds ratio of breast cancer in participants exposed to typical vs atypical antipsychotics

Secondary outcomes comparing the effects of prolactin (PRL) increasing or sparing antipsychotics on breast cancer outcomes suggested that PRL-increasing and PRL-sparing antipsychotics pose a similar risk of breast cancer (OR, 1.13; 95% CI 0.97–1.31) (Figure 7), with very low heterogeneity. Two of the studies suggest that people exposed to antipsychotics at maximum doses are more likely to suffer from breast cancer than people exposed to the minimum dose.

Figure 7: Odds ratio of breast cancer in prolactin increasing vs sparing antipsychotics

Author's conclusions: Antipsychotic exposure is an independent risk factor for breast cancer. No significant difference in the risk of breast cancer between typical and atypical antipsychotics was noted. Those exposed to antipsychotics at higher doses are more likely to suffer from breast cancer.

Comments:
These results suggest that the underlying condition of schizophrenia/mental health disorders and disease severity (requiring higher doses of antipsychotics) may be an important risk factor for breast cancer. Given there is no statistically significant increased risk for breast cancer by antipsychotic type, there is no clear evidence to suggest hyperprolactinemia as a cause for an increased risk of breast cancer.

3.1.3 Leung et al 2022 – Association of antipsychotic use with breast cancer: a systematic review and meta-analysis of observational studies with over 2 million individuals [13]

Aim: To examine existing observational data in the literature and determine the association between breast cancer risk with antipsychotic use in women.

Methods: The authors followed the PRISMA checklist in conducting this review. Cohort and observational studies were searched on Embase, PubMed and Web of Science. Studies were included if they were in English, quantified the association between antipsychotic use (vs no use) with breast cancer in individuals 16 years and over.

The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS which has 9 as the highest quality). A pooled odds ratio (OR) and pooled hazard ratio (HR) using a random-effects model was generated to quantify the association between breast cancer and antipsychotic users vs non-users from cohort and case-control studies respectively.

The inverse variance weighting method was used to determine the relative importance between studies while the I^2 statistic was used to examine the heterogeneity of the estimates across studies.

Results: Nine observational studies, including five cohort and four case-control studies were included in this systematic review (n=2,031,380) and seven for the meta-analysis (n=1,557,013).

All studies received satisfactory quality assessment score of 7 to 9 stars. Of these, six studies reported a significant association with antipsychotic use and breast cancer, and a stronger association with longer duration of use, particularly for antipsychotics with prolactin-elevating properties.

The pooled HR extracted from the four cohort studies (Figure 8) and pooled OR from three case-control studies (Figure 9) were 1.39 [95% confidence interval (CI) 1.11 to 1.73] and 1.37 (95% CI 0.90 to 2.09) respectively, suggesting a moderate association of antipsychotic use (versus no use) with breast cancer, although the pooled OR in the case-control studies did not reach statistical significance. The I^2 were 75% and 93% respectively.

Figure 8: Forest plot showing HRs generated from retrieved individual cohort studies (*n* = 4) using Cox proportional hazard models and the pooled HR

Figure 9: Forest plot showing ORs generated from retrieved individual case-control studies (*n* = 3) using logistic regression and the pooled OR.

Discussion and author's conclusions:

There was a moderate positive association with antipsychotic use and breast cancer with a >30% elevated risk. From the literature, typical antipsychotics were reported to have a higher occurrence of elevated serum prolactin compared to atypical antipsychotics. However atypical antipsychotics have a higher risk of metabolic syndrome, including central obesity and hyperlipidaemia – both which potentially increase the risk of breast cancer. Therefore, the association between antipsychotic use and breast cancer may possibly be explained by more than one physiological mechanism.

3.1.4 Indrakusuma et al 2022 – The risk of antipsychotic drugs on breast cancer: a systematic review and meta-analysis [14]

Aim: To conduct a systematic review and meta-analysis on the risk of antipsychotic use and breast cancer incidence.

Methods: PubMed, Science Direct, Cochrane, Medline and other sources were used to gather articles using the keywords 'antipsychotics', 'breast cancer' and 'risk'. Studies were included if they reported an association between use of antipsychotics and breast cancer, had an OR reported and a non-randomised controlled study design (either case-control or cohort), and the article was published in English or Indonesian. NOS was used to assess the quality of the selected studies.

A pooled OR with a 95% CI was calculated using a random effect model. The heterogeneity level was assessed using the Q-test with a significance value at $p<0.10$ and an assessment of the I^2 statistic.

Results: Eleven studies met the inclusion criteria of which five were suitable for the meta-analysis. The study quality ranged from 5 points (moderate) to 8 points (high) with an average of 6.7 points, indicating that the overall quality was suitable for the meta-analysis.

The meta-analysis included 81,766 breast cancer patients and 1,150,316 controls. There was no significant association between use of antipsychotics and breast cancer incidence (OR: 1.06, 95% CI 0.94 to 1.19, p=0.36) (Figure 10). The relationship between different antipsychotics on breast cancer could not be analysed because of inadequate subgroup data.

Figure 10: Forest plot regarding the overall use of antipsychotic drugs against breast cancer.

There was evidence of heterogeneity ($p<0.10$) in the overall analysis. The I^2 statistical assessment also demonstrated heterogeneity (I^2 >75%). Therefore, this finding supports using a random effect model to determine the correlation and effect estimation on data synthesis. The risk of publication bias was evaluated using the Egger's test and funnel plot symmetry assessment. The Egger's test revealed significant publication bias in the results of quantitative analysis ($p<0.05$).

Discussion and author's conclusions: Antipsychotic use did not significantly increase breast cancer risk.

3.1.5 Karimi et al 2025 – Antipsychotic use increases the risk of breast cancer in Woman: Findings from systematic review and meta-analysis of observational studies [7]

Aim: To conduct a systematic review and meta-analysis on the association between antipsychotic use and the risk of breast cancer in females.

Methods: A literature search was conducted using Medline, PubMed, ISI Web of Science covering the period from inception to 1 May 2025. The search was specifically designed to identify observational studies reporting effect sizes of the association between antipsychotics use and the risk of breast cancer.

Studies were included if they were observational in design, examined antipsychotic use as the exposure, reported breast cancer risk in females as the outcome, and provided sufficient data to calculate effect estimates such as hazard ratios (HR), relative risks (RR), or odds ratios (OR) with 95% confidence intervals (CI). There were no restrictions applied to language or publication date to ensure a comprehensive approach.

NOS was used to evaluate the quality of the included studies.

Meta-analyses were performed to estimate the cumulative effect of antipsychotic and breast cancer compared to patients who had not received antipsychotic treatment, based on the random-effects model (inverse variance method). Subgroup analyses were conducted for antipsychotic generation (first vs. second). Furthermore, a sensitivity analysis was performed using both Leave-one-out and Fixed-effects models to assess the robustness of the synthesised results. Between-study heterogeneity was evaluated using Cochrane's Q statistic and I^2 statistic.

Results: 13 observational studies (seven cohort and six case-control studies) met the inclusion criteria and were included in the final meta-analysis. These studies were of good quality, scoring a NOS between 7 to 9.

The 13 studies provided 14 effect sizes as shown in Figure 11. Female antipsychotic users had a 23% higher risk of breast cancer compared to non-users (OR: 1.23, 95 % CI: [1.12 to 1.35], $p<0.001$). The analysis also revealed a substantial heterogeneity among studies (I^2 = 69.7 %, $p<0.001$).

Figure 11: Forest plot using random effect model detailing the overall odds ratio (OR) for the association between antipsychotic users compared with nonusers and risk of breast cancer in women.

Subgroup analysis by antipsychotic generation showed that first and second generation antipsychotics were associated with a 22% (OR: 1.22, 95% CI 1.03 to 1.45, p=0.023) and 8% (OR: 1.08, 95% CI 1.04 to 1.13, p<0.001) increased risk of breast cancer respectively.

The leave-one-out sensitivity analysis forest plot demonstrated the robustness of the overall effect estimate by sequentially omitting each study. The results indicate that no single study significantly alters the pooled estimate, as the effect sizes remain consistent across iterations.

Discussion and author's conclusion: A significant association was identified through pooled analysis of observational studies, with an increased risk of breast cancer among female users of antipsychotics vs non-users. Subgroup analyses further reveal that first-generation antipsychotics were associated with a more pronounced risk of breast cancer compared to second-generation antipsychotics. This difference may be scientifically justified by the higher propensity of first-generation antipsychotics to elevate serum prolactin levels due to their stronger dopamine D2 receptor antagonism.

Significant heterogeneity was noted among the included studies. This is due to differences in study design and population characteristics. There is also the potential for residual confounding. Finally, the findings are based on observational data and therefore causal relationships cannot be firmly established, highlighting the need for well-designed prospective studies to confirm these associations.

OBSERVATIONAL STUDIES

3.1.6 Yang et al 2025 – Breast cancer risk among women with schizophrenia and association with duration of antipsychotic use: population-based cohort study in South Korea [15]

Aim: To estimate the risk of breast cancer among people with schizophrenia treated with antipsychotics compared with people with other psychiatric disorders and people in the general population.

Method*:* Review of medical claims data of women aged 18-80-years in the Korean National Health Information Database from 2007 to 2018 with a diagnosis of schizophrenia. The control groups were defined as women with other psychiatric disorders, and women in the general population. Cases and controls were matched by index date and age in a 1:1:2 ratio. Cox proportional hazard models adjusted for insurance premiums and medical comorbidities were used to estimate the hazard of breast cancer. Among the people with schizophrenia, the landmark method was used to estimate the association between duration of antipsychotic medicine use and the incidence of breast cancer.

Results: In multivariable cox regression models, the hazard rate of breast cancer was 1.26 times higher in people with schizophrenia than in the general population (95% CI: 1.20–1.32) (Figure 12). In comparison with

the group of patients with other psychiatric disorders, the hazard ratio was 1.17 (95% CI: 1.11–1.28). Among women with schizophrenia, the hazard of breast cancer was greater among those who took antipsychotic medicines for 1 year or more compared with those who took antipsychotics for less than 6 months.

Figure 12: Hazard rates of breast cancer in patients with schizophrenia

Conclusion: Women with schizophrenia have an elevated risk of breast cancer and long-term use of antipsychotics is associated with an increased risk of breast cancer.

Comment:

Authors used a match cohort design to compare the incident of breast cancer outcomes in three groups of women. This was a large cohort study (224,612 patients in the schizophrenia and in the other psychiatric disorder groups matched with 449,224 women in the general population control group) and authors adjusted for comorbidities, medical utilisation, and social economic status. Further statistical and sensitivity analysis was conducted by age stratification, a 2-year-wash out period, and duration and type of antipsychotic use. They found the rate of breast cancer is higher in women with schizophrenia compared to the other comparator groups.

There are several limitations to the study specifically a lack of information on: antipsychotic used by patients with schizophrenia (names and doses), menopausal status and age of menopause, genetic predisposition factors, obesity, diet, substance use, and smoking status. These factors are known risk factors for breast cancer.

3.1.7 Kern et al 2024 – Association between prolactin increasing antipsychotic use and the risk of breast cancer: a retrospective observational cohort study in a US Medicaid population [16]

Aim*:* To assess the association between use of high prolactin increasing antipsychotics (HPD) and the incidence of breast cancer. Specifically, to estimate the relative risk of a new diagnosis of breast cancer among new users of HPDs compared with new users of non/low prolactin increasing drugs (NPDs).

Method*:* Retrospective longitudinal comparative cohort study using US insurance claims data and propensity scoring. Women over 18 years old who had been diagnosed with schizophrenia within 365 days prior to starting an antipsychotic were included. Participants were categorised into groups of HPD users, moderate prolactin increasing drugs (MPDs) users, and NPD users. Index date is the date when the prescription was first filled and exposure ended 30 days beyond supply of the last prescription, or if an outcome occurred, or record of a patient switching antipsychotic. The outcome of interest was newly diagnosed breast cancer. Propensity score modelling was used to capture patient variables (demographics, comorbid conditions, prior and concomitant medicine use, healthcare utilisation). The at-risk period started 180 days after the index date.

Results: There was no statistically significant association between the exposure to HPD use and risk of incident breast cancer in any of the analyses, and Hazard Ratios remained close to the null effect of 1.0, ranging from 0.96 (95% confidence interval 0.62-1.48) to 1.28 (0.40 – 4.07) across different analysis variants.

Conclusions: This retrospective cohort study adds to the knowledge of no association between prolactin raising antipsychotic use and breast cancer in women diagnosed with schizophrenia.

Comment:

The authors conducted a retrospective cohort design study to review the risk of breast cancer in new users of antipsychotics and compared HPD to MPD and LPD (control). Two different algorithms for breast cancer diagnosis were used and propensity scoring, and cox regression were used to minimise confounding and risk of biases.

There was no information on biomarkers, cancer grading/tumour staging, or serum prolactin levels. It is unclear whether a lack of an association is due to lack of significant increase in prolactin levels, or if prolactin levels were increased but this did not result in an increased risk of incidence of breast cancer. The mean follow-up period of this study was 4 years- this time period may be too short to detect an increased risk of breast cancer if truly present.

3.1.8 Rahman et al 2022 – Risk of breast cancer with prolactin elevating antipsychotic drugs: an observational study of US women (aged 18-64) [17]

Aim: To observe breast cancer risk associated with prolactin elevating antipsychotic drugs by level of prolactin elevating properties and compared to users of anticonvulsant and/or lithium.

Method: Retrospective observational cohort study using Medicaid claims data for women 18-64 years old exposed to antipsychotics, anticonvulsants +/- lithium and diagnosis of breast cancer. New users were those with at least 12 months of continuous medical and prescription drug insurance enrolment prior to the first claim for a study medicine, the fill date of which was used as the index date.

Exposure to antipsychotics were classed into three categories based on the medicine's propensity to elevate prolactin (1 being high, 2 being mid and 3 being low).

- Category 1: chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, paliperidone, perphenazine, pimozide, prochlorperazine, risperidone, thioridazine, trifluoperazine
- Category 2: iloperidone, lurasidone, olanzapine
- Category 3: aripiprazole, asenapine, brexpiprazole, ariprazine, clozapine, quetiapine, ziprasidone.

Anticonvulsants/lithium were used as comparator medicines as they are not known to elevate prolactin.

The outcome was invasive breast cancer. This was determined from ICD-9/ICD- 10 codes for invasive breast cancer on claim accompanied by surgical pathology, chemotherapy, or breast surgery billing codes, or at least 2 outpatient codes or one inpatient code for invasive breast cancer.

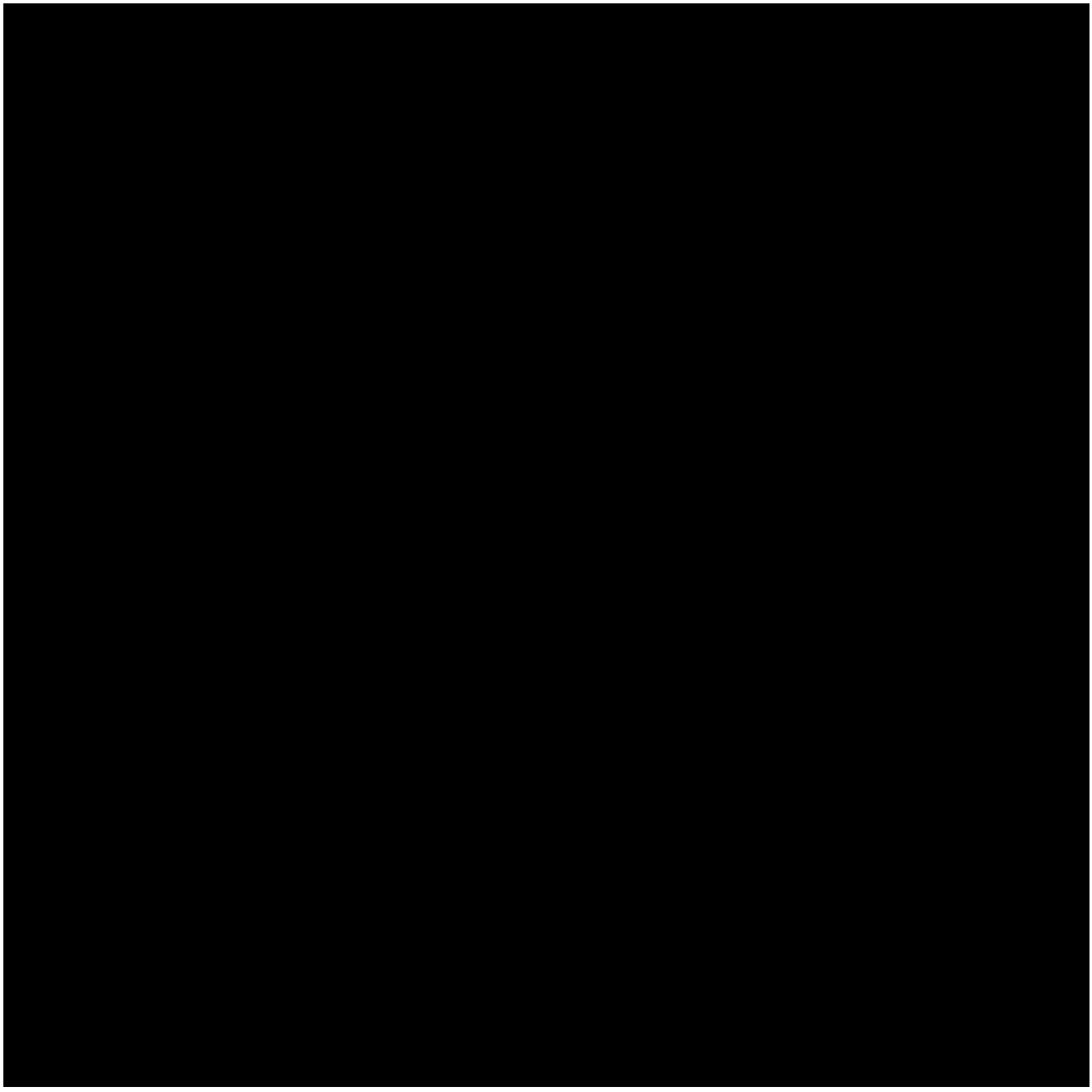
Covariates included in the multivariable adjusted models were mental health diagnoses (schizophrenia, bipolar disorder, depression), known risk factors for breast cancer (hormone replacement therapy (oestrogen/progesterone or oestrogen only), diabetes, obesity, alcohol abuse if documented, and benign breast disease), and age. To increase sensitivity, covariate definitions included prescriptions for various relevant medicines.

Patients were followed for six years after the initial prescription unless censored for disenrollment, death, or evidence of pre-existing breast cancer (eg, a prescription for tamoxifen).

The statistical analysis used the Cox proportional hazards method with adjustment for covariates. The primary metric of risk was the hazard ratio (HR) for an average daily dose during follow-up of 1 DDD of antipsychotic, relative to users of anticonvulsants and lithium.

Results: Out of 540,737 women included in the review,914 were newly diagnosed with breast cancer. Exposure to all antipsychotics was independently associated with a 35% increased risk of breast cancer (aHR 1.35 95% CI (1.14–1.61). Category 1 drugs (high prolactin) were associated with a 62% increased risk (aHR 1.62, 95%CI (1.30–2.03), category two drugs a 54% increased risk (aHR 1.54 95% CI (1.19–1.99), while category three drugs were not associated with breast cancer risk. The results were similar when adjusted for known risk factors. The significant associations of drug categories 1 and 2 remained after adjustment for known risk factors plus mental health conditions (Figure 13).

Figure 13: Hazard ratios for risk of breast cancer in patients on antipsychotics by dose



Conclusions: There was a higher risk between antipsychotic use in US women and breast cancer, with a higher association with antipsychotics that elevate prolactin compared to women taking anticonvulsants and/or lithium. The authors note that prospective investigation of antipsychotic related breast cancer risk, including studies of prolactin effects on breast tissue density (a strong correlate for breast cancer risk) are needed.

Comment:

Authors identified an increased risk of breast cancer in women taking prolactin increasing antipsychotics compared to women taking non-prolactin increasing medicines (anticonvulsants +/- lithium).

Note that the choice of comparator medicine may not be appropriate as these can be used for non-mental health related conditions (epilepsy) or other psychiatric conditions that may not be comparable with schizophrenia. This may contribute to confounding by indication. Other study limitations include a short duration of follow up (4 years) which may not capture the development of breast cancer relative to the increase in serum prolactin. Authors note that they could not control for residual confounding (parity, menopausal status, family history, obesity, race). Prescribing practices, mental health disease severity, and insurance coverage may also contribute to the choice of antipsychotic use and potential confounding/biases.

3.1.9 Hicks et al 2020 – Post-diagnostic antipsychotic use and cancer mortality: a population-based cohort study [18]

Aim*:* To investigate if antipsychotic use is associated with an increased risk of cancer-specific mortality among breast cancer patients.

Method*:* Cohort study of women newly diagnosed with primary breast cancer between January 1998 and December 2012 using linked cancer registries in the UK. Time-dependent Cox proportional hazards models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer-specific mortality comparing use of antipsychotics with non-use, overall, and by prolactin elevating activity. Further analyses were repeated and restricted to patients with a history of severe mental illness.

Results*:* In total 848 patients were prescribed an antipsychotic of which 162 died due to their breast cancer. Compared with non-use, antipsychotic use was associated with an increased risk of breast-cancer specific mortality (HR 2.25, 95%CI 1.90–2.67), but this did not follow a dose response relation. Restricting the cohort to patients with severe mental illness attenuated the association between antipsychotic use and breast cancer-specific mortality (HR 1.11, 95%CI 0.58–2.14).

Conclusions*:* The use of antipsychotics was associated with increased breast cancer-specific mortality, there was a lack of a dose response, and importantly null associations were observed in patients with severe mental illness, suggesting the observed association is likely a result of confounding by indication.

3.1.10 Pottegård et al 2018 – Use of antipsychotics and risk of breast cancer: a Danish nationwide case-control study [19]

Aim*:* To review the association between antipsychotic use and incidence of breast cancer in women.

Method*:* Case-control study using the Danish Cancer Registry to identify women with a first-time diagnosis of breast cancer between 2000-2015. For each case, there were 10 age-matched female population controls.

Exposure to different antipsychotics was standardised using olanzapine equivalent. For antipsychotics not assigned a conversion factor, one defined daily dose (DDD) per WHO dentitions, was considered equivalent to 10 mg olanzapine. For dose–response analyses, the following prespecified categories were used: 0–4999 mg, 5,000–9,999 mg, 10,000–19,999 mg, 20,000–49,999 mg and ≥50,000 mg. 'Long-term use' was defined as a cumulative exposure of 10,000 mg olanzapine.

The authors used conditional logistic regression to calculate odds ratios for breast cancer associated with antipsychotics. Each antipsychotic was stratified by first- and second-generation status and by ability to induce elevation of prolactin. The following confounders were adjusted for: medicines suspected to modify breast cancer risk, diabetes, COPD, and alcohol abuse.

Results*:* In total 4,951 cases and 47,643 controls had been exposed to an antipsychotic.

Long term use prolactin-inducing antipsychotic was associated with a slightly higher risk of breast cancer (adjusted OR 1.18, 95% CI 1.06 to 1.32) compared to non-users. A weak dose response pattern was seen with the OR increasing to 1.27, 95%CI 1.01 to 1.59 for olanzapine doses >50,000mg.

The associations were similar for long-term use of FGA (ORs 1.17, 95% CI 1.04 to 1.32) and SGA (OR 1.11, 95% CI 0.92 to 1.35), but also for long-term use of non-prolactin inducing antipsychotics (OR 1.17, 95% CI 0.88 to 1.55).

Conclusions*:* The study suggests a modest association between antipsychotic use, especially prolactin-inducing antipsychotics, and breast cancer risk. However, the absolute risk increase is small.

Comment:

This large study of over >50,000 breast cancer cases found weak evidence of an association between prolactin inducing antipsychotics and risk of breast cancer. Subgroup analyses via dose exposure, antipsychotic subtype did not find a statistically significant increase for breast cancer. Notable strengths of this paper were the large sample size and coverage of an entire nation, long duration of follow up (20 years), high validity data sources (Danish Prescription and Cancer registries). Not being able to control for confounders that affect the risk of breast cancer such as obesity, smoking and alcohol consumption were noted to be limitations.

3.1.11 Taipale et al 2021 – Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland [11]

Aim*:* To identify whether the use of prolactin-increasing antipsychotics in women with schizophrenia is associated with a cumulative dose-dependent risk of breast cancer.

Method*:* Nationwide Finnish nested case-control study using registries for hospital treatment, prescriptions, and cancer diagnosis. The cohort included women aged 16 years and over diagnosed with schizophrenia between 1972 to 2014 in Finland. Cases were defined as women with a first-time diagnosis of breast cancer (after their diagnosis of schizophrenia) and had at least 5 years of follow-up medicine use before their index date. Each case was matched with 5 controls without breast cancer. Matching was by age, time of first schizophrenia diagnosis, and not having a diagnosis of any cancer before the matching.

The main exposure was to antipsychotics. These were further categorised as prolactin-increasing and sparing. Prolactin-increasing and prolactin-sparing antipsychotic use was categorised as cumulative duration in terms of duration exposed: up to 1 year, 1–4 years, and 5 or more years.

Secondary exposure measures were cumulative duration of antipsychotic use. Cumulative DDD exposure levels were grouped as 500, 1000, 2000, and 5000.

The analyses were done with conditional logistic regression, by adjusting for comorbid conditions (number of children, diabetes, substance misuse) and concomitant medicines that could affect the risk of breast cancer. The reference was exposure was use for <1 years (this included non-users).

Results*:* 1,069 women were identified with breast cancer and matched with 5,339 controls. The mean age of cases and controls was 62 years.

Overall, there was an association between any antipsychotic use for ≥5 years and breast cancer (aOR: 1.74, 95% CI 1.38 to 2.21) compared to <1 year of use. Only ≥5 years of prolactin-increasing antipsychotic use showed a statistically significant association of breast cancer (aOR: 1.56, 95% CI 1.27 to 1.92) compared to <1 year of use. Prolactin-sparing antipsychotic use of any duration was not associated with a statistically significant association with breast cancer (Table 2).

Table 2: Association between duration of exposure to any antipsychotics, prolactin-increasing antipsychotics, and prolactin-sparing antipsychotics and risk of breast cancer with 1-year lag window for exposure

Exposure to prolactin-increasing antipsychotics of DDD ≥5000 was associated with an increased odds of breast cancer (aOR: 1.36, 95% CI 1.09 to 1.70) compared with exposure of up to up to 500 DDDs. For exposure to prolactin-sparing antipsychotics, there was no association between high and low DDD exposure and increased odds of breast cancer.

Discussion and conclusions*:* Long-term exposure to prolactin-increasing, but not to prolactin-sparing, antipsychotics was significantly associated with increased odds of breast cancer. This may be explained via hyperprolactinemia, although in this study, actual prolactin concentrations were not considered.

The limitations included not being able to adjust for important confounders such as BMI, smoking, family history of breast cancer, severity of illness and lifestyle factors. Controls were also schizophrenic patients who used little antipsychotics, but the reasons for their sparse use of antipsychotics were unclear and they may not have had comparable degrees of illness from cases.

3.1.12 Solmi et al 2024 – Antipsychotic Use and Risk of Breast Cancer in Women With Severe Mental Illness: Replication of a Nationwide Nested Case–Control Database Study [20]

Aim: To investigate the relationship between antipsychotic exposure and breast cancer by replicating the Finnish nested case-control from Taipale et al 2021 (see 3.1.11 above) using Swedish nationwide registers.

Methods: Swedish national registries were used to extract cases and controls. The cohort included women aged 16 years and over with at least one diagnosis of schizophrenia/schizoaffective/other non-affective psychotic disorder/bipolar disorder in Sweden between 2006 and 2021.

Cases were women aged 18 to 85 years of age with a diagnosis of schizophrenia/schizoaffective/other non-affective psychotic disorder/bipolar disorder and with first diagnosis of breast cancer between 2010 to 2021. Cases were matched with up to five controls of similar age, primary psychiatric diagnosis and disease duration.

The main exposure was antipsychotics categorised as prolactin sparing (clozapine, quetiapine, aripiprazole, brexpiprazole and cariprazine) or prolactin-increasing (all other) antipsychotics. Antipsychotic use was categorised according to cumulative duration (<1 year, 1 to <5 years, ≥5 years) and cumulative dose (<500, 500 to <1000, 1000 to <2000, ≥2000 cumulative sum of DDD).

Many covariates, including diabetes, other medicines increasing the risk of breast cancer, cardiovascular disease were adjusted in the statistical analysis.

Matched conditional logistic regression analyses were performed. Multivariable models were adjusted for the above covariates, and matching factors were controlled for by study design. The main analysis was the association between the cumulative duration of exposure to prolactin-increasing and prolactin-sparing antipsychotics and breast cancer, with exposure of <1 year as the reference. Sensitivity analyses were performed with different exposure modes (cumulative dispensed dose in DDD).

Results: Of 132,061 women with schizophrenia/schizoaffective disorder/other nonaffective psychotic disorder/bipolar disorder, there were 1,642 cases (1.24%) of incident breast cancer between 2010 and 2021 included in the study, matched with 8,173 controls.

All cases had ≥4.5 years of antipsychotic medicine use data prior to their index date. The mean age of breast cancer diagnosis was 63.2 years for cases and 63.3 years for controls. Most characteristics between cases and controls were similar.

There were significant increased odds of breast cancer when any antipsychotic was used from 1 to <5 years (aOR: 1.32, 95% CI 1.13 to 1.53) compared to <1 year of use. The odds were higher with ≥5 years use (aOR: 1.52, 95% CI 1.31 to 1.76) (Table 3). A similar association was found when exposed to ≥5 years of prolactin-increasing antipsychotics; aOR of 1.47 (95% CI, 1.26 to 1.71). No association was found between duration of exposure to prolactin-sparing antipsychotics and breast cancer.

Table 3: Association Between Duration of Use of Any or Prolactin-Increasing or Prolactin-Sparing Antipsychotics and Risk of Breast Cancer With 1-Year Lag Window for Exposure

Higher cumulative exposure (500 to ≥2000 DDD) to any antipsychotic was associated with an increased odds of breast cancer compared to minimal antipsychotic exposure of <500 DDD (Table 4). Similarly, higher exposure to prolactin-increasing antipsychotics (DDD >1000) was associated with an increased odds of breast cancer compared to lower cumulative exposure. There was also no association between any of the cumulative exposure categories of prolactin-sparing antipsychotics and breast cancer compared with minimal antipsychotic exposure (<500 DDD).

Table 4: Association Between Cumulative Dispensed Defined Daily Doses of Any or Prolactin-Increasing or prolactin-Sparing Antipsychotics and Risk of Breast Cancer With 1-Year Lag Window for Exposure

The results were consistent across sensitivity analyses (age groups, cancer types, psychiatric diagnoses).

Discussion and conclusions: This Swedish nested case-control study showed a 20% increased odds of breast cancer in women with schizophrenia, schizoaffective disorder, other nonaffective psychotic disorders, and bipolar disorder who used prolactin-increasing antipsychotics for 1–4 years, and 47% increased odds in those with cumulative use of 5 years or more. In contrast, long-term exposure to prolactin-sparing antipsychotics (ie, clozapine, quetiapine, third-generation antipsychotics, aripiprazole) was not associated with decreased or increased odds of breast cancer. These findings are consistent with the Finnish nested case–control study by Taipale et al 2021.

Limitations of this study include the case-control design which meant that causality cannot be assessed. The analysis could not account for potential unmeasured confounders such as physical activity level, BMI, alcohol consumption, smoking and family history of breast cancer which could have affected the association.

3.1.13 Li et al 2024 – Exposure to psychotropic drugs and breast cancer risk in patients with bipolar disorder and major depressive disorder: a nested case–control study [21]

Aim: To comprehensively assess the risk of breast cancer associated with the prescription of psychotropic medicines (antipsychotics, antidepressants, and mood stabilisers) among a large cohort of patients with major depressive disorder (MDD) and bipolar disorder (BD) through a nestled case-control study.

Methods: The study used two linked databases within the Taiwanese National Health Insurance Research Database. This database includes all medical records (mental and non-mental) of insured individuals with mental disorders, and the Catastrophic Illness database, which includes diagnoses of catastrophic illnesses (such as malignant cancers) and the diagnosis date.

The cohort consisted of women aged 20 years and over with a diagnosis of BD or MDD and no history of malignant cancer. The follow-up period was calculated from the enrolment date (a diagnosis of BD or MDD) to the endpoint date (diagnosis of breast cancer).

Cases were those who were subsequently diagnosed with breast cancer. Ten controls were matched for each case based on birthdate, diagnosis date, follow-up duration, medical and mental comorbidities, income and area of residence. A control did not have a diagnosis of any malignancies.

The cumulative defined daily dose (cDDD) was calculated for all first and second generation antipsychotics, mood stabilisers and antidepressants during the follow-up period.

Logistic regression analyses were performed with adjustments for demographic characteristics, medical and mental comorbidities, Charlson Comorbidity Index (CCI) scores, and all-cause clinical visits to calculate the odds ratio (OR) and 95% confidence interval (CI) of the association between cumulative psychotropic use (cDDD) categories: < 30, 30–179, 180–364, and ≥ 365) and subsequent breast cancer risk.

Results: 1,564 women with BD or MDD were included as cases and matched with 15,540 controls. Cases and controls did not significantly differ in terms of co-morbidities and demographic characteristics, however cases had a significantly higher CCI score and number of all-cause clinical visits.

The mean age was similar between the groups (50.42 years) as well as the follow up duration (around 4 years).

Only analysis involving antipsychotics is summarised below.

Long term use (cDDD ≥ 365) of second and first generation antipsychotics showed a decreased risk of breast cancer (OR: 0.80, 95% CI 0.61 to 1.05 and 0.72, 95% CI 0.52 to 1.01 respectively), although these were not statistically significant. Short-term use (cDDD 30-179) of second generation antipsychotics overall, olanzapine, risperidone and chlorpromazine were significantly associated with a decreased risk of breast cancer compared to their respective use with a cDDD <30. The only antipsychotic that showed a statistically increased risk of breast cancer was for ziprasidone with a cDDD of 180-364 compared to the group with a cDDD <30 (OR: 4.70, 95% CI, 1.47 to 15.07).

Discussion and conclusions: Use of antipsychotics in women for MDD or BD was associated with a decreased risk of breast cancer. This finding differs from previous literature that report an association between breast cancer incidence with the use of antipsychotics. While some studies have suggested that prolactin stimulates cellular proliferation, differentiation, and angiogenesis of breast cancer, other studies have not supported this hypothesis. There is also evidence suggesting that prolactin may have a protective effect and suppress breast cancer cell growth. Additionally, antipsychotics may improve the severity of the psychiatric illness thereby helping with early identification of breast abnormalities during the pre-cancer stage.

Comment:
The authors note that dose of antipsychotics for schizophrenia can be higher compared to BD or MDD. This may explain why there was no observed differences with use of antipsychotics and breast cancer in this study, if a dose-response relationship exists.
As with other observational studies, the authors acknowledge there is residual confounding factors that may still exist.

3.1.14 Joo et al 2022 – Risk of breast cancer in association with the use of second generation antipsychotics [22]

Aim: To investigate the risk of breast cancer with second-generation antipsychotics (SGA) and the period of time where subjects exposed to SGA had a significantly higher incidence of breast cancer compared to controls. Additionally, to determine whether there is a relationship between the cumulative antipsychotic dose used and the risk of breast cancer.

Methods: The Health Insurance Review Agency database in South Korea was used to source cases and controls. Cases were female patients aged 18 to 79 years, prescribed an SGA for more than 30 days within a year from the index date. Controls were female patients not prescribed SGA and were matched for age in a 1:2 ratio.

Exposure to SGA was categorised into three groups according to their propensity for inducing hyperprolactinemia.

- Group A (high risk): amisulpride, risperidone, paliperidone, and zotepine
- Group B (moderate risk): olanzapine and ziprasidone
- Group C (low risk): aripiprazole and quetiapine.

For both case and control groups, the follow-up time was from 30 days following the index date to the occurrence of breast cancer, death, or the end of the study period (31 December 2019), whichever occurred first.

Cox proportional hazards regression model was used for calculating hazard ratio (HR) and 95% confidence interval (CI) of the association between breast cancer and second-generation antipsychotics. Further analysis was done by age at the index date (18−44 years, 45−64 years, 65−79 years). Regarding the relationship between the risk of breast cancer, and the observational period and cumulative antipsychotic dose, person-years of all subjects whose observational period or cumulative antipsychotic dose met a certain criterion were calculated (ie, for the observational period, < 3, 3 to < 6, or ≥ 6 years, and for the cumulative antipsychotic dose, more or less than 10,000 mg of olanzapine equivalent dose).

Results: A total of 498,970 cases and 997,940 controls were included. The mean age for cases and control was 52.6 years and the average follow-up period was 68.2 months.

Cases had a significantly increased risk of breast cancer compared to the control group (HR: 1.08, 95% CI 1.04 to 1.13, p< 0.001). All antipsychotic groups showed a significantly increased risk of breast cancer compared to their matched controls (group A: HR= 1.65, 95% CI 1.49−1.84, p<0.001, group B: HR= 1.29, 95% CI 1.01−1.65, p=0.04, group C: HR =1.10, 95% CI 1.02−1.18, p=0.01) (Table 5).

Table 5: Risk of breast cancer in association with the use of second-generation antipsychotics[a]

Table 6 shows the risk of breast cancer according to age group, observation period and cumulative olanzapine equivalent dose. Cases aged 45-64 years at the index date had a significantly increased risk of breast cancer compared to controls (HR: 1.17, 95% CI 1.09 to 1.24, p<0.001). After six years, the increased risk of breast cancer from SGA became statistically significant. Finally, a higher risk of breast cancer was observed in subjects prescribed with ≥10,000 mg of total olanzapine equivalent dose compared to those with < 10,000 mg total olanzapine equivalent dose.

Table 6: Risk of breast cancer by the age group, observation period and cumulative olanzapine equivalent dose

Discussion and conclusion: There was a 8% increased risk of breast cancer in subjects exposed to SGA. All antipsychotic groups showed a significantly higher risk of breast cancer compared with matched control. The association was stronger for SGA that are known to have a higher risk of hyperprolactinemia, however this could be explained by uneven distribution of confounding variables for the risk of breast cancer among the three SGA groups.

The association with breast cancer with SGA was significant after six year observation period and higher cumulative olanzapine equivalent dose (≥10,000 mg).

The study did not consider whether subjects were exposed to SGA few years before the index date. Only a period of one year was used to exclude the effect of previous SGA use. Additionally, there were confounding variables that were not adjusted for such as smoking, alcohol use, family history of breast cancer and diabetes. Finally, it is possible that the association between longer use of SGA and breast cancer may be confounded by indication as patients on long-term SGA reflect chronicity of schizophrenia.

3.1.15 Chu et al 2023 – Breast cancer risks following antipsychotic use in women with bipolar versus schizophrenia: A territory-wide nested case-control study spanning two decades [23]

Aim: A nested case-control study to examine the association between antipsychotics and breast cancer in women with bipolar disorder compared to schizophrenia.

Methods: Using a longitudinal electronic health record system in Hong Kong, women aged 18 years and over that was first diagnosed with schizophrenia or bipolar disorder between 1 January 1999 to 31 December 2018 without a history of breast cancer were included. The underlying cohort was identified upon schizophrenia or bipolar disorder diagnosis and followed up until the first breast cancer diagnosis, all-cause mortality, or the end of data availability, whichever was the earliest.

Subjects diagnosed with breast cancer were identified as cases. Up to ten controls without a diagnosis of breast cancer were matched by birth year and healthcare setting (inpatient vs outpatient).

Exposure was defined as the use of antipsychotics (FGA or SGA) for more than one year, based on dispensing records**.**

Multivariable conditional logistic regression was used to examine the association of antipsychotics with breast cancer. The adjusted OR of breast cancer was estimated with the use of FGA and SGA compared to non-users (non-users were defined as no use or less than 1 year of antipsychotic use). The results were stratified by use for schizophrenia vs bipolar disorder.

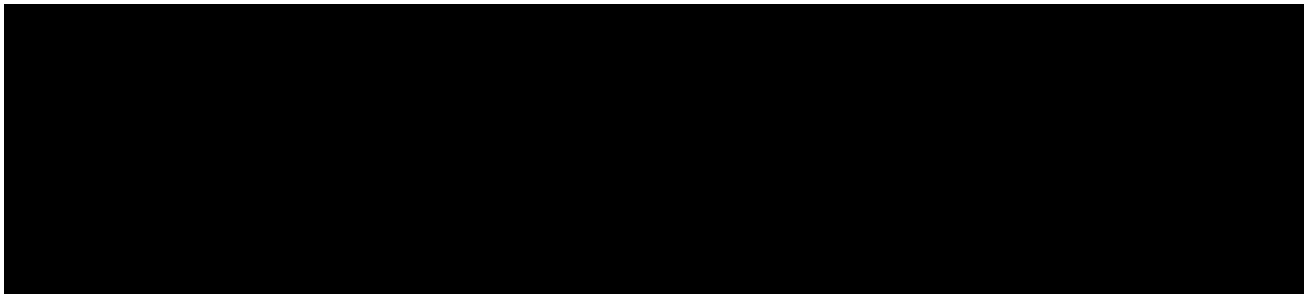
The authors adjusted for the following covariates: time since first psychiatric diagnosis, cardiovascular disease, hypertension, obesity, diabetes, asthma, alcohol abuse, and prior use of various medicines.

To examine a potential dose-response relationship, the use of FGAs and SGAs were further categorised into non-use, one to four years of use, and five or more years of use to observe the change in the strength of associations with the varying duration of use.

Results: During the observation period, 672 subjects were diagnosed with breast cancer (563 with schizophrenia and 109 with bipolar disorder). The cases were matched with 6,450 controls (5,519 with schizophrenia and 931 with bipolar disorder).

Among subjects with schizophrenia and bipolar disorder, there was a statistically significant association between FGA use and breast cancer compared to non-users (Table 7). There was an approximate 1.5-fold increase in the odds of breast cancer associated with SGA in women with bipolar disorder (aOR 2.49, 95% CI 1.29 - 4.79) compared with non-use, while no significant association of SGA with breast cancer was observed in women with schizophrenia.

Table 7: Adjusted odds ratios (aOR) of breast cancer by antipsychotic use status and psychiatric disorder (schizophrenia versus bipolar disorder)



In women with schizophrenia, 5 years or longer of FGA use was associated with increased odds of breast cancer versus non-use group (aOR: 1.74, 95% CI 1.33 to 2.28).

In women with bipolar disorder, 1-4 years of both FGA (aOR: 1.90, 95% CI 1.16 to 3.10) and SGA (aOR: 2.27, 95% CI 1.15 to 4.49) use were associated with an increased odds of breast cancer. The aOR for SGA use over 5 years or more did not reach statistical significance ($p > 0.05$).

In a combined model including women with the two conditions, the interaction between various durations of antipsychotic use (either FGA or SGA) and bipolar disorder was non-significant ($p > 0.05$), suggesting no evidence of a different association between different durations of antipsychotic use and breast cancer in women with bipolar disorder compared with women with schizophrenia.

Discussion and conclusions: Use of FGAs was associated with an increased odds of breast cancer among women with schizophrenia and bipolar disorder compared to non-users. The use of SGAs was found to be associated with an approximate 1.5-fold increase in the odds of breast cancer only in women with bipolar disorder.

It is possible that metabolic abnormalities following SGAs use are more pronounced in women with bipolar disorder than in women with schizophrenia so that SGA use was only associated with breast cancer in women with bipolar disorder. The authors note a previous matched comparison between bipolar disorder and schizophrenia, where people with bipolar disorders had significantly higher cholesterol levels and hip/waist ratio. These metabolic effects may also be a risk factor for breast cancer. Additionally, the difference may be from the specific agents used for the two different conditions. The study did not account for potential differences in doses of antipsychotics that are used in the two indications which could also explain for the observed differences.

[redacted]

3.3 Spontaneous case reports

3.3.1 New Zealand

Up to 6 September 2025, there have been 13 case reports of breast cancer where an antipsychotic was reported as a suspect medicine (Table 8). All cases were in women. The suspected antipsychotics were clozapine, risperidone and amisulpride.

Table 8: Cases of breast cancer where an antipsychotic was reported as a suspect medicine, 6 September 2025

Case No. (year reported)	Age in years, sex	Suspect medicine(s)	Reaction terms [redacted]
86511 (2009)	50, F	Risperidone [redacted]	Somnolence [redacted] Postural hypotension [redacted] Galactorrhoea [redacted] Breast neoplasm malignant female [redacted]
103192 (2012)	53, F	Risperidone [redacted]	Hyperprolactinemia [redacted] Lactation nonpuerperal [redacted] Breast neoplasm malignant female [redacted]

103197 (2012)	48, F	Risperidone [redacted]	Hyperprolactinemia [redacted] Breast neoplasm malignant female [redacted]
104649 (2012)	76, F	Clozapine [redacted]	Breast neoplasm malignant female [redacted] Myoclonus [redacted] Fall [redacted] Bipolar affective disorder [redacted] Neutrophilia [redacted]
105350 (2013)	63, F	Clozapine [redacted]	Breast neoplasm malignant female [redacted]
106585 (2013)	UNK, F	Clozapine [redacted]	Breast neoplasm malignant female [redacted]
110621 (2014)	43, F	Amisulpride Risperidone Spironolactone [redacted] Estradiol [redacted] Cyproterone [redacted]	Breast cancer Metastasis Medication error
114416 (2014)	UNK, F	Risperidone [redacted]	Breast neoplasm malignant female [redacted] Muscle wasting [redacted]
116236 (2015)	46, F	Clozapine [redacted]	Breast cancer neoplasm malignant female [redacted] Glycosylated haemoglobin increased [redacted] Dyslipidaemia [redacted] Weight increase [redacted]
116651 (2015)	39, F	Clozapine [redacted] Antineoplastic agent NOS	Progression of disease [redacted] Leucopoenia [redacted] Neutropenia [redacted] Haemoglobin decreased [redacted] Breast neoplasm malignant female [redacted]
116788 (2015)	45, F	Clozapine [redacted]	Breast neoplasm malignant female [redacted]
117558 (2015)	53, F	Clozapine [redacted]	Breast neoplasm malignant female [redacted] Metastases NOS [redacted]
117669 (2015)	43, F	Clozapine [redacted]	Breast neoplasm malignant female [redacted] Metastases NOS [redacted]

Comments: [redacted] Some cases had a very short time to onset from starting the antipsychotic and the development of breast cancer. Most cases involved clozapine. In this case it is likely because of the blood monitoring system and pharmaceutical companies reporting these events.

[redacted]

3.4 Prescribing information

The data sheets for prolactin-inducing antipsychotics are reviewed (Tables 10 and 11) for information on hyperprolactinemia and the risk of breast cancer (highlighted in yellow) and comparedto information in Australian, United Kingdon and United States product information.

Table 10: Review of the data sheets of first-generation antipsychotics

Chlorpromazine			
NZ Largactil	**AU Largactil**	**UK Chloractil**	**US Chlorpromazine**
Section 4.8: Hyperprolactinemia which may result in galactorrhoea, erectile dysfunction with an ADR frequency 'not known'		**Section 4.8** Hyperprolactinemia as a common ADR.	**Precaution:** Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately 1/3 of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.
Haloperidol			
NZ Serenace	**AU Serenace**	**UK Haloperidol**	**US Haldol**
Section 4.3 Contraindicated in patients with prolactin dependent tumours. **Section 4.4** *Hyperprolactinaemia*	**Section 4.3** Contraindicated in patients with prolactin dependent tumours. **Carcinogenicity and mutagenicity** In female mice, there was a statistically significant increase in mammary gland	Similar to NZ, with the additional information in section 5.3 Preclinical safety data: In a carcinogenicity study of haloperidol, dose-dependent increases in pituitary gland adenomas and mammary gland carcinomas were seen in female mice. These tumours may be caused by prolonged dopamine D2	**Carcinogenesis** In female mice there was a statistically significant increase in mammary gland neoplasia and total tumor incidence at doses approximately 0.3 and 1.2 times the MRHD based on mg/m ^{2} body surface area and there was a statistically significant increase in pituitary gland neoplasia at approximately 1.2 times the MRHD In male mice, no

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea. **Carcinogenicity and mutagenicity** In female mice, there was a statistically significant increase in mammary gland neoplasia and total tumour incidence following oral administration of haloperidol at doses of 1.25 and 5mg/kg/day (less than, and about twice, the maximum recommended human dose based on body surface area). Haloperidol increases prolactin levels, which may affect human breast cancers, one-third of which are prolactin dependent in vitro. Although clinical studies have not shown a clear association between chronic administration of antipsychotic agents (including haloperidol) and an increase in the incidence of breast cancers, it may be a factor of importance when prescribing haloperidol for patients in which breast cancer was previously detected. **Section 4.8:** Hyperprolactinemia	neoplasia and total tumour incidence following oral administration of haloperidol at doses of 1.25 and 5mg/kg/day (less than, and about twice, the maximum recommended human dose based on body surface area). Haloperidol increases prolactin levels, which may affect human breast cancers, one-third of which are prolactin dependent in vitro. Although clinical studies have not shown a clear association between chronic administration of antipsychotic agents (including haloperidol) and an increase in the incidence of breast cancers, it may be a factor of importance when prescribing haloperidol for patients in which breast cancer was previously detected. **Section 4.8:** Hyperprolactinemia	antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown	statistically significant differences in incidences of total tumors or specific tumor types were noted. Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer. **Adverse reactions** Hyperprolactinemia, agalactorrhea, breast discomfort
Pericyazine			
NZ Neulactil	**AU** Neulactil	**UK** Pericyazine	No product information in US
Section 4.8 Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea, erectile dysfunction and frigidity.			
Prochlorperazine			

NZ Stemetil	AU Stemetil	UK Stemetil	US Prochlorperazine
Section 4.8 Less common: Endocrine disturbances including elevated prolactin levels,... galactorrhoea, gynaecomastia, amenorrhoea, erectile dysfunction.		**Section 4.8** Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea and impotence	**Precautions** Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.
Zuclopenthixol			
NZ Clopixol	**AU Clopixol**	**UK Clopixol**	No product information in US.
Section 4.4 An increase in the incidence of mammary adenocarcinomas is a common finding for D2 antagonists which increase prolactin secretion when administered to rats... The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. **Section 4.6** In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, erectile dysfunction and ejaculation failure have been reported. If clinical significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered. The effects are reversible on discontinuation. **Section 4.8** Hyperprolactinemia, gynaecomastia, galactorrhoea, as rare ADRs.		**Section 4.6** In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, erectile dysfunction and ejaculation failure have been reported. If clinical significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered. The effects are reversible on discontinuation. **Section 4.8** Hyperprolactinemia, gynaecomastia, galactorrhoea, as ADRs.	

Flupentixol			
NZ Fluanxol	**AU** Fluanxol	**UK** Depixol	No product information in US.
Section 4.6 In humans, adverse events such as hyperprolactinaemia, galactorrhoea, amenorrhoea, libido decreased, female orgasmic disorder, vulvovaginal dryness, erectile dysfunction and ejaculation failure have been reported (see Section 4.8 Undesirable effects). These events may have a negative impact on female and/or male sexual function and fertility. If clinical significant hyperprolactinaemia, galactorrhoea, amenorrhoea or sexual dysfunctions occur, a dose reduction (if possible) or discontinuation should be considered. The effects are reversible on discontinuation. **Section 4.8** Elevated serum prolactin levels may cause hormonal effects in some patients e.g. menstrual disturbance, galactorrhoea in men and women.			
Levomepromazine			
NZ Nozinan	No product information in AU.	**UK** Levomepromazine	No product information in US.
Section 4.6 In humans, levomepromazine interacts with dopamine receptors, which may cause hyperprolactinaemia. This can be associated with impaired fertility in women. Some data suggests that levomepromazine treatment is associated with impaired fertility in men. **Section 4.8** Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhea, erectile dysfunction – with an ADR frequency 'not known'.		**Section 4.6** In humans because of the interaction with dopamine receptors, levomepromazine may cause hyperprolactinaemia which can be associated with impaired fertility in women. Some data suggest that levomepromazine treatment is associated with impaired fertility in men. **Section 4.8** Hyperprolactinaemia (including galactorrhoea, gynaecomastia, amenorrhoea, impotence)	

Table 11: Review of the data sheets of second-generation antipsychotics known to increase prolactin levels

Risperidone (oral)			
NZ Risperdal	**AU** Risperdal	**UK** Risperidone	**US** Risperdal
Section 4.8	**Section 4.8**	**Section 4.4**	**Warnings and precautions**

Blood prolactin increase, hyperprolactinemia, amenorrhoea, breast discharge, ejaculation disorder, erectile dysfunction, Gynaecomastia	Blood prolactin increase, hyperprolactinemia, amenorrhoea, breast discharge, ejaculation disorder, erectile dysfunction, Gynaecomastia **Section 5.3 Carcinogenicity** Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times the maximum human dose of 10 mg/day (mice) or 0.6, 2.5 and 10 times the maximum human dose (rats) on a mg/m2 basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats. Antipsychotic medicines have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL elevated serum prolactin levels more than	**Hyperprolactinaemia** Hyperprolactinaemia is a common side-effect of treatment with Risperidone. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side-effects (e.g. gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhea). Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours. **Section 4.8** Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction. **Section 5.3 Preclinical safety** In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D_2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.	**Hyperprolactinemia** As with other drugs that antagonize dopamine D 2receptors, RISPERDAL elevates prolactin levels and the elevation persists during chronic administration. RISPERDAL is associated with higher levels of prolactin elevation than other antipsychotic agents. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer. **Adverse reactions** Hyperprolactinemia **Non-clinical toxicology** Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to approximately 0.2, 0.75, and 3 times (mice) and 0.4, 1.5, and 6 times (rats) the MRHD of 16 mg/day, based on mg/m ^{2}body surface area. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine

	haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these medicines and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, RISPERDAL should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia		pancreas adenomas, and mammary gland adenocarcinomas. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5–6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear.
Risperidone IM depot			
NZ Risperdal Consta	**AU** Risperdal Consta	**UK** Risperdal Consta	**US** Risperdal Consta
Section 4.8 Hyperprolactinemia, Breast discharge, Ejaculation disorder, Erectile dysfunction, Gynaecomastia, Sexual dysfunction, **Section 5.3 Carcinogenicity** Risperidone was administered in the diet to Swiss albino mice for 18 months and to Wistar rats for 25 months at doses equivalent to 0.3, 1.3 and 5 times the maximum human dose of 10 mg/day (mice) or 0.6, 2.5 and 10 times the maximum human dose (rats) on a mg/m2 basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary and endocrine pancreas neoplasms has been found in rodents after chronic administration of other dopamine receptor antagonists and is considered to be prolactin mediated.		**Section 4.4** **Hyperprolactinaemia** **Hyperprolactinaemia** Hyperprolactinaemia is a common side effect of treatment with RISPERDAL CONSTA. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side effects (e.g., gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, galactorrhoea). Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. RISPERDAL CONSTA should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.	**Warnings and precautions** **Hyperprolactinemia** As with other drugs that antagonize dopamine D 2receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland,

In a 2 year IM carcinogenicity study in rats, increased incidences of mammary gland adenocarcinoma, pancreatic islet-cell adenoma, adrenal gland phaeochromocytoma, pituitary gland adenoma and renal corticotubular adenoma were observed with systemic exposure (plasma AUC) to risperidone plus 9-hydroxyrisperidone) about twice that anticipated in humans at the maximal recommended clinical dose of RISPERDAL CONSTA. Increased incidences of mammary adenocarcinoma were also observed at doses for which the plasma AUC of risperidone plus 9-hydroxy risperidone was less than anticipated clinical exposure, a no-effect dose for this finding was not determined. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis. However, since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, RISPERDAL should be used cautiously in patients with previously detected breast cancer or in patients with pituitary tumours. Possible manifestations associated with elevated prolactin levels are amenorrhoea, galactorrhoea and menorrhagia	**Section 4.8** Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction. **Section 5.3** As expected for a potent dopamine D2 antagonist, in oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. In an intramuscular carcinogenicity study with RISPERDAL CONSTA in Wistar (Hannover) rats (doses of 5 and 40 mg/kg/2 weeks), increased incidences of endocrine pancreas, pituitary gland, and adrenal medullary tumours were observed at 40 mg/kg, while mammary gland tumours were present at 5 and 40 mg/kg. These tumours observed upon oral and intramuscular dosing can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Hypercalcemia, postulated to contribute to an increased incidence of adrenal medullary tumours in RISPERDAL CONSTA-treated rats, was observed in both dose groups. There is no evidence to suggest that hypercalcemia might cause phaeochromocytomas in humans.	mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer. **Adverse reactions** Hyperprolactinemia **Nonclinical toxicology** **Carcinogenicity - oral** Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to approximately 0.2, 0.75, and 3 times (mice) and 0.4, 1.5, and 6 times (rats) the MRHD of 16 mg/day, based on mg/m ^{2} body surface area. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas, endocrine pancreatic adenomas, and mammary gland adenocarcinomas. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5–6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear. **Carcinogenicity - IM** Risperidone was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with intramuscular (IM) injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m ^{2} basis. A control group received

			injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m ^{2} basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m ^{2} basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m ^{2} basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD. Dopamine D 2 receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with risperidone every 2 weeks IM. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.
Paliperidone			
NZ Invega Sustenna	**AU** Invega Sustenna	**UK** Trevicta	**US** Invega Sustenna
Section 4.4 **Hyperprolactinaemia** Like other drugs that antagonise dopamine D2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone,		**Section 4.4** **Use in patients with prolactin-dependent tumours** Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the	**Warnings and precautions** **Hyperprolactinemia** Like other drugs that antagonize dopamine D 2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with

a drug that is associated with higher levels of prolactin than other antipsychotic drugs. Hyperprolactinaemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinaemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see section 5.3 – Carcinogenicity). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive. **Section 4.8** Hyperprolactinaemia **Section 5.3** **Carcinogenicity** The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in a longterm study in rats. There was an increase in mammary gland adenocarcinomas in female rats at 10, 30, and 60 mg /kg/month, associated with respective exposures (plasma AUC) of 0.4, 1.6 and 3 times clinical exposure at the maximum recommended 150 mg dose of INVEGA SUSTENNA. A no-effect dose was not established. Male rats showed an increase in total mammary gland tumoursat 30 and 60 mg /kg/month, associated with respective exposures (plasma AUC) of 1 and 2 times clinical exposure. A carcinogenicity study in mice has not been conducted with paliperidone palmitate. Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats, equivalent to	administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with a pre-existing tumour that may be prolactin-dependent. **Section 4.8** ***Hyperprolactinaemia*** During the double-blind phase of the long-term randomised withdrawal study, elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) were noted in a higher percentage of males and females in the TREVICTA group than in the placebo group (9% vs. 3% and 5% vs. 1%, respectively). In the TREVICTA group, the mean change from double-blind baseline to double-blind end point was +2.90 ng/mL for males (vs. -10.26 ng/mL in the placebo group) and +7.48 ng/mL for females (vs. -32.93 ng/mL in the placebo group). One female (2.4%) in the TREVICTA group experienced an adverse reaction of amenorrhea, while no potentially prolactin related adverse reactions were noted among females in the placebo group. There were no potentially prolactin related adverse reactions among males in either group. **5.3 Preclinical safety data** Repeat-dose toxicity studies of intramuscularly injected paliperidone palmitate (the 1-monthly formulation) and orally administered paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. In animals treated with paliperidone palmitate an inflammatory reaction was seen at the intramuscular injection site. Occasionally abscess formation occurred. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas	risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats [see Nonclinical Toxicology (13.1)] . Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer. **Carcinogenesis** The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg/kg/month, which is 0.6, 2, and 4 times, respectively, the MRHD of 234 mg of INVEGA SUSTENNA based on mg/m ^{2} body surface area. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 2 and 4 times the MRHD based on mg/m ^{2}body surface area. A carcinogenicity study in mice has not been conducted with paliperidone palmitate. Carcinogenicity studies with risperidone, which is extensively converted to paliperidone in rats, mice, and

0.3, 1.3 and 5 times (mice) and 0.6, 2.5 and 10 times (rats) the maximum human dose on a mg/m2 basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D2-receptor antagonism and hyperprolactinaemia. The relevance of these tumor findings in rodents in terms of human risk is unknown		(mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg/kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 0.6 and 1.2 times the exposure level at the maximum recommended human 525 mg dose. These tumours can be related to prolonged dopamine D2-antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.	humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone based on mg/m ^{2} body surface area (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D 2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear.
Amisulpride			
NZ **Sulprix**	**AU Solian**	**UK Amisulpride**	No US product information available for oral product.
Section 4.3 Contraindicated with concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas or breast cancer. **Section 4.4** Amisulpride causes an increase in plasma prolactin levels which is reversible after discontinuation of the medicine. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, orgasmic dysfunction and impotence. **Breast cancer** Amisulpride may increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during amisulpride therapy. **Section 4.8** Amisulpride causes an increase in plasma prolactin levels, which is reversible after medicine discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction. **Section 5.3**		**Section 4.3** Contraindicated with concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas or breast cancer (see sections 4.4 and 4.8) **Section 4.4** **Breast cancer** Amisulpride causes an increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during amisulpride therapy. Amisulpride is contraindicated in patients with breast cancer (see sections 4.3 and 4.8). **Section 4.8** *Common:* amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea,	

Carcinogenicity In carcinogenicity studies, amisulpride was administered in the diet of mice and rats for up to two years. Treatment of mice was associated with increases in malignant mammary gland tumours and pituitary adenomas in females at all dose levels, but there was no tumourigenic response in males (doses were equivalent to 0.1, 0.2 and 0.5 times the maximum human dose of 1200 mg/day on a body surface area basis). Treatment of rats resulted in increased incidences of malignant mammary gland tumours in both sexes, malignant pituitary tumours and adrenal medullary phaeochromocytomas in males, and malignant pancreatic islet cell tumours in both sexes, at doses achieving lower systemic medication exposure (plasma AUC) than in humans at the maximal recommended dose. Increases in mammary gland, pituitary, adrenal and pancreatic endocrine tumours in rodents have been reported for other antipsychotic medicines, and are considered to result from increased prolactin secretion. The relevance of prolactin-mediated endocrine tumours in rodents for human risk is unknown. In clinical trials, amisulpride substantially elevated plasma prolactin concentrations, although to date neither clinical nor epidemiological studies have shown an association between chronic administration of neuroleptic medicines and mammary tumourigenesis. However, since tissue culture experiments indicate that about one-third of human breast cancers are prolactin-dependent in vitro, amisulpride should be used cautiously in patients with previously-detected breast cancer or in patients with pituitary tumours (see section 4.3).	amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.	

4 DISCUSSION AND CONCLUSIONS

There are concerns that antipsychotic-induced hyperprolactinemia can potentially increase the risk of breast cancer. These concerns were first identified in pre-clinical rodent studies. Earlier observational studies have reached inconsistent conclusions. More recent studies have provided some evidence of a potential association between antipsychotic use and breast cancer, [redacted]

Summary of recent literature

Systematic reviews and meta-analyses: Bird 2025 found a modest association between any antipsychotic use and breast cancer. There was also a statistically significant association between long-term use (4 years or greater) and use of antipsychotics that elevate prolactin, and breast cancer. Gao 2022 found an association between any antipsychotic use and breast cancer, however no significant difference was observed between FGA and SGA, suggesting hyperprolactinemia may not be the cause of an increased risk of breast cancer. Karimi 2025 found an association between antipsychotic use and breast cancer, with FGA having a stronger association than SGA. In contrast, Indrakusuma 2022 did not find an association between any antipsychotic use and breast cancer. Of note, these findings generally apply to women treated with antipsychotics – there were insufficient cases in men to be included in the meta-analyses. Finally, significant heterogeneity among studies was noted. It is interesting to note that the meta-analyses largely reviewed the same studies, but with varying results.

From individual observational studies, some studies found an association between antipsychotic use and breast cancer. The effect was more pronounced with longer duration of antipsychotic use and antipsychotics that elevate prolactin.

Overall, some studies observed a potential association between antipsychotic use and breast cancer. Case control and cohort studies were used to explore the relationship with the usual limitations such as recall and selection bias, use of inappropriate control groups that can vary in disease severity from cases, and the inability to control for unmeasured and unaccounted confounders that may influence the risk of breast cancer. Additionally, the observed association in some studies may be due to confounding by indication as schizophrenia/mental health disorders and disease severity (requiring higher doses of antipsychotics) are important risk factors for breast cancer.

Spontaneous case reports

Internationally and locally, clozapine has the highest number of case reports. This antipsychotic is is less likely to cause hyperprolactinemia compared to other antipsychotics, suggesting the reporting of breast cancer may be related to other factors.

Review of information in the NZ data sheets pertaining to hyperprolactinemia

All data sheets for FGA and SGA (that are prolactin-increasing) have information on hyperprolactinemia and consequences of this, such as galactorrhea, gynecomastia and decreased libido. The location of this information in the data sheet varies (section 4.4, 4.6 and/or 4.8).

Review of information in the NZ data sheet pertaining to the risk of breast cancer

Non-clinical studies: Most data sheets have information on specific animal studies for that antipsychotic or a general statement that an increased risk of mammary neoplasms have been found in rodents after chronic administration of antipsychotics in general. However, this is not present in the data sheets for chlorpromazine, periciazine, prochlorperazine, flupentixol and levomepromazine, and risperidone (oral).

Epidemiological studies: In data sheets that do outline findings in epidemiological studies, none specifically say there is a causal association:

- Haloperidol: "Clinical studies have not shown a clear association between chronic administration of antipsychotic agents (including haloperidol) and an increase in the incidence of breast cancers"
- Risperidone IM: "The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown. In controlled clinical trials, RISPERDAL elevated serum prolactin levels more than haloperidol, although to date neither clinical studies nor epidemiological studies have shown an association between chronic administration of these drugs and mammary tumorigenesis.
- Paliperidone: "Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive".
- Amisulpride: "The relevance of prolactin-mediated endocrine tumours in rodents for human risk is unknown. In clinical trials, amisulpride substantially elevated plasma prolactin concentrations, although to date neither clinical nor epidemiological studies have shown an association between chronic administration of neuroleptic medicines and mammary tumourigenesis".

Finally, some data sheets overseas advise to use antipsychotics with caution in patients with tumors that may be prolactin dependent.

5 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence for an association between the use of antipsychotics and the risk of breast cancer, and whether there is evidence of a link between breast cancer and
  - First generation vs second generation antipsychotics
  - Antipsychotics that increase prolactin vs those that do not
  - Any other factors (eg, dose, duration).
- Whether regulatory action is required (eg, updates to the data sheets)?
- Whether further communication is required, other than in MARC's remarks?

6 ANNEXES

Annex 1 – Rahman et al 2022

Annex 2 – Chu et al 2023

Annex 3 – Taipale et al 2021

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