Prolactin-Elevating Antipsychotics and the Risk of Endometrial Cancer

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ABSTRACT

Background: The use of antipsychotics may increase the risk of endometrial cancer through elevation of prolactin levels. We investigated the association between antipsychotics that are known to cause prolactin elevation and the risk of endometrial cancer.

Methods: In data from the United Kingdom Clinical Practice Research Datalink, all women who were newly treated with antipsychotics from 1990–2013 were identified and followed until 2014. Within this cohort of antipsychotic users, a nested case-control analysis was conducted. Main exposure was nonsporadic use of prolactin-elevating antipsychotics, and the active comparator was prolactin-sparing antipsychotics. Cases were women newly diagnosed with endometrial cancer (*ICD-10*) matched with up to 20 controls on age, calendar year of cohort entry, linkability to the Hospital Episode Statistics repository, and duration of follow-up. Conditional logistic regression models were used to determine the association of prolactin-elevating antipsychotics and endometrial cancer compared with prolactin-sparing antipsychotics. All analyses were adjusted for relevant potential confounders, including smoking, obesity, and diabetes mellitus.

Results: The cohort included 65,930 women. During 366,112 person-years of follow-up, there were 139 cases of endometrial cancer (incidence rate: 38/100,000 person-years), which were matched to 1,603 controls. Compared with the use of prolactin-sparing antipsychotics, the use of prolactin-elevating antipsychotics was not associated with an increased risk of endometrial cancer (adjusted odds ratio [aOR] = 1.00; 95% CI, 0.68–1.48). These findings remained similar with different durations of use (≤ 1 year, aOR = 1.07; 95% CI, 0.64–1.78, and > 1 year, aOR = 0.95; 95% CI, 0.58–1.54) and were robust to various sensitivity analyses.

Conclusions: Prolactin-elevating antipsychotics were not associated with an increased risk of endometrial cancer.

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The use of antipsychotics has increased over the past two decades, particularly for individuals without a severe mental illness, including youth and young adults.[1–4] Thus, the safety of these drugs represents a major public health concern. While much attention has been given to acute adverse cardiovascular and cerebrovascular events associated with antipsychotic use,[5] a possible long-term association with carcinogenesis has been primarily investigated in breast cancer.[6]

The implication of antipsychotic use and hormone-sensitive breast cancer has centered on the sustained elevations of prolactin levels induced by these medications.[7,8] Hyperprolactinemia, ie, prolactin levels exceeding 530 mIU/L (25 ng/mL) in nonpregnant, non-nursing women,[9] is a known adverse effect of all first-generation and some second-generation antipsychotics.[10] Prolactin excess may also be associated with an increased risk of another hormone-sensitive cancer, namely endometrial cancer.[11] This cancer is the sixth most common cancer in women worldwide, with 320,000 new cases in 2012.[12] Although no study has investigated prediagnostic prolactin levels and the risk of endometrial cancer, human endometrial tumors have been shown to express prolactin receptors and prolactin to induce the proliferation of endometrial cancer cell lines and their expression of oncogenes.[11] Further, patients with endometrial cancer have been demonstrated to have elevated prolactin levels,[13] and tumor prolactin expression may be associated with worse survival of women with endometrial cancer.[14]

Notwithstanding, observational evidence for an association between antipsychotic use and endometrial cancer comes from only 1 study,[15] reporting a 5-fold increased risk of endometrial cancer associated with the use of primarily first-generation antipsychotics. Given the scarcity of the data and the diverse effect of second-generation antipsychotics on prolactin, with risperidone and amisulpride leading to greater rates of hyperprolactinemia than first-generation antipsychotics,[16] we aimed to examine the association of prolactin elevation by antipsychotics and the risk of endometrial cancer. The use of prolactin-elevating antipsychotics was thus compared with the use of prolactin-sparing antipsychotics. The clinical equipoise of these 2 exposure groups[17] makes it probable that the main difference between them was the differential prolactin effect.

METHODS

Data Sources

This study was conducted using medical data extracted from the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The CPRD contains demographic information and electronic medical charts of more than 13 million individuals enrolled in more than 680 general practices. It can be accessed at https://www.cprd.com. Trained general practitioners record in the CPRD clinical diagnoses and prescriptions that have been shown to be of high validity.[18,19] General practices that contribute data to the CPRD undergo periodic

audits that deem them "up-to-standard." We also used the Hospital Episode Statistics (HES) repository, which is currently linkable to 55% of the CPRD general practices, as a supplementary data source. The HES contains hospital-related information, including primary and secondary diagnoses (coded using the *International Classification of Diseases, Tenth Revision* [*ICD-10*]), and related procedures.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 15_074) and the Research Ethics Board of the Jewish General Hospital, Montreal, Quebec, Canada.

Study Population

We assembled an inception cohort of all women with a first-ever prescription for an antipsychotic between January 1, 1990, and December 31, 2013. Cohort entry was defined as the date of the first antipsychotic prescription. All cohort members were required to be at least 18 years of age at cohort entry and have at least 1 year of medical information in an up-to-standard general practice prior to cohort entry. We excluded women with a history of prolactinoma, previous diagnosis of endometrial cancer, or hysterectomy identified in CPRD and HES at any time prior to cohort entry. Finally, to account for latency and minimize detection bias, we excluded women with less than 1 year of follow-up after cohort entry. Thus, the start of follow-up was set to the year after cohort entry.

Patients were followed from cohort entry until an incident diagnosis of endometrial cancer (defined in the next section) or were censored upon the date of hysterectomy, death from any cause, end of registration with the general practice, or end of study period (December 31, 2014), whichever occurred first.

Case Ascertainment and Control Selection

A nested case-control analysis was conducted within the cohort defined. Cases consisted of all patients newly diagnosed with endometrial cancer during the study period. Diagnoses were identified in the CPRD by Read codes (available by request from the authors) or in HES by *ICD-10* codes (D07.0, C54, and C55). The date of the endometrial cancer diagnosis was defined as the index date. To account for diagnostic delays, patients who had diagnoses of endometrial cancer up to 3 months following a hysterectomy were also considered as cases and were assigned the date of the hysterectomy. The concordance rate of these cancer diagnoses recorded in the CPRD with UK cancer registries has been shown to be in excess of 80%.[20] Up to 20 controls were randomly selected and matched to each case on age, year of cohort entry, HES linkability, and duration of follow-up. The index date of the case was assigned to the corresponding matched controls.

Exposure to Antipsychotics

Our exposure definition consisted of all antipsychotics, including first-generation and second-generation, that were available in the UK during the study period. We classified antipsychotics into 2 mutually exclusive groups based on their potential to increase prolactin levels, irrespective of their classification as first- or second-generation. Thus, the main exposure was prolactin-elevating antipsychotics, with the active comparator being prolactin-sparing antipsychotics.[10,16,21–23] All first-generation antipsychotics and 4 of the second-generation antipsychotics (amisulpride, paliperidone, risperidone, and zotepine) were classified as prolactin-elevating, while the remaining second-generation antipsychotics were classified as prolactin-sparing (Table 1).

Cases and matched controls were considered ever exposed to prolactin-elevating antipsychotics if they had received at least 3 prescriptions within a 12-month period between cohort entry and the year prior to index date (ie, after applying a 1-year lag period). This exposure definition was designed to capture regular, nonsporadic use of these drugs,[24] and the 1-year lag period was necessary for latency considerations and to minimize detection bias. In a secondary exposure definition, we calculated cumulative duration of use among patients deemed to be ever exposed to prolactin-elevating antipsychotics. This was achieved by summing all the prescription durations for prolactin-elevating antipsychotics from cohort entry until the index date. The reference category for all analyses consisted of all the patients who had at least 1 prescription for an antipsychotic before the index date and did not meet the definition for the use of prolactin-elevating antipsychotics.

Clinical Points

- Limited data suggest antipsychotics increase the risk of endometrial cancer through elevation of prolactin.
- No difference in endometrial cancer risk was seen between antipsychotics that raise prolactin and those that have mild or no effect on prolactin.

Table 1. Classification of the Antipsychotics Included in the Study by Their Prolactin-Elevating Potential

Prolactin-Elevating Antipsychotics	Prolactin-Sparing Antipsychotics
Benperidol	Aripiprazole
Chlorpromazine	Asenapine
Droperidol	Clozapine
Flupentixol	Olanzapine
Fluphenazine	Quetiapine
Fluspirilene	Sertindole
Haloperidol	
Levomepromazine	
Loxapine	
Oxypertine	
Pericyazine	
Perphenazine	
Pimozide	
Pipotiazine	
Promazine	
Sulpiride	
Thioridazine	
Trifluoperazine	
Trifluperidol	
Zuclopenthixol	
Amisulpride	
Paliperidone	
Risperidone	
Zotepine	

Potential Confounders

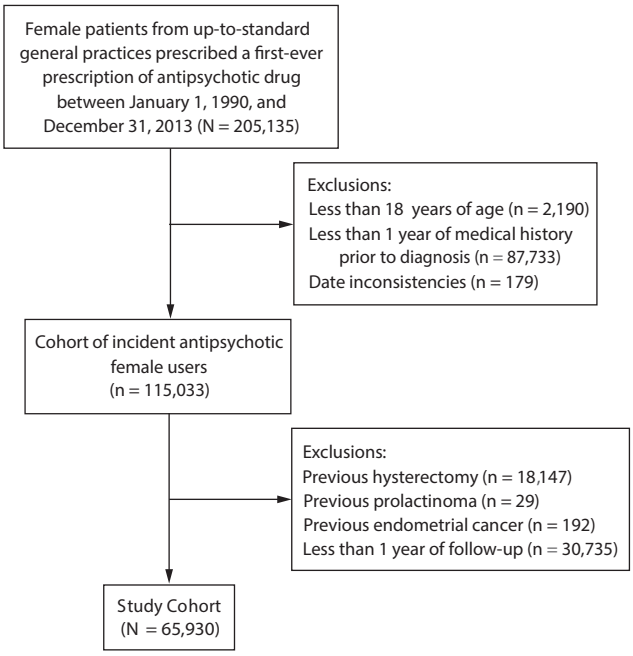
Controls were matched to cases on year of birth, year of cohort entry, HES linkability, and duration of follow-up. The models were also adjusted for last measured body mass index (BMI) and further baseline confounders (measured at any time before cohort entry): excessive alcohol use (alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), smoking status (ever, never, and unknown), hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidemia, and personal history of cancer (other than endometrial or nonmelanoma skin cancer). The models were also adjusted for the use of medications that have been associated with the incidence of endometrial cancer: ever use of statins, fibrates, antidiabetic drugs (metformin, sulfonylureas, insulin, and other agents), oral contraceptives, hormone replacement therapy, and intrauterine contraceptive devices. Finally, we adjusted for the use of antiparkinsonian drugs (levodopa, carbidopa, selegiline, rasagiline, entacapone, tolcapone, apomorphine, bromocriptine, pramipexole, ropinirole, and rotigotine), as they have been reported to suppress prolactin levels.[25] Missing data have been categorized as "unknown."

Statistical Analyses

Descriptive statistics were used to assess differences in baseline characteristics between cases and controls. Mental health conditions at baseline were identified using a previously published algorithm using primary care data from the UK.[26] Briefly, the patients were divided into 3 categories: severe mental illness (schizophrenia and related disorders, bipolar disorders, and nonorganic psychosis), nonsevere mental illness (depression, anxiety disorders, dementia, sleep disorders, attention-deficit/hyperactivity disorder, personality disorders, posttraumatic stress disorder, obsessive-compulsive disorder, autistic spectrum disorders, and other) and unknown. The crude incidence rate of endometrial cancer and 95% confidence intervals (CIs) based on the Poisson distribution were calculated by dividing the number of patients with endometrial cancer over the person-years at risk. Conditional logistic regression models were used to estimate odds ratios (ORs) of endometrial cancer, along with 95% CIs.

For the primary analysis, we assessed whether ever use of prolactin-elevating antipsychotics, when compared with ever use of prolactin-sparing antipsychotics, was associated with the incidence of endometrial cancer. We further conducted 2 secondary analyses. First, we assessed whether there was a duration-response relationship between the cumulative duration of the use of prolactin-elevating antipsychotics and the risk of endometrial cancer. This variable was categorized according to cumulative durations of ≤ 1 year and > 1 year. Second, we conducted an age-stratified analysis. Following reports that prolactin levels were more strongly associated with breast cancer risk in postmenopausal women,[27] we repeated the primary analysis stratified by 3 age groups of treatment initiation: < 51 years, 51 to 74 years, and ≥ 75 years.

Figure 1. Study Flow Diagram



The age groups were defined on the basis of a report that 61% of the women in the UK experience menopause at 50 years of age or later.[28] A *P* value for heterogeneity across the strata was calculated.

Sensitivity Analyses

Four sensitivity analyses were conducted to examine the robustness of our findings. Given uncertainties related to the length of the latency time window, the first analysis varied the duration of the lag period prior to index date, using alternative lags of 2 and 3 years. The second assessed the validity of our case definition by restricting endometrial cancer cases to those that also had records of hysterectomy, medroxyprogesterone treatment, or radiotherapy, as was done in a previous CPRD study.[29] In the third analysis we repeated the primary analysis after excluding patients with a history of cancer. The fourth analysis aimed to examine our primary exposure definition that required 3 prescriptions. We therefore repeated the primary analysis by considering the patients' exposure period as starting 1 year from their first prescription and continuing up until the event. Lastly, we explored possible bias caused by missing data by repeating the primary analysis with multiple imputations for unknown BMI and smoking status. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 65,930 women newly prescribed antipsychotic drugs met the study inclusion criteria (Figure 1). More than 75% of the patients had identified indications for the use of antipsychotics, and < 25% of those identified had severe mental illness. With the exception of dementia, which was

more prevalent with prolactin-elevating antipsychotics, there were no apparent differences in the indications among the groups (Supplementary eTable 1 at PSYCHIATRIST.COM). During 366,112 person-years of follow-up, 139 incident cases of endometrial cancer were identified, generating a crude incidence rate of 38.0 (95% CI, 32–45) per 100,000 person-years. These cases were matched with 1,603 controls. Table 2 shows the baseline characteristics of the cases and matched controls. Compared to controls, cases were more likely to have been obese, have hypertension, have dyslipidemia (and statin use), have a personal history of cancer, and to have ever used tamoxifen, all of which have been reported to be risk factors for endometrial cancer.

Table 3 presents the results of our primary analysis and secondary duration-response analysis. When compared with the use of prolactin-sparing antipsychotics, the use of prolactin-elevating antipsychotics was not associated with an increased risk of endometrial cancer (adjusted OR [aOR] = 1.00; 95% CI, 0.68–1.48). Similarly, we did not observe a duration-response relationship in terms of cumulative duration of use (< 1 year, aOR = 1.07; 95% CI, 0.64–1.78 and ≥ 1 year, aOR = 0.95; 95% CI, 0.58–1.54).

Table 4 shows the results of endometrial cancer risk stratified by the age at antipsychotic initiation. For presumed premenopausal women (aOR = 1.73; 95% CI, 0.76–3.92) and those aged ≥ 75 (aOR = 1.63; 95% CI, 0.73–3.68), the point estimates were numerically elevated but did not achieve statistical significance, whereas for the women who initiated antipsychotics between 51 and 74 years of age, the point estimate was below the null and nonsignificant (aOR = 0.65; 95% CI, 0.38–1.12). The *P* value for heterogeneity across these age groups was .14.

Overall, our findings were robust to sensitivity analyses (Figure 2). Lagging the exposure to antipsychotics by 2 or 3 years prior to index date led to similar findings (aOR = 1.12; 95% CI, 0.74–1.70 and aOR = 1.20; 95% CI, 0.76–1.88, respectively; Supplementary eTables 2 and 3). Our results also were not changed by using a stricter definition for endometrial cancer (aOR = 0.92, 95% CI, 0.58–1.47; Supplementary eTable 4) or excluding patients with previous cancer (aOR = 0.90, 95% CI, 0.58–1.39; Supplementary eTable 5). Lastly, changing the exposure definition to 1 prescription (aOR = 1.01, 95% CI, 0.50–2.04; Supplementary eTable 6) and using multiple imputation (aOR = 1.01, 95% CI, 0.69–1.49) led to similar point estimates.

Table 2. Characteristics of Cases and Matched Controls[a]

Characteristic	Cases (n = 139)	Controls (n = 1,603)
At index date		
Years of follow-up, mean (SD)[b]	5.8 (4.7)	5.8 (4.1)
At cohort entry		
Age, y, mean (SD)[b]	62.2 (14.3)	62.2 (14.9)
HES linkage ability[b]	100 (71.9)	1,244 (77.6)
Excessive alcohol use	S[c]	92 (5.7)
Smoking status		
Never	68 (48.9)	769 (48.0)
Ever	49 (35.3)	584 (36.4)
Unknown	22 (15.8)	250 (15.6)
Body mass index		
< 25 kg/m^2	30 (21.6)	608 (37.9)
25–30 kg/m^2	26 (18.7)	355 (22.1)
≥ 30 kg/m^2	51 (36.7)	257 (16.0)
Unknown	32 (23.0)	383 (23.9)
Hypertension	56 (40.3)	552 (34.4)
Diabetes mellitus	18 (13.0)	193 (12.0)
Polycystic ovarian syndrome	S[c]	12 (0.7)
Myocardial infarction	S[c]	37 (2.3)
Ischemic stroke	S[c]	60 (3.7)
Transient ischemic attack	S[c]	50 (3.1)
Dyslipidemia	12 (8.6)	103 (6.4)
Statins	13 (9.4)	120 (7.5)
Fibrates	S[c]	10 (0.6)
Antiparkinsonian drugs	7 (5.0)	58 (3.6)
Oral contraceptives	5 (3.6)	194 (12.1)
Hormonal replacement therapy	26 (18.7)	372 (23.2)
History of cancer[d]	23 (16.5)	145 (9.0)
Tamoxifen	7 (5.0)	28 (1.7)

[a]All values are n (%) unless otherwise stated.
[b]Matching variables (along with year of cohort entry).
[c]Numbers less than 5 are suppressed, as per the confidentiality policies of the Clinical Practice Research Datalink.
[d]Other than endometrial or nonmelanoma skin cancer.
Abbreviation: HES = Hospital Episode Statistics repository, S = suppressed.

DISCUSSION

To our knowledge, this is the first population-based study to investigate the association between the use of prolactin-elevating antipsychotics and the risk of endometrial cancer. Our findings indicate that, when compared with prolactin-sparing antipsychotics, the use of prolactin-elevating antipsychotics is not associated with an increased risk of endometrial cancer. Similarly, we did not observe a duration-response relationship, and the findings remained consistent in other secondary and sensitivity analyses.

Our findings differ from the previous clinic-based case-control study[15] on endometrial cancer and antipsychotics, which reported high increased risk of endometrial cancer (OR = 5.42; 95% CI, 1.12–26.44). However, confounding by indication is a concern, since those authors compared users of antipsychotics to never users. Thus, the effects of the underlying condition on the outcome cannot be disentangled from the exposure.[30] Indeed, schizophrenia itself has been previously associated with an increased risk of endometrial cancer.[31] Further, the previous analysis was based on 41 cases of endometrial cancer that were

Table 3. Prolactin-Elevating Antipsychotics and the Risk of Endometrial Cancer

Antipsychotic Use	Cases (n = 139)	Controls (n = 1,603)	Crude OR	Adjusted OR (95% CI)[a]
Use of prolactin-sparing antipsychotics, n (%)	88 (63.3)	1,036 (64.6)	1.00 [Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics, n (%)	51 (36.7)	567 (35.4)	1.01	1.00 (0.68–1.48)
Cumulative duration of use, n (%)				
≤ 1 year	24 (17.3)	253 (15.8)	1.05	1.07 (0.64–1.78)
> 1 year	27 (19.4)	314 (19.6)	0.98	0.95 (0.58–1.54)

[a]Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidemia, statins, fibrates, antiparkinsonian drugs, oral contraceptives, hormone replacement therapy, cancer (other than endometrial or nonmelanoma skin cancer), and tamoxifen at baseline.
Abbreviation: OR = odds ratio, Ref = reference value.

matched to 123 controls. Finally, in the previous study,[15] informed consent was obtained only from the exposed cases, raising concerns of recall bias.

Similarly, the results of our study do not support the proposed role for prolactin in endometrial tumorigenesis, ie, high expression of prolactin and prolactin receptor in endometrial tumor tissue and high circulating levels of prolactin in endometrial cancer patients, found in other studies.[11,13] However, prolactin may merely be a mediator of estrogen tumorigenesis and not an independent risk factor. Unopposed estrogen is central to the development of endometrial cancer, and uterine expression of prolactin and prolactin receptor was shown to be induced by progesterone and estrogen.[32,33] In addition, thioridazine, a prolactin-elevating antipsychotic, has been shown to induce apoptosis in endometrial cancer cells.[34] Taken together, prolactin is unlikely to play an important role in the pathogenesis of endometrial cancer.

Table 4. Prolactin-Elevating Antipsychotics and the Risk of Endometrial Cancer, Stratified by Age at Initiation

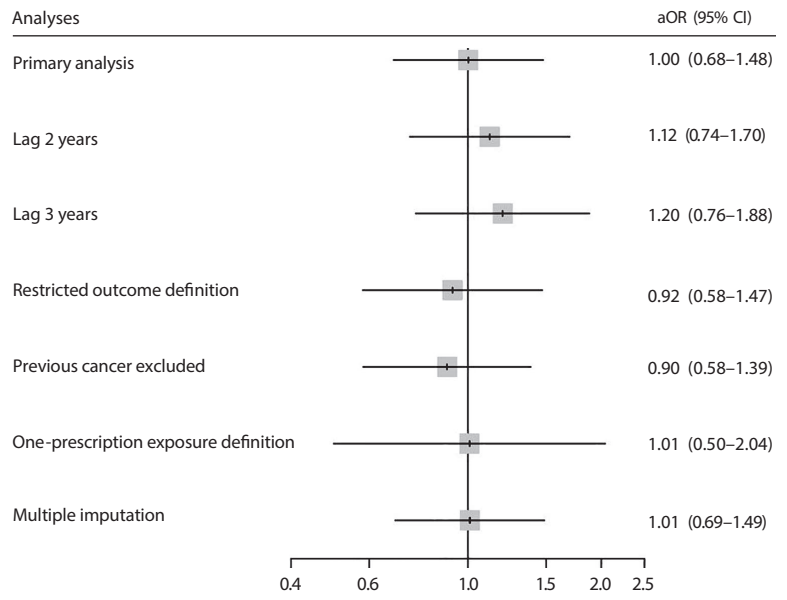
Patient Age Category	Crude OR	Adjusted OR (95% CI)[a]
<51		
Use of prolactin-sparing antipsychotics	1.00 [Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics	1.63	1.73 (0.76–3.92)
≥51 and ≤74		
Use of prolactin-sparing antipsychotics	1.00 [Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics	0.70	0.65 (0.38–1.12)
≥75		
Use of prolactin-sparing antipsychotics	1.00 [Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics	1.59	1.63 (0.73–3.68)
P value[b]		.14

[a]Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidemia, statins, fibrates, antiparkinsonian drugs, oral contraceptives, hormone replacement therapy, cancer (other than endometrial or nonmelanoma skin cancer), and tamoxifen at baseline.
[b]*P* value represents nonsignificant heterogeneity in the risk of endometrial cancer among age groups.
Abbreviation: OR = odds ratio, Ref = reference value.

Our study has several strengths. First, we assembled a large population-based cohort of patients newly treated with antipsychotics and followed for up to 24 years. Second, the use of an inception cohort of new users of antipsychotics in both the exposure and the reference groups balanced out the underlying mental illness. Third, our use of the CPRD allowed us to adjust the models for smoking, alcohol use, and body mass index, often missing in administrative databases. Lastly, the selection of controls with the same duration of use of antipsychotics enabled us to use a time-dependent exposure definition, whereby all person-time at risk was appropriately allocated. If a patient entered the cohort using a prolactin-sparing antipsychotic and later switched to a prolactin-elevating one, the period from cohort entry to the switch was allocated as reference, and from the switch to the index date as exposure.

Our study also had some potential limitations. First, as with many mental illnesses, underreporting of endometrial cancer is possible.[35] To maximize detection, we added hospital-based cases identified in the HES and matched them to controls linkable to HES. Even given this limitation, we were able to reject an increased risk above 48% (the upper CI limit), which is far less than previously reported.[15] Further, any underdetection was nondifferential across users of antipsychotics and thus was unlikely to change our results. Second, the accuracy of endometrial cancer diagnoses recorded by general practitioners may be a concern. However, a sensitivity analysis with a restrictive case ascertainment yielded a similar OR. Third, some residual confounding with the severity of the underlying mental illness is possible. This was partially addressed by the assembly of a cohort of new users of antipsychotics and matching cases and controls on duration of use. Additionally, there were no apparent differences in the indications for the use of prolactin-sparing and prolactin-elevating antipsychotics. Thus, the severity of mental illness was unlikely to affect our results. Fourth, we had no data on reproductive factors, which have been associated with endometrial cancer,[36] or on breastfeeding, which has been associated with prolactin levels.[37] Fifth, exposure misclassification is possible with prescription data. However, we used an exposure definition that was designed to capture nonsporadic use. Further, changing the exposure definition did not affect our point estimate. Lastly, we did not have data on serum prolactin levels, and the classification of antipsychotic exposure with respect to prolactin was based on the current literature, which is consistent with the poor reporting of prolactin levels in published studies.[16] On a larger scale of comparison between groups of antipsychotics, between-person differences

Figure 2. Sensitivity Analyses



Abbreviation: aOR = adjusted odds ratio.

in prolactin levels most likely played a very minor role and were balanced.

Our findings suggest that hyperprolactinemia induced by antipsychotics is not an important uterine carcinogen. While these findings provide reassurance to prescribers and users of these drugs, they mainly contrast the hypothesis that antipsychotic-induced prolactin elevation may promote neoplastic changes in the uterus and do not refute other possible mechanisms.

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Drug names: apomorphine (Apokyn), aripiprazole (Abilify), asenapine (Saphris), bromocriptine (Parlodel, Cycloset, and others), carbidopa (Lodosyn and others), chlorpromazine (Thorazine, Promapar, and others), clozapine (Clozaril, FazaClo, and others), droperidol (Inapsine and others), entacapone (Comtan and others), fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), levodopa (Dopar, Larodopa, and others), levomepromazine (Levoprome), loxapine (Loxitane and others), medroxyprogesterone (Provera, Cycrin, and others), metformin (Glucophage and others), olanzapine (Zyprexa and others), paliperidone (Invega), perphenazine (Trilafon and others), pimozide (Orap and others), pramipexole (Mirapex and others), promazine (Sparine), quetiapine (Seroquel and others), rasagiline (Azilect and others), risperidone (Risperdal and others), ropinirole (Requip and others), rotigotine (Neupro), selegiline (Eldepryl and others), thioridazine (Mellaril and others), tolcapone (Tasmar), trifluoperazine (Stelazine and others).

Author contributions: Dr Klil-Drori designed the study, did the analysis, and wrote the manuscript. Dr Azoulay obtained funding, designed and supervised the study, obtained the data, did the analysis, and critically reviewed the manuscript. Dr Yin did the analysis. Dr Abenhaim and Dr Galbaud du Fort critically reviewed the manuscript. Dr Azoulay had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Material

Article Title: Prolactin-Elevating Antipsychotics and the Risk of Endometrial Cancer

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The Use of Prolactin-Elevating Antipsychotics and the Risk of Endometrial Cancer: Supplementary Material

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Supplementary Table 1. Indications for antipsychotic use stratified by prolactin-sparing and prolactin-elevating drugs[a]

Indication	Prolactin-elevating (n=21,533)	Prolactin-sparing (n=44,397)
Severe mental illness		
Schizophrenia	1348 (6.3)	1830 (4.1)
Bipolar disorder	721 (3.4)	2277 (5.1)
Non-organic psychosis	1769 (8.2)	2854 (6.4)
Non-severe mental illness		
Depression	10,789 (50.1)	24,655 (55.5)
Anxiety disorders	4885 (22.7)	11,598 (26.1)
Dementia	3296 (15.3)	2594 (5.8)
Sleep disorders	4244 (19.7)	8403 (18.9)
Attention-deficit hyperactivity disorder	16 (0.1)	71 (0.2)
Personality disorders	671 (3.1)	1174 (2.6)
Post-traumatic stress disorder	90 (0.4)	352 (0.8)
Obsessive-compulsive disorder	205 (1.0)	583 (1.3)
Autistic spectrum disorders	49 (0.2)	46 (0.1)
Other	960 (4.5)	2268 (5.1)
Unknown	5105 (23.7)	10,984 (24.7)

[a] Values are number (%)

Supplementary Table 2. Prolactin-elevating antipsychotics and the risk of endometrial cancer (varying lag period to 2 years)

	Cases (n=119)	Controls (n=1307)	Crude OR	Adjusted OR (95% CI)[a]
Use of prolactin-sparing antipsychotics, n (%)	67 (56.3)	766 (58.6)	1.00[Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics, n (%)	52 (43.7)	541 (41.4)	1.09	1.12 (0.74-1.70)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidaemia, statins, fibrates, oral contraceptives, hormonal replacement therapy, cancer (other than endometrial or non-melanoma skin cancer), and tamoxifen at baseline.

Supplementary Table 3. Prolactin-elevating antipsychotics and the risk of endometrial cancer (varying lag period to 3 years)

	Cases (n=105)	Controls (n=1127)	Crude OR	Adjusted OR (95% CI)[a]
Use of prolactin-sparing antipsychotics, n (%)	61 (58.1)	695 (61.7)	1.00 [Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics, n (%)	44 (41.9)	432 (38.3)	1.12	1.20 (0.76-1.88)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidaemia, statins, fibrates, oral contraceptives, hormonal replacement therapy, cancer (other than endometrial or non-melanoma skin cancer), and tamoxifen at baseline.

Supplementary Table 4. Prolactin-elevating antipsychotics and the risk of endometrial cancer (restricting endometrial cancer events to those with a record of hysterectomy, medroxyprogesterone or radiotherapy)

	Cases (n=105)	Controls (n=1231)	Crude OR	Adjusted OR (95% CI)[a]
Use of prolactin-sparing antipsychotics, n (%)	70 (66.7)	811 (65.9)	1.00[Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics, n (%)	35 (33.3)	420 (34.1)	0.92	0.92 (0.58-1.47)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidaemia, statins, fibrates, oral contraceptives, hormonal replacement therapy, cancer (other than endometrial or non-melanoma skin cancer), and tamoxifen at baseline.

Supplementary Table 5. Prolactin-elevating antipsychotics use and the risk of endometrial cancer (exclude previous cancer)

	Cases (n=116)	Controls (n=1458)	Crude OR	Adjusted OR (95% CI)[a]
Use of prolactin-sparing antipsychotics, n (%)	73 (62.9)	931 (63.9)	1.00[Ref]	1.00 [Ref]
Use of prolactin-elevating antipsychotics, n (%)	43 (37.1)	527 (36.2)	0.99	0.90 (0.58-1.39)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidaemia, statins, fibrates, oral contraceptives, and hormonal replacement therapy at baseline.

Supplementary Table 6. Prolactin-elevating antipsychotics use and the risk of endometrial cancer (exposure defined by one prescription)

	Cases (n=116)	Controls (n=1458)	Crude OR	Adjusted OR (95% CI)[a]
Use of prolactin-sparing antipsychotics, n (%)	13 (9.4)	168 (10.5)	1.00[Ref]	1.00 (Reference)
Use of prolactin-elevating antipsychotics, n (%)	126 (90.7)	1435 (89.5)	1.04	1.01 (0.50-2.04)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Adjusted for excessive alcohol use, smoking status, hypertension, diabetes mellitus, polycystic ovarian syndrome, myocardial infarction, ischemic stroke, transient ischemic attack, dyslipidaemia, statins, fibrates, oral contraceptives, hormonal replacement therapy, cancer (other than endometrial or non-melanoma skin cancer), and tamoxifen at baseline.