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ORIGINAL RESEARCH

A real-world analysis of healthcare costs and relative risk of hyperprolactinemia associated with antipsychotic treatments in the United States

Martin Cloutier[a], Mallik Greene[b], Maëlys Touya[c], Patrick Gagnon-Sanschagrin[a] and Annie Guerin[a]

[a]Analysis Group, Inc., Montreal, QC, Canada; [b]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; [c]Lundbeck, Deerfield, IL, USA

ABSTRACT

Aims: Antipsychotic medications are associated with an increased risk of hyperprolactinemia, but differ in their propensity to cause this complication. This study aimed to assess the economic burden of hyperprolactinemia, and to compare its risk among adult patients using atypical antipsychotics (AAs) with a mechanism of action associated with no/low vs high/moderate prolactin elevation.

Methods: This retrospective cohort study was based on US Commercial and Medicaid claims databases. Healthcare costs were compared between matched hyperprolactinemia and hyperprolactinemia-free cohorts using a two-part model. Risk of hyperprolactinemia was compared between patients receiving AAs with a mechanism of action associated with no/low (no/low prolactin elevation cohort) vs high/moderate prolactin elevation (high/moderate prolactin cohort) using logistic regression.

Results: In the commercially insured sample, compared to the hyperprolactinemia-free cohort ($n = 499$), the hyperprolactinemia cohort ($n = 499$) was associated with incremental total healthcare costs of $5,732 ($20,081 vs $14,349; $p = .004$), and incremental medical costs of $3,861 ($13,218 vs $9,357; $p = .040$), mainly driven by hyperprolactinemia-related costs. In the Medicaid-insured sample, compared to the hyperprolactinemia-free cohort, the hyperprolactinemia cohort was associated with incremental total healthcare costs of $10,773 ($30,763 vs $19,990; $p = .004$), and incremental medical costs of $9,246 ($20,859 vs $11,613; $p = .004$), mainly driven by hyperprolactinemia-related and mental health-related costs. The odds of hyperprolactinemia in the no/low prolactin elevation cohort were 4–5-times lower than that in the high/moderate prolactin elevation cohort (odds ratio $=0.21$; $p < .001$).

Limitations: Hyperprolactinemia may be under-reported in claims data.

Conclusions: Hyperprolactinemia is associated with substantial healthcare costs. AAs associated with no/low prolactin elevation reduce the risk of hyperprolactinemia by 4–5-times compared to AAs associated with moderate/high prolactin elevation. Treatment options with minimal impact on prolactin levels may contribute to reducing hyperprolactinemia burden in AA-treated patients.

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Introduction

Hyperprolactinemia is characterized by elevated levels of the hormone prolactin, secreted mainly by the lactotroph cells of the anterior pituitary gland. Although prolactin is a vital hormone involved in a myriad of functions, including reproduction, metabolism, and immunoregulation, elevated levels are associated with several complications. These complications include endocrine, reproductive, and sexual dysfunction, such as galactorrhea and hypogonadotropic hypogonadism, manifesting as oligomenorrhea or amenorrhea in women, erectile dysfunction in men, and loss of libido and infertility in both sexes[1–3].

The underlying etiology of hyperprolactinemia is diverse, and includes physiologic (e.g. physical exertion, pregnancy and post-partum period, nursing), pathologic (e.g. pituitary/hypothalamic disorders, pituitary tumors, primary hypothyroidism, untreated psychosis), and pharmacologic (e.g. antipsychotics, antihypertensives, antidepressants) processes[4–7]. Antipsychotic medications used to treat a range of psychiatric disorders, including schizophrenia, bipolar disorder, and major depressive disorder, are associated with a range of side-effects, including pharmacologically induced hyperprolactinemia[8–10].

The clinical consequences of hyperprolactinemia may affect patients' quality-of-life and increase healthcare costs. Indeed, in addition to treating the associated symptoms and complications of hyperprolactinemia (e.g. detection tests, follow-up visits, fertility treatments), hyperprolactinemia may lead to the discontinuation or switch of the antipsychotic treatment received, which may further complicate the management of the patient's condition[1].

Most antipsychotic drugs exert their antipsychotic effect primarily by blocking dopamine D_2 receptors, which in turn

CONTACT Mallik Greene mallik.greene@otsuka-us.com Health Economics & Outcomes Research, Otsuka Pharmaceutical Development & Commercialization, Inc., 508 Carnegie Center, Princeton, NJ 08540, USA

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causes prolactin secretion to increase. Antipsychotics, particularly atypical antipsychotics (AAs), have diverse mechanisms of action, which affect their propensity to cause hyperprolactinemia[11,12] due to differences in D_2 receptor binding activity and duration, and having partial agonist activity, in some cases. Dopamine antagonists reduce dopamine levels, leading to higher serum prolactin levels, while dopamine partial agonists tend to lower the risk of increased prolactin levels[1,13–15]. The relationship between antipsychotic use and hyperprolactinemia has been commonly studied in clinical trials, and these studies have shown great variability depending on the antipsychotic studied[13]; abnormally high prolactin levels may be experienced by up to 50% of patients with schizophrenia, depending on the antipsychotics used[16].

Although the association of antipsychotics with risk of hyperprolactinemia has been examined in clinical trials, there is a dearth of real-world evidence on the economic burden and the relative risk of hyperprolactinemia associated with a range of different antipsychotic treatments. The objectives of this study were two-fold: (1) to assess the economic burden of hyperprolactinemia; and (2) to compare the risk of hyperprolactinemia among adults using antipsychotics associated with no/low vs high/moderate prolactin elevation.

Methods

Data source

The analyses were performed using data from the Truven Health Analytics MarketScan Commercial Claims and Encounters (commercial) database (January 1, 2006–September 30, 2016) and the Truven Health Analytics MarketScan Medicaid Multi-State (Medicaid) database (January 1, 2006–June 30, 2016). The commercial database consists of employer- and health plan-sourced data containing medical and pharmacy claims data for beneficiaries, comprising employees, their spouses, and dependents who are covered by employer-sponsored private health insurance. The Medicaid database consists of employer-, health plan-, and state Medicaid agency-sourced data containing medical and pharmacy claims of Medicaid enrollees. The databases are fully compliant with the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations, and thus no ethics board review was required.

Assessment of the economic burden of hyperprolactinemia

Study design, sample selection, and study cohorts

A retrospective matched-cohort design was employed. Patients were categorized into two mutually exclusive cohorts: the "hyperprolactinemia cohort" and the "hyperprolactinemia-free cohort". The hyperprolactinemia cohort consisted of patients who (1) had at least one recorded diagnosis of hyperprolactinemia at any time; (2) were continuously enrolled in their health insurance plan for at least 12 months prior to and following their index date; (3) had at least one claim for an oral or injectable antipsychotic in the 12-month period prior to their index date; and (4) were at least 18 years old as of their index date. Patients with a recorded diagnosis of pituitary gland hyperfunction or tumor, end-stage renal disease, and pregnancy-related diagnosis at any point during the entire period covered by the data were excluded, as these conditions may be associated with non-treatment induced hyperprolactinemia. The hyperprolactinemia-free cohort consisted of patients who met all the criteria for the hyperprolactinemia cohort but had no recorded diagnosis of hyperprolactinemia or any indicators of hyperprolactinemia (i.e. a diagnosis for amenorrhea, galactorrhea [not associated with childbirth], gynecomastia, hyperprolactinemia, or hypogonadism, or a procedure for an assay of prolactin, a mammary ductogram, or a galactogram) at any point during the entire period covered by the data.

For the hyperprolactinemia cohort, the index date was defined as 14 days before the first diagnosis of hyperprolactinemia or the first indicator of hyperprolactinemia, whichever occurred first. Since hyperprolactinemia may first be identified through commonly related symptoms, and/or may require some tests to confirm the diagnosis, indicators of hyperprolactinemia were considered in the selection of the index date, and a 14-day period prior to the hyperprolactinemia diagnosis or indicators was applied to capture medical services associated with hyperprolactinemia before the diagnosis was observed in the claims database. For the hyperprolactinemia-free cohort, the index date was randomly selected using equal probability sampling among all potential dates for which matched patients had the same demographics and similar antipsychotic treatment history, comorbidity profile, and mental-health medical services as patients in the hyperprolactinemia cohort. For both cohorts, the baseline period was defined as 12 months prior to the index date, and the study period was defined as 12 months following the index date (Figure 1).

To assess the incremental cost associated with hyperprolactinemia, patients in the hyperprolactinemia cohort were matched exactly to patients in the hyperprolactinemia-free cohort with similar characteristics prior to or on the index date, so that the cost difference observed between the two cohorts would likely be attributed to hyperprolactinemia and not to other differences in patient characteristics. Matching was done on a 1:1 ratio based on the following characteristics measured on the index date: age, sex, region of residence (for the commercially insured population only), race (for the Medicaid-insured population only), health insurance plan type, and calendar year. Patients were also matched based on the following characteristics measured during the baseline period: number of distinct antipsychotic medication(s) used, route of administration of the antipsychotic(s) used (injectable or oral), mental health-related services used (any setting), mental health-related inpatient (IP) psychiatric facility admissions, neoplasms, bone fractures, and Charlson Comorbidity Index (CCI). In addition, patients were matched based on conditions for which antipsychotic medications are indicated (i.e. autistic disorder, dementia, mood disorder,

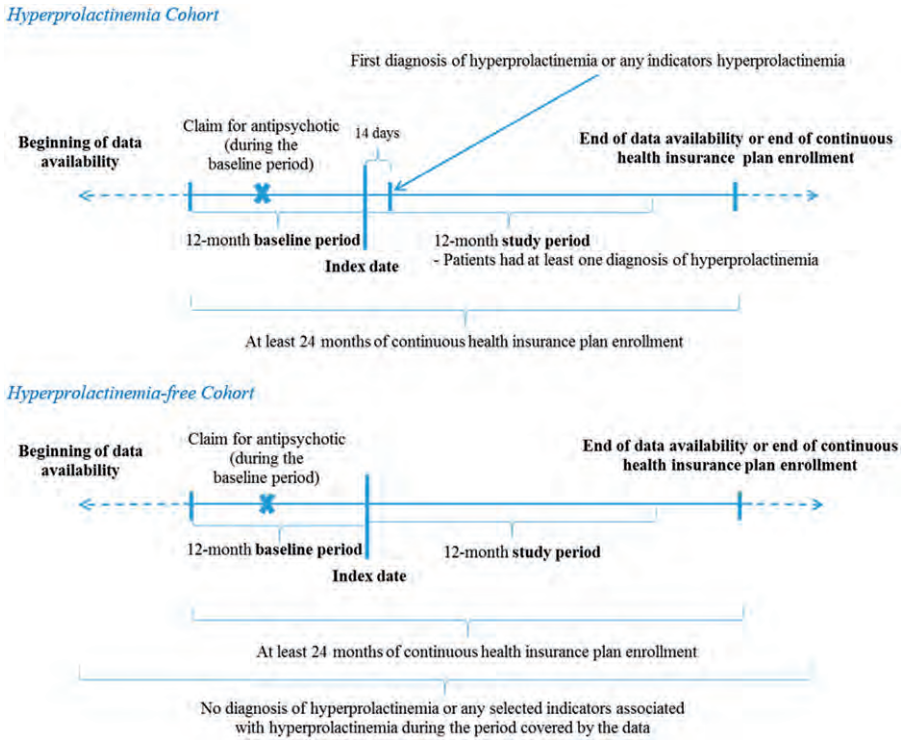

Figure 1. Study design—economic burden of hyperprolactinemia.

psychosis, schizophrenia, Tourette's disorder, other mental disorder), measured at any point during the entire period covered by the data.

Outcomes and statistical analysis

Healthcare costs were measured from a payers' perspective (amount reimbursed by the commercial plan and coordination of benefits) during the study period (i.e. 12-month period following the index date) and compared between matched cohorts. Costs were reported per patient per year (PPPY), adjusted for inflation, and expressed in 2016 US dollars (i.e. latest year available in the data) using the medical care component of the Consumer Price Index (CPI) for the following components: medical costs (excluding costs of antipsychotics reimbursed by medical benefits), medical costs potentially related to hyperprolactinemia (hyperprolactinemia-related; identified based on a diagnosis of hyperprolactinemia or an indicator of hyperprolactinemia), mental health-related medical costs (identified based on a code for a mental-health related service [i.e. place of service, provider type, revenue code, procedure code, diagnosis code]), pharmacy costs (including costs for antipsychotics reimbursed by medical or pharmacy benefits), and total healthcare costs (medical and pharmacy costs).

Incremental healthcare costs associated with hyperprolactinemia were estimated using two-part models, where the first part was a logistic model with a binomial distribution, and the second part was a generalized linear regression model with a log link and a gamma distribution. Results were reported as unadjusted cost differences with their 95% confidence intervals (CIs) and *p*-values.

Comparison of the risk of hyperprolactinemia

Study design, sample selection, and study cohorts

Patients were classified into two mutually exclusive cohorts based on whether they were treated with AAs associated with no/low prolactin elevation or high/moderate prolactin elevation: the "no/low prolactin elevation cohort" and the "high/moderate prolactin elevation cohort". The list of AAs associated with no/low or high/moderate prolactin elevation was based on the literature and is presented in Table 1[1].

Patients were included in the study sample if they (1) were continuously enrolled in their health insurance plan for at least 12 months prior to the initiation date of their first antipsychotic (the 12-month washout period free of antipsychotic was used to identify the first line of antipsychotic therapy and subsequently to number lines of therapy); (2) were at least 18 years old as of the initiation date of their first antipsychotic treatment; (3) had at least one oral or injectable AA treatment episode in monotherapy; and (4) were continuously enrolled in their health insurance plan for at least 12 months prior to and 1 month following the initiation date of this treatment episode. Those who had a recorded diagnosis of pituitary gland hyperfunction or tumor, end-stage renal disease, and pregnancy-related diagnosis at any point during the entire period covered by the data were excluded.

A treatment episode (and study period) spanned from the treatment episode initiation date, defined as the initiation date of an AA, until treatment discontinuation (gap in treatment of at least 180 days), treatment switch, end of data availability (September 30, 2016), or end of continuous health insurance plan enrollment, whichever occurred first. Each AA treatment episode was considered. Therefore,

Table 1. Risk of hyperprolactinemia by atypical antipsychotic.

	Commercially insured patients			Medicaid-insured patients		
	Number of treatment episodes	Number of HPRL events P100PY	Prevalence	Number of treatment episodes	Number of HPRL events P100PY	Prevalence
High/moderate prolactin elevation	77,532	0.58	0.31%	58,447	0.42	0.30%
Asenapine	4,884	0.51	0.23%	3,452	0.28	0.12%
Paliperidone	4,535	1.11	0.57%	9,288	0.69	0.46%
Risperidone	68,113	0.55	0.30%	45,707	0.37	0.28%
No/low prolactin elevation	446,673	0.10	0.06%	177,379	0.10	0.07%
Aripiprazole	175,094	0.08	0.06%	51,151	0.06	0.04%
Aripiprazole lauroxil	0	—	—	0	—	—
Brexpiprazole	2,164	0.00	0.00%	490	0.00	0.00%
Cariprazine	279	0.00	0.00%	51	0.00	0.00%
Clozapine	719	0.76	0.70%	1,466	0.19	0.20%
Iloperidone	710	0.00	0.00%	1,012	0.35	0.20%
Lurasidone	13,920	0.35	0.17%	10,110	0.24	0.12%
Olanzapine	45,810	0.16	0.09%	20,648	0.20	0.13%
Quetiapine	184,899	0.07	0.05%	77,937	0.08	0.06%
Ziprasidone	23,078	0.20	0.11%	14,514	0.17	0.11%

Abbreviations. HPRL, hyperprolactinemia; P100PY, per 100 patients per year.

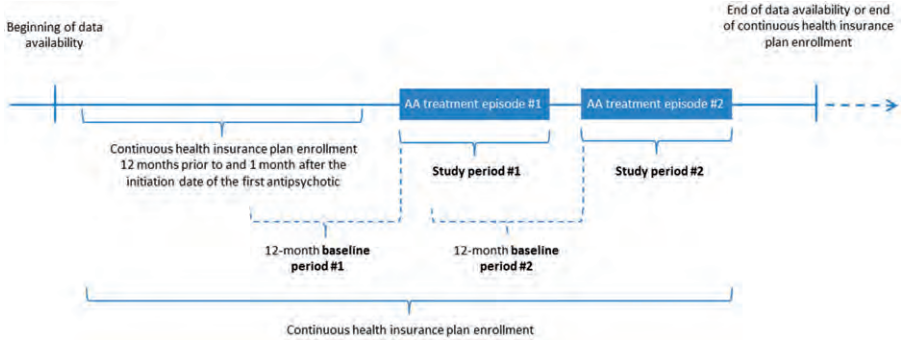

Figure 2. Study design—risk of hyperprolactinemia. Note, patients may have used typical antipsychotics prior to the first AA treatment episode.

patients initiated on more than one AA agent over the period covered by the data could be included more than once. The baseline period was defined as 12 months prior to the treatment episode initiation date (Figure 2).

Outcomes and statistical analysis

To compare the risk of hyperprolactinemia between the no/low prolactin elevation cohort and the high/moderate prolactin elevation cohort, entropy balancing was carried out to reweight patient characteristics to balance patient characteristics between cohorts prior to treatment initiation, especially those characteristics that may affect the risk of developing hyperprolactinemia.

The following characteristics measured as of the treatment episode initiation date were used to balance the cohorts: age, sex, region of residence (for the commercially insured population only), race (for the Medicaid-insured population only), health insurance plan type, calendar year, and treatment episode number (where treatment episodes were chronologically numbered from first line antipsychotic initiation). Characteristics measured during the baseline period used to balance the cohorts included the following: number of distinct antipsychotic medication(s) used, route of administration of the antipsychotic(s) used (injectable or oral), mental health-related service used (any setting), mental health-related IP psychiatric facility admission, and CCI. In addition, conditions for which antipsychotic medications are indicated, measured at any point during the entire period covered by the data, were balanced between the cohorts.

The number of patients with a diagnosis of hyperprolactinemia during the study period was measured for each cohort. Odds ratios (ORs) for hyperprolactinemia were estimated using weighted logistic regression models. Results were reported as unadjusted ORs with their 95% CIs and *p*-values.

Sensitivity analyses

Sensitivity analyses were conducted based on a broader definition of hyperprolactinemia. Based on the assumption that hyperprolactinemia may be under-reported in claims data using diagnosis codes, an algorithm was developed to identify patients who did not have a diagnosis of hyperprolactinemia, but had various indicators suggesting that they may have hyperprolactinemia. These indicators were based on the most common comorbidities/symptoms, procedures, and tests associated with hyperprolactinemia that are less likely to be associated with other conditions. Patients with indicators of hyperprolactinemia were identified based on the presence of at least two claims for distinct indicators associated with hyperprolactinemia within 30 days of each other, at any time. All analyses on the economic burden of hyperprolactinemia and on the risk of hyperprolactinemia were replicated

Table 2. Patient characteristics (after matching)—assessment of the economic burden of hyperprolactinemia.

Patient characteristics	Commercially insured patients		Medicaid-insured patients	
	HPRL cohort ($n = 499$)	HPRL-free cohort ($n = 499$)	HPRL cohort ($n = 257$)	HPRL-free cohort ($n = 257$)
As of the index date				
Age, years; mean ± SD [median]	38.9 ± 12.8 [40.0]	38.9 ± 12.8 [40.0]	34.1 ± 11.0 [34.0]	34.1 ± 11.0 [34.0]
Female, *n* (%)	382 (76.6%)	382 (76.6%)	177 (68.9%)	177 (68.9%)
During the baseline period				
Number of distinct antipsychotic(s) (distinct active ingredient and ROA) used; mean ± SD [median]	1.3 ± 0.6 [1.0]	1.3 ± 0.6 [1.0]	1.4 ± 0.7 [1.0]	1.4 ± 0.7 [1.0]
CCI, mean ± SD [median]	0.2 ± 0.4 [0.0]	0.2 ± 0.4 [0.0]	0.3 ± 0.6 [0.0]	0.3 ± 0.6 [0.0]
Healthcare resource use, mean ± SD [median]				
Patients with ≥1 mental health-related service (any setting)	458 (91.8%)	458 (91.8%)	255 (99.2%)	255 (99.2%)
Patients with ≥1 mental health-related IP admission to a psychiatric facility	56 (11.2%)	56 (11.2%)	30 (11.7%)	30 (11.7%)
Any time during the period covered by the data				
Conditions for which antipsychotics are indicated, *n* (%)				
Autistic disorder	11 (2.2%)	11 (2.2%)	30 (11.7%)	30 (11.7%)
Dementia (including Alzheimer's disease)	7 (1.4%)	7 (1.4%)	5 (1.9%)	5 (1.9%)
Mood disorder	462 (92.6%)	462 (92.6%)	216 (84.0%)	216 (84.0%)
Bipolar disorder	238 (47.7%)	238 (47.7%)	131 (51.0%)	131 (51.0%)
Depressive disorder	402 (80.6%)	402 (80.6%)	184 (71.6%)	184 (71.6%)
Major depressive disorder	330 (66.1%)	330 (66.1%)	119 (46.3%)	119 (46.3%)
Psychosis	51 (10.2%)	51 (10.2%)	68 (26.5%)	68 (26.5%)
Schizophrenia	35 (7.0%)	35 (7.0%)	96 (37.4%)	96 (37.4%)
Schizoaffective disorder	26 (5.2%)	26 (5.2%)	66 (25.7%)	66 (25.7%)
Tourette's disorder	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Other mental disorder	29 (5.8%)	29 (5.8%)	10 (3.9%)	10 (3.9%)

Abbreviations. CCI, Charlson Comorbidity Index; HPRL, hyperprolactinemia; IP, inpatient; ROA, route of administration; SD, standard deviation.

Results

Economic burden of hyperprolactinemia

Among commercially insured patients ($n = 499$ in each cohort), mean age was 39 years and 77% of patients were female. In the Medicaid-insured cohorts ($n = 257$ in each cohort), mean age was 34 years and 69% of patients were female (Table 2).

Among commercially insured patients, compared to the hyperprolactinemia-free cohort, the hyperprolactinemia cohort was associated with incremental total healthcare costs of $5,732 ($20,081 vs $14,349; $p = .004$), and incremental medical costs of $3,861 ($13,218 vs $9,357; $p = .040$), which were mainly driven by hyperprolactinemia-related ($2,592 vs $501; $p = .004$) costs, accounting for 54% of the medical cost difference between the two cohorts. Among Medicaid-insured patients compared to the hyperprolactinemia-free cohort, the hyperprolactinemia cohort was associated with incremental total healthcare costs of $10,773 ($30,763 vs $19,990; $p = .004$), and incremental medical costs of $9,246 ($20,859 vs $11,613; $p = .004$), which were mainly driven by hyperprolactinemia-related ($1,504 vs $204; $p = .004$) and mental health-related ($14,915 vs $8,774; $p = .032$) costs, accounting for 14% and 66% of the medical cost difference, respectively (Table 3).

Risk of hyperprolactinemia

Among commercially insured patients, 446,673 and 77,532 AA patient-treatment episodes were identified in the no/low and high/moderate prolactin elevation cohorts, respectively. Mean age was 42 years and 60% of the patients were female. Among Medicaid-insured patients, 177,379 and 58,447 AA patient-treatment episodes were identified in the no/low and high/moderate prolactin elevation cohorts, respectively. Mean age was 43 years and 63% of the patients were female (Table 4). The most commonly used AAs were quetiapine, aripiprazole, and olanzapine in the no/low prolactin elevation cohorts, and risperidone, asenapine, and paliperidone in the high/moderate prolactin elevation cohorts for both commercially and Medicaid-insured patients. The prevalence of hyperprolactinemia during treatment episodes was considerably lower in the no/low prolactin elevation cohort (0.06% commercial, 0.07% Medicaid) compared to the high/moderate prolactin elevation cohort (0.31% commercial, 0.30% Medicaid) (Table 1).

The odds of hyperprolactinemia in the no/low prolactin elevation cohort ($n = 446,673$) were 5-times lower than that in the high/moderate prolactin elevation cohort ($n = 77,532$) among commercially insured patients (OR =0.21; $p < .001$). Similarly, the odds of hyperprolactinemia in the no/low prolactin elevation cohort ($n = 177,379$) were 4-times lower than that in the high/moderate prolactin elevation cohort ($n = 58,447$) among Medicaid-insured patients (OR =0.26; $p < .001$) (Table 5).

Sensitivity analyses

Results from the sensitivity analyses, that is, based on the presence of indicators of hyperprolactinemia, were consistent with those from the core analyses. Patients in the hyperprolactinemia cohort had substantially higher costs compared to patients in the hyperprolactinemia-free cohort. Compared to the hyperprolactinemia-free cohort, the hyperprolactinemia cohort was associated with incremental total healthcare costs of $5,084 ($18,042 vs $12,957; $p = .004$) and $2,788 ($19,529 vs $16,740; $p = .008$) for commercially insured and Medicaid-insured patients, respectively (Supplementary Table 1). Patients receiving AAs associated with no/low prolactin

Table 3. Average costs per patient per year: hyperprolactinemia cohort vs hyperprolactinemia-free cohort.

Direct healthcare costs,[a] 2016 USD	Commercially insured patients				Medicaid-insured patients			
	HPRL cohort [A] ($n = 499$)	HPRL-free cohort [B] ($n = 499$)	Cost difference (95% CI) [A] – [B]	*p*-value	HPRL cohort [A] ($n = 257$)	HPRL-free cohort [B] ($n = 257$)	Cost difference (95% CI) [A] – [B]	*p*-value
Medical service costs	13,218 ± 27,905	9,357 ± 22,975	$3,861 (732–6,976)	0.040*	20,859 ± 42,759	11,613 ± 19,375	$9,246 (3,317–15,504)	0.004*
HPRL-related[b]	2,592 ± 12,521	501 ± 4,128	$2,092 (1,081–3,522)	0.004*	1,504 ± 4,863	204 ± 1,221	$1,300 (736–2,054)	0.004*
Mental health-related	6,750 ± 25,417	4,265 ± 16,931	$2,486 (−240–5,189)	0.068	14,915 ± 35,344	8,774 ± 18,389	$6,141 (798–11,820)	0.032*
Pharmacy costs	6,863 ± 10,669	4,991 ± 9,714	$1,872 (571–3,041)	0.004*	9,905 ± 10,923	8,377 ± 17,672	$1,527 (–1,032–3,719)	0.284
Total healthcare costs	20,081 ± 31,732	14,349 ± 25,825	$5,732 (2,455–9,166)	0.004*	30,763 ± 45,400	19,990 ± 27,091	$10,773 (4,028–17,194)	0.004*

Abbreviations. CI, confidence intervals; HPRL, hyperprolactinemia.
*denotes $p<0.05$.
[a]Healthcare costs were measured during the 12-month period following the index date.
[b]Costs potentially related to hyperprolactinemia were identified claims with the following conditions and/or tests: hyperprolactinemia, amenorrhea, galactorrhea (not associated with childbirth), gynaecomastia, hypogonadism, hypothyroidism, infertility, oligomenorrhea, renal disease, sexual dysfunction, galactogram, mammary ductogram, and assay of prolactin.

Table 4. Patient characteristics (after reweighting)—comparison of the risk of hyperprolactinemia.

Patient characteristics[a]	Commercially insured patients		Medicaid-insured patients	
	No/low prolactin elevation cohort ($n = 446,673$)	High/moderate prolactin elevation cohort ($n = 77,532$)	No/low prolactin elevation cohort ($n = 177,379$)	High/moderate prolactin elevation cohort ($n = 58,447$)
As of the index date				
Age, years; mean ± SD [median]	42.4 ± 13.4 [44.0]	42.4 ± 13.4 [44.0]	42.6 ± 11.8 [43.5]	42.6 ± 11.8 [43.6]
Female, *n* (%)	266,091 (59.6%)	46,161 (59.5%)	112,401 (63.4%)	37,031 (63.4%)
During the baseline period				
Number of distinct antipsychotic(s) (distinct active ingredient and ROA) used; mean ± SD [median]	0.4 ± 0.7 [0.0]	0.4 ± 0.7 [0.0]	0.5 ± 0.9 [0.0]	0.5 ± 0.9 [0.0]
Number of patients with ≥1 one prescription fill for an antipsychotic, *n* (%)	126,515 (28.3%)	21,984 (28.4%)	64,111 (36.1%)	21,129 (36.1%)
CCI, mean ± SD [median]	0.5 ± 1.1 [0.0]	0.5 ± 1.1 [0.0]	0.9 ± 1.5 [0.0]	0.9 ± 1.5 [0.0]
Healthcare resource use, mean ± SD [median]				
Patients with ≥1 mental health-related service (any setting)	395,196 (88.5%)	68,602 (88.5%)	161,811 (91.2%)	53,317 (91.2%)
Patients with ≥1 IP mental health-related psychiatric facility admission	90,888 (20.3%)	15,817 (20.4%)	33,681 (19.0%)	11,100 (19.0%)
Any time during the period covered by the data				
Conditions for which antipsychotics are indicated, *n* (%)				
Autistic disorder	2,502 (0.6%)	444 (0.6%)	3,572 (2.0%)	1,179 (2.0%)
Dementia (including Alzheimer's disease)	20,912 (4.7%)	3,640 (4.7%)	16,775 (9.5%)	5,529 (9.5%)
Mood disorder	402,916 (90.2%)	69,918 (90.2%)	161,059 (90.8%)	53,063 (90.8%)
Bipolar disorder	145,686 (32.6%)	25,295 (32.6%)	74,765 (42.1%)	24,632 (42.1%)
Depressive disorder	370,275 (82.9%)	64,248 (82.9%)	145,611 (82.1%)	47,973 (82.1%)
Major depressive disorder	289,796 (64.9%)	50,284 (64.9%)	104,945 (59.2%)	34,574 (59.2%)
Psychosis	62,933 (14.1%)	10,993 (14.2%)	44,737 (25.2%)	14,747 (25.2%)
Schizophrenia	28,755 (6.4%)	5,064 (6.5%)	47,411 (26.7%)	15,634 (26.7%)
Schizoaffective disorder	16,642 (3.7%)	2,887 (3.7%)	28,975 (16.3%)	9,507 (16.3%)
Tourette's disorder	838 (0.2%)	148 (0.2%)	390 (0.2%)	129 (0.2%)
Other mental disorder	36,452 (8.2%)	6,317 (8.1%)	8,744 (4.9%)	2,880 (4.9%)

Abbreviations. CCI, Charlson Comorbidity Index; ROA, route of administration; SD, standard deviation.
[a]Patients in the high/moderate prolactin elevation cohort were reweighted so that patient characteristics from the high/moderate prolactin elevation cohort had the same mean and standard deviation as those from the no/low prolactin elevation cohort.

Table 5. Comparison of the risk of hyperprolactinemia.

	Number of treatment episodes with HPRL		No/low prolactin elevation cohort vs high/moderate prolactin elevation cohort	
	No/low prolactin elevation cohort, *n*	High/moderate prolactin elevation cohort, *n*	Odds ratio (95% CI)	*p*-level
Commercially insured patients	446,673	77,532		
Episodes with HPRL	285	244	0.21 (0.18–0.25)	<.001*
Medicaid-insured patients	177,379	58,447		
Episodes with HPRL	130	174	0.26 (0.21–0.33)	<.001*

Abbreviations. CI, confidence intervals; HPRL, hyperprolactinemia.
*denotes $p<0.05$.

elevation had a lower risk of developing hyperprolactinemia compared to those receiving AAs associated with high/moderate prolactin elevation. The odds of hyperprolactinemia in the no/low prolactin elevation cohort were 2-times lower than those in the high/moderate prolactin elevation cohort among both commercially insured and Medicaid-insured patients (Supplementary Table 2).

Discussion

To our knowledge, this is the first study to assess the economic burden associated with hyperprolactinemia among patients treated with antipsychotics. In this study of patients treated with antipsychotics in real-world practices, hyperprolactinemia was associated with significant incremental total healthcare costs (medical and pharmacy costs). The incremental medical costs associated with hyperprolactinemia were mainly driven by hyperprolactinemia-related and mental health-related costs, each component accounting for up to 66% of the medical cost differences.

Results of the study were robust for both commercially insured and Medicaid-insured populations, and were substantiated by sensitivity analyses based on the presence of indicators of hyperprolactinemia consistently showing that patients in the hyperprolactinemia cohort had substantially higher costs compared to patients in the hyperprolactinemia-free cohort. Moreover, analysis of short-term medical services potentially associated with hyperprolactinemia using a 6-month study period showed that costs tended to be concentrated in the 6-month period neighboring the diagnosis; however, they remained substantial over time. This suggests that costs associated with hyperprolactinemia can be related to the short-term (e.g. multiple visits related to diagnostic work-up and treatment) as well as the long-term (e.g. follow-up medical visits, long-term complications) management of symptoms due to the complexity of diagnosis and heterogeneity of symptoms.

Clinical trials have shown that the risk of hyperprolactinemia is relatively high; however, direct comparisons of the risk of hyperprolactinemia between multiple antipsychotics of different mechanisms of action, particularly in the same study, remain scarce. A recent meta-analysis of the efficacy and tolerability of 15 common antipsychotic medications in patients with schizophrenia found that the difference between antipsychotics with respect to hyperprolactinemia was large. Some antipsychotics had a considerable impact on serum prolactin levels; for example, paliperidone and risperidone increased prolactin levels by more than one standard deviation compared with placebo. In contrast, other antipsychotics, such as aripiprazole and quetiapine, did not significantly increase prolactin concentrations compared to placebo[13]. Other antipsychotics expected to exert minimal effects on prolactin levels, including aripiprazole lauroxil, cariprazine, and brexpiprazole, were not assessed in this meta-analysis. Results of the present study are in accordance with the above findings showing that antipsychotics differ greatly in their propensity to cause hyperprolactinemia[8,9,11]. Indeed, AAs associated with no/low prolactin elevation were found to reduce the risk of developing hyperprolactinemia by 4–5-times compared to AAs associated with high/moderate prolactin elevation. Again, results were robust for both commercially insured and Medicaid-insured populations, and were consistent with sensitivity analyses, based on the presence of indicators of hyperprolactinemia showing that patients receiving AAs associated with no/low prolactin elevation had a lower risk of developing hyperprolactinemia compared to those receiving AAs associated with high/moderate prolactin elevation. In addition to using data from a real-world setting, a notable advantage of the present study is that patient characteristics (demographic, comorbidities, and mental health-related services) were balanced so that patients in both cohorts had a similar risk of developing hyperprolactinemia prior to treatment initiation. This is important as risk of hyperprolactinemia is affected by antipsychotic treatment-related as well as by patient-related factors[8].

Considering the incremental costs of hyperprolactinemia estimated in this study and the prevalence of hyperprolactinemia among patients treated with AAs, hyperprolactinemia likely poses a significant economic burden on payers, adding to the already high burden of schizophrenia. For example, assuming a hypothetical commercial health plan with one million insured individuals, if all individuals receiving AAs associated with high/moderate prolactin elevation were to be prescribed an AA associated with no/low prolactin elevation, this would result in a total hyperprolactinemia annual cost saving of $4.5 million (Supplementary Table 3).

While the short-term complications associated with hyperprolactinemia may negatively affect medication adherence and treatment response in patients treated with antipsychotics[17], the effects of potentially lifelong treatment with antipsychotic medications may have a long-term severe impact on the patients' physical health, especially given the broad range of clinical consequences related to hyperprolactinemia[18]. Therefore, prioritizing treatment options that reduce the risk of developing hyperprolactinemia has the potential to decrease the burden on patients as well as reduce healthcare costs.

The present study should be interpreted in light of certain limitations. First, direct healthcare costs were assessed for patients with a recorded diagnosis of hyperprolactinemia, who may represent more severe cases. For example, patients who present with a higher degree of symptomatology are more likely to require higher dosages of antipsychotic medication, which may increase their likelihood of experiencing hyperprolactinemia, irrespective of the drug's propensity to induce this side-effect. Second, hyperprolactinemia may be under-reported in claims data, and a portion of patients potentially eligible for this study might not have been selected for the analyses. However, the relative risk of hyperprolactinemia across antipsychotic medications is unlikely to be affected as both cohorts are affected to a similar extent (crude risk estimates may not be representative). Third, considering the complexity of prolactin regulation, many factors may cause hyperprolactinemia, and the effects of antipsychotic medications on serum prolactin are likely multifactorial. Although known important factors such as age, sex,

and antipsychotic medication type were balanced between cohorts, some unmeasured or unknown factors that could potentially affect prolactin levels may not have been accounted for (e.g. dosage, treatment duration, and other medications that may be associated with hyperprolactinemia). Finally, this study is subject to limitations inherent in analyses of healthcare claims data such as occasional coding errors and inaccurate or missing data on prescriptions, procedures, or diagnoses. However, potential inaccuracies are expected to affect study cohorts to a similar extent.

Conclusions

Hyperprolactinemia is associated with substantial healthcare costs. AAs associated with no/low prolactin elevation may reduce the risk of hyperprolactinemia by 4–5-times compared with AAs associated with moderate/high prolactin elevation. Therapeutic options with no/low impact on prolactin levels may be considered, instead of therapeutic options with moderate/high prolactin elevation, in treatment decision-making to reduce the burden of hyperprolactinemia in patients receiving antipsychotics. This study provides healthcare stakeholders with additional information on the use of antipsychotic medications in relation to the risk and burden of a common and important complication that can help optimize treatment decision-making.

Transparency

Declaration of funding

This research was funded by Otsuka Pharmaceuticals, Inc. and Lundbeck, LLC. The study sponsor was involved in all stages of the study and in the decision to submit this work for publication.

Declaration of financial/other relationships

MC, PG-S, and AG are employees of Analysis Group Inc., a consulting company that has received consulting fees from Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC. MG is an employee of Otsuka Pharmaceutical Development & Commercialization, Inc. MT is an employee of Lundbeck, LLC. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Compliance with ethics guidelines

The databases used in this study are fully compliant with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations, and thus no ethics board review was required.

Data availability statement

The claims database (Truven Health Analytics MarketScan) is proprietary, provided by a third-party vendor, and the authors do not have permission to disseminate the data without the vendor's approval. The study sponsor has purchased access to the database (the authors have been granted access to the data on a contract per project use). Access to this data set is available to any other interested parties for a fee set by Truven Health Analytics MarketScan (https://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases).

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