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# Metabolic adverse events associated with antipsychotic polypharmacy versus monotherapy among new pediatric users

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## Abstract

**Purpose**: Limited information is available on antipsychotic polypharmacy and associated metabolic adverse events in a pediatric population. This study sought to determine the risk of metabolic adverse events associated with antipsychotic polypharmacy compared to antipsychotic monotherapy use among commercially insured pediatric antipsychotic users.

**Methods**: This was a retrospective cohort study of commercial health plans claims data. New users of antipsychotic medication(s) aged 1-17 years on the date of the first antipsychotic prescription were selected and followed for up to one year after antipsychotic initiation. Patients with pre-existing metabolic conditions were excluded. Antipsychotic polypharmacy was defined as concurrent use of two or more chemically distinctive antipsychotic agents. Metabolic adverse events were captured using diagnosis or medication use during the one-year post-index period. Survival analyses using Cox regression models with time-varying exposure variables (any antipsychotic use, antipsychotic dose, antipsychotic exposure-dose combination and antipsychotic type) were conducted adjusting for baseline patient demographic and clinical characteristics.

**Results**: The study included 3,038 pediatric patients with antipsychotic use and 11.06% of them received antipsychotic polypharmacy during the one-year follow-up period. Compared to monotherapy, no statistically significant effect of antipsychotic polypharmacy was found for metabolic adverse events However, high total daily dose of antipsychotics was found to be significantly associated with metabolic adverse events (HR: 2.42 CI: 1.35-4.32).

**Conclusion:** Although no clear increase in risk of metabolic adverse events were detected for antipsychotic polypharmacy use compared to monotherapy, high daily dose of total antipsychotic use was associated with elevated risk for metabolic adverse events in pediatric patients.

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## Introduction

Despite the limited indications, antipsychotics are increasingly used in pediatric populations [1,2]. From 1995 to 2005, children under 18 who used antipsychotics increased eight fold from 0.3 million in 1995 to 2.4 million in 2005 [1]. Second Generation Antipsychotics (SGAs) have gained wide popularity in the pediatric population in recent times [3], accounting for 92.3% of antipsychotic medications prescribed among youths between 2000 and 2002 [2].

More concerning is that 3-27% of children and adolescents in the US were treated with antipsychotic polypharmacy, although the estimates vary by the definition used, study population, and clinical setting [4-6]. This is alarming because existing randomized clinical trials [7-15] do not show clear evidence of a beneficial effect of antipsychotic polypharmacy compared to monotherapy except for augmentation of clozapine in antipsychotic monotherapy treatment resistant patients [16,17]. Consistent with this lack of evidence for efficacy, treatment guidelines either do not recommend use of antipsychotic polypharmacy or limit its use to patients with refractory schizophrenia for short periods of time [18-21]. A large proportion of multiple antipsychotic use comprises of two or more SGAs or a SGA plus a First Generation Antipsychotic (FGA) [2,6]. Significant adverse metabolic side effects have been reported in adults and children with the use of antipsychotics, especially with the use of SGAs [3,22]. Compared with adults, children and adolescents appear to be at greater risk of weight gain and metabolic abnormalities when using antipsychotics [23].

Although studies have examined antipsychotic use in the pediatric population [24-30] data on the metabolic adverse events associated with antipsychotic polypharmacy use is limited for pediatrics. In a few observational studies that examined the safety of antipsychotics use in children, the risk of metabolic side effects appeared to increase with multiple antipsychotics use [6,31].

This study addressed the gaps in knowledge and aimed to compare the risk of metabolic adverse events between antipsychotic polypharmacy and antipsychotic monotherapy in a sample of pediatric population obtained from a large national commercially insured population.

Exposure to antipsychotics as well as the intensity of exposure defined by antipsychotic dose and the type of antipsychotic agents (SGA vs. FGA) were examined, all of which were defined as time-varying variables to account for changes in exposure during the one year follow-up period after initiation. We hypothesized that antipsychotic polypharmacy use would be associated with increased risk of metabolic adverse events compared to monotherapy.

## Methods

### Study design and data source

A retrospective cohort design was used. This study utilized a 10% random sample of the PharMetrics Patient-Centric Database (IMS' LifeLink™ Health Plan Claims data obtained from PharMetrics Inc., Watertown, MA), derived from insurance claims of over 98 managed care plans all across United States for over 61 million unique patients. Data from July 1, 1999 to December 31, 2009 were used in this study.

### Patient selection

The study population consisted of new users of antipsychotic medications aged 1-17 years on the date of the first antipsychotic use ("index date") between January 1, 2000 and December 31, 2008. A "new user" was defined as an incident antipsychotic user with no prior exposure in the 180 days before the index date ("pre-index period") and have at least 30 days of cumulative use of any antipsychotics during the one year after the index prescription. Selected subjects must have continuous plan enrollment and pharmacy benefits from 6 months before to 12 months after the index date. A subject was followed from the index date until the occurrence of an adverse metabolic event or the end of one year post-index period ("follow-up period"), whichever occurred first. Patients with pre-existing metabolic condition(s) were excluded.

### Time-varying antipsychotic use

Antipsychotic agents were identified from pharmacy claims using GPI code 59.xx. Exposure to antipsychotic agents was checked for each day of the follow-up period. For each day, the following time-varying exposure variables were defined: any exposure (three levels: no antipsychotic use, antipsychotic monotherapy and antipsychotic polypharmacy), antipsychotic dose (three levels: no use, low dose and high dose), antipsychotic exposure-dose combination (four levels: no use, monotherapy-low dose, monotherapy- high dose and polypharmacy-any dose) and type of antipsychotic agents used (three levels: no use, FGA [with or without SGA], and SGA only). These exposure variables were examined in separate analyses.

Daily antipsychotic exposure was defined by the number of chemically distinct antipsychotic prescriptions with days of supply covering that day. Polypharmacy use was defined as concurrent use of two chemically distinct antipsychotics on the same day. If only one antipsychotic was prescribed for that day, it was considered as monotherapy. To account for potential delayed effect of antipsychotic exposure on metabolic adverse outcomes, antipsychotic exposure time was extended to 30 days after exhausting the days of supply of each antipsychotic prescription.

For each antipsychotic prescription, daily dose was first calculated by dividing the total dose over the days of supply of that prescription. This daily dose was assigned to each day the medication was prescribed. The total daily dose of antipsychotics was then calculated by summing up the average daily dose of all antipsychotic agents prescribed for that day for each patient. Doses of antipsychotics were converted to chlorpromazine equivalent doses, obtained from an international consensus study conducted in 2007-2008 [32]. Per the consensus guideline, the median recommended chlorpromazine dose was 600 mg/day. Based on age, the consensus recommends lowering median daily oral antipsychotic dose by 60% for children (chlorpromazine equivalent dose: 240 mg/day) and by 30% for adolescents (chlorpromazine equivalent dose: 420 mg/day). We used these median daily doses for children (age 1 – 12) and adolescents (age 13 – 17) as cut points to divide daily doses into high dose and low dose.

For the daily exposure-dose combination, we created a time-varying variable differentiating the high and low dose monotherapy and polypharmacy use on each day. Due to limited sample size of polypharmacy use, we were not able to separately assess the risk of metabolic adverse events associated with the high and low dose polypharmacy use. Therefore, polypharmacy at any dose was compared to monotherapy-low dose, monotherapy-high dose and no use.

In addition, given the differential risk of metabolic side effects between FGAs and SGAs, daily exposure to any FGAs (alone or with SGAs) and that to SGAs alone were also compared.

**Outcome events**

The outcome events included the occurrence of metabolic adverse events during the follow-up period. These events were identified using ICD-9-CM diagnoses codes from the inpatient/outpatient claims and medications used specifically for treatment of these conditions: Type II diabetes mellitus (250.x0-250.x2 and antidiabetic agents), obesity or abnormal weight change (278.xx, 783.1, 783.2, and antiobesity agents), dyslipidemia (272.xx and antihyperlipidemic agents). This approach has been used in other studies using claims data [33].

Due to low incidence counts of these adverse events, particularly among polypharmacy users, individual metabolic events were not assessed separately.

**Covariates**

Selection of covariates was undertaken systematically. We started with an exhaustive list of variables that may affect the metabolic outcomes and antipsychotic prescribing based on previous studies and clinical (or pharmacology) textbooks (e.g. Harrison's Principles of Internal Medicine, 18e). The final model included only covariates that were statistically significantly associated with any polypharmacy use (>=1 day overlap in the use of >=2 antipsychotics) at $P<0.05$. Also, for categorical variables, at least 10 cases in each category must be present in order to be retained in the final model. Demographic characteristics and mental health-related characteristics (psychiatric disorder, psychotropic medication use and psychiatric related hospitalization) were forced to be retained in the final model regardless of their statistical significance. Demographic characteristics (age groups [1-6 years, 7-12 years, 13-15 years and 16-17 years], gender, and geographic regions [East, Mid-west, South and West]) were measured on the index date. Pre-existing psychiatric and physical health disorders were assessed during the 6-month pre-index period. Because of the significant overlap in psychiatric diagnoses and psychotropic medication use, psychiatric disorders were defined using a combination of diagnosis (Table S1 for list of ICD-9 codes) and medication use and categorized into seven categories: psychotic disorders, disruptive behavior disorder including Attention-Deficit Hyperactivity Disorder (ADHD) medications use, mood disorder including antidepressants use, pervasive developmental disorder, antianxiety and/or sedatives use, mood stabilizers, and other mental disorders. In addition, the number of different diagnosed psychiatric disorders and the number of different psychotropic medication classes other than antipsychotics (ADHD medications, antianxiety drugs, antidepressant drugs, mood stabilizers and sedative/hypnotics), as well as any psychiatric related hospitalizations during the 6-month pre-index period were included as proxies for the severity of mental health problems. Physical comorbidity burden was measured during the pre-index period and assessed using the Charlson comorbidity score. To control for temporal changes over time, we included indicators for the year of index antipsychotic prescription ("index-year"). Specialty of the most frequently reported provider associated with antipsychotic prescriptions during the one year post-index period was also examined.

**Data analysis**

For descriptive analysis, patients with at least one day of polypharmacy use during the one-year follow-up period were compared to those without any overlapped use. Pearson Chi-square tests were used for comparisons of baseline characteristics across the two groups.

Incident Rate Ratios (IRR) of metabolic adverse events defined as the ratio of the incident rates occurring during the antipsychotic polypharmacy time over the incidence rate during antipsychotic monotherapy time were calculated. As a descriptive analysis, we also calculated the average daily dose of antipsychotics during monotherapy exposure time and that during polypharmacy exposure time. For both analyses, antipsychotic monotherapy time was defined as the days between antipsychotic index date and the date of either antipsychotic polypharmacy initiation, first metabolic event, or the end of the one-year follow-up period, whichever occurred first. Antipsychotic polypharmacy time was calculated as the days between antipsychotic polypharmacy initiation and the date of the first metabolic event or end of the study period, whichever was earliest. If a polypharmacy user experienced an event prior to polypharmacy initiation, no antipsychotic polypharmacy time was counted for that subject. These definitions of antipsychotic monotherapy and polypharmacy exposure times are different from the time-varying exposure time defined earlier, which were used in the multivariate analyses below using time-varying exposure variables.

Multivariate analyses using Cox's regression models examined the association between various time-varying antipsychotic exposure measures described above and metabolic adverse events, adjusting for covariates described earlier. In all comparisons, hazard ratios were reported with no antipsychotic use as the reference group against monotherapy and polypharmacy use/exposure/dose level groups respectively. Wald tests were then used to compare polypharmacy and monotherapy use. To facilitate comparison with previous studies, unadjusted and adjusted analyses using logistic regression and Cox's regression with time in-varying antipsychotic use variables (i.e. any polypharmacy exposure during the one-year follow-up period vs. monotherapy only use) were also conducted.

**Sensitivity analysis**

To account for potential delayed effect of antipsychotic exposure, in the main analysis, we extended antipsychotic exposure time to 30 days after exhausting the days of supply of each antipsychotic prescription. Sensitivity analyses were conducted using different extension windows (0 days [i.e. no time considered exposed beyond prescription supply], 7 days, or 60 days) after exhaustion of each antipsychotic prescription. In the most liberal definition to define polypharmacy exposure, once a person had a day of overlapped use of two or more antipsychotics, all subsequent days were considered as days for polypharmacy use.

For antipsychotic dose, we conducted sensitivity analysis to assess potential delayed effect of antipsychotic dose on adverse events by extending the total daily dose beyond 30 days. The dosing extension windows were hierarchically applied with high-dose extends over the subsequent days with no or low-dose use and low-dose use over no dose days. For instance, days with high-dose exposure will not be affected by the extended dose from a previous prescription. However, for days with low-dose or no exposure, if the previous prescription within 30 days was of high dose, these days were recorded as high-dose exposure days as a result of this extension.

Since polypharmacy use for a short period could represent a switch in therapy rather than polypharmacy, a sensitivity analysis was also conducted by excluding subjects with less than 14 days of overlapped use [34]. This analysis was repeated for all four time-varying antipsychotic use definitions.

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). This study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

## Results

The study identified 3,038 new antipsychotic pediatric users and 88.9% of them used antipsychotic monotherapy throughout the follow-up period. Patients with at least one day of antipsychotic polypharmacy use were more likely to have pre-existing mood disorder (including antidepressants use) or used mood stabilizer medications in the previous 6 months. Increased antipsychotic polypharmacy was also associated with the use of two or more different classes of other psychotropic medications or having three different types of psychiatric disorders (Table 1).

The average daily chlorpromazine-equivalent dose was 385 mg during polypharmacy exposure time. This was nearly three times the average daily dose during low-dose monotherapy exposure time (114 mg) but 25% lower than that during high-dose monotherapy exposure time (516 mg) (Table 2).

Overall, 5.83% of patient experienced a metabolic adverse event within one year after initiation of antipsychotics. The proportion of patients that developed metabolic adverse events trended higher among polypharmacy users, although not statistically significantly different (5.66% vs 7.14% respectively, p=0.2753). Similarly, the incident rates per 1000 person-years trended higher during the polypharmacy time compared to monotherapy time, although remains statistically insignificant (IRR: 1.18; 95% CI: 0.65-1.70) (Table 3).

Cox-regression models with time-varying any antipsychotic exposure variable found no statistically significant effect of antipsychotic polypharmacy exposure or antipsychotic monotherapy exposure on metabolic adverse events compared to no use. Logistic regressions (unadjusted and adjusted) and Cox regression using time-invarying exposure variable found similar results (Table 4, *for complete regression model results refer to supplemental tables S2-S6*).

Cox-regression models with time-varying antipsychotic dose level showed a dose response relationship for metabolic adverse events. Compared to no use, high daily dose of antipsychotics was associated with statistically significant risk of metabolic adverse events (HR: 2.42, CI: 1.35-4.32) (Table 4). Wald test for difference between higher and lower antipsychotic doses were also statistically significant (p= 0.0197).

Cox-regression using time-varying exposure-dose combination variable showed that the risk of metabolic adverse events nearly doubled in antipsychotic high-dose monotherapy use compared to non-exposure (HR: 2.34, CI 1.26-4.36) (Table 4). Polypharmacy use regardless of dose has an equally high hazard of experiencing metabolic side effect compared to no use, although not statistically significant (HR=2.34, CI: 0.85-6.46). Wald test comparing polypharmacy-any dose and high-dose monotherapy shows no statistically significant difference (p=0.9986). However, statistically significant difference for metabolic outcomes were found between low-dose monotherapy compared to high-dose monotherapy (Wald test, p=0.0347).

No statistically significant effect of exposure to FGA (alone or in combination with SGAs) and SGA only were observed for metabolic adverse events (Table 4).

Sensitivity analyses using different extension windows for antipsychotic exposure (0 day, 7 days, 60 days, or the most liberal definition where the time after initiation of antipsychotic polypharmacy use were all attributed to polypharmacy use) or excluding patients with less than 14 days of overlapped use did not materially affect the findings. (Supplemental Tables S2-S6).

Several other factors were statistically significantly associated with metabolic adverse events. Age groups 1-6 years (HR: 0.39, CI: 0.17-0.90) and 7-12 years (OR: 0.63, CI: 0.42-0.97), and western region (HR: 0.55, CI: 0.31-0.97) were associated with lower risk of metabolic adverse events compared to 16-17 years and mid-west region respectively (Supplemental Table S4).

## Discussion

In this study of commercially insured new antipsychotic pediatric users, we found no evidence of differential metabolic adverse events between antipsychotic monotherapy and polypharmacy use. However, risk of metabolic adverse events was found to increase with high daily doses of antipsychotics.

The crude incidence rate of metabolic adverse events was found to be 5.83% within one year of antipsychotic initiation, which was similar to those reported in other studies [6,31]. However, the adjusted hazard ratios of developing metabolic adverse events during monotherapy and polypharmacy exposure time were not statistically significant, but trended towards an increased risk with polypharmacy use.

Previous studies assessing the risk of metabolic adverse events associated with antipsychotic polypharmacy use in pediatric patients were scarce. Two studies of pediatric populations found use of multiple antipsychotics was associated with elevated risk of Type II diabetes, dyslipidemia and weight gain [6,31]. However, differences in study design and analytical methodology prevent a direct comparison with our study: different study populations (Medicaid vs. commercially insured population in our study), different definitions of antipsychotic polypharmacy use (multiple antipsychotics use including both sequential use and concurrent use vs. only overlapped use of two or more antipsychotic agents in our study), nonusers of any psychotropic agents as control groups in their studies. More importantly, unlike previous studies, we defined antipsychotic polypharmacy and monotherapy exposure as time-varying variables to account for changes in antipsychotics use over time. To allow comparison with other studies, we also defined antipsychotic exposure as time-invarying variables but still did not find statistically significant effects of polypharmacy. Larger studies of pediatric populations are needed to confirm our findings.

We found a dose effect antipsychotic exposure on metabolic adverse events. However, this appeared to be mostly attributed to high-dose antipsychotic monotherapy use, which was found to be associated with increased risk of metabolic adverse events compared to no exposure. In this study, the average daily antipsychotics dose prescribed during low-dose and high-dose polypharmacy exposure time were both higher, but did not double the average daily dose during low-dose and high-dose monotherapy exposure time respectively. This finding is consis-

tent with previous literature [35-37] and suggests that polypharmacy may have been employed to reduce the risk of side effect(s) of any individual antipsychotic agents involved by using multiple antipsychotics at lower individual doses [17,38].

Results of this study should be interpreted while considering the following limitations. Due to small sample size, we defined antipsychotic polypharmacy as the use of two or more antipsychotic agents for at least one day. This approach may have included titration period when switching one antipsychotic to another. However, sensitivity analysis by excluding patients with less than 14 days of overlapped use found similar results. The exact duration for the delayed effect of antipsychotic exposure was unknown. We extended the antipsychotic exposure to 30-day post prescription supply in our main analysis but conducted sensitivity analysis with different extension windows and the results were largely consistent. The sample was extracted from a large commercially insured population and therefore the results may not generalize to other pediatric populations or other insurance setting. Outcome events were ascertained based on diagnoses codes or medication use in the medical and pharmacy claims, which are prone to coding errors and misclassification and may understate the metabolic adverse events in our study. Moreover, no details on the inpatient medication use were available, which may have led to underestimation of medication use and potentially antipsychotic polypharmacy use. Pharmacy claims report prescription fills which do not necessarily translate into actual patient use. Additionally, the insurance claims data lacked information on lifestyle factors, race/ethnicity, rural/urban place of residence and genetic composition which may have caused omitted variable bias. Due to the observational study design, these results were only indicative of association between exposure and outcome, if any, and cannot ascertain the direction of causality.

In conclusion, although no increase in the risk of metabolic adverse events was detected with the use of antipsychotic polypharmacy, using high daily doses of antipsychotics was associated with elevated risk for metabolic adverse events. This finding was applicable to both monotherapy and polypharmacy use.

## Acknowledgements

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## Tables

**Table 1:** Baseline characteristics across monotherapy and any polypharmacy treatment groups for metabolic adverse events (N=3038, events=177)

| Variables | Total | Total (%) | Mono-therapy | Mono-therapy (%) | Any poly-pharmacy | Any poly-pharmacy (%) | P |
|---|---|---|---|---|---|---|---|
| **N** | 3038 | 100.00 | 2702 | 88.94 | 336 | 11.06 | |
| **Age group** | | | | | | | |
| 1-6 years | 259 | 8.53 | 228 | 8.44 | 31 | 9.23 | 0.6257 |
| 7-12 years | 1188 | 39.10 | 1049 | 38.82 | 139 | 41.37 | 0.3671 |
| 13-15 years | 876 | 28.83 | 779 | 28.83 | 97 | 28.87 | 0.9883 |
| 16-17 years | 715 | 23.54 | 646 | 23.91 | 69 | 20.54 | 0.1693 |
| **Gender** | | | | | | | |
| Male | 1993 | 65.60 | 1771 | 65.54 | 222 | 66.07 | 0.8478 |
| **Region** | | | | | | | |
| East | 508 | 16.72 | 451 | 16.69 | 57 | 16.96 | 0.8994 |
| Mid-west | 1556 | 51.22 | 1373 | 50.81 | 183 | 54.46 | 0.2068 |
| South | 580 | 19.09 | 523 | 19.36 | 57 | 16.96 | 0.2928 |
| West | 394 | 12.97 | 355 | 13.14 | 39 | 11.61 | 0.4307 |
| **Index year** | | | | | | | |
| 2000-2002 | 355 | 11.69 | 319 | 11.81 | 36 | 10.71 | 0.5569 |
| 2003 | 287 | 9.45 | 244 | 9.03 | 43 | 12.80 | 0.0260 |
| 2004 | 409 | 13.46 | 363 | 13.43 | 46 | 13.69 | 0.8968 |
| 2005 | 418 | 13.76 | 360 | 13.32 | 58 | 17.26 | 0.0481 |
| 2006 | 527 | 17.35 | 466 | 17.25 | 61 | 18.15 | 0.6784 |
| 2007 | 574 | 18.89 | 524 | 19.39 | 50 | 14.88 | 0.0463 |
| 2008 | 468 | 15.40 | 426 | 15.77 | 42 | 12.50 | 0.1178 |
| **Common antipsychotic provider** | | | | | | | |
| Psychiatrist | 827 | 27.22 | 713 | 26.39 | 114 | 33.93 | 0.0034 |
| Pediatrician | 181 | 5.96 | 159 | 5.88 | 22 | 6.55 | 0.6282 |
| Psychologist | 158 | 5.20 | 141 | 5.22 | 17 | 5.06 | 0.9016 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| General practice/family practice | 147 | 4.84 | 135 | 5.00 | 12 | 3.57 | 0.2510 |
| Other | 834 | 27.45 | 743 | 27.50 | 91 | 27.08 | 0.8723 |
| Missing | 891 | 29.33 | 811 | 30.01 | 80 | 23.81 | 0.0185 |
| **Any psychiatric related pre period hospitalization** | | | | | | | |
| Yes | 532 | 17.51 | 466 | 17.25 | 66 | 19.64 | 0.2757 |
| **Mental health (psychiatric disorder and/or psychotropic medication use)** | | | | | | | |
| Psychotic disorder | 243 | 8.00 | 208 | 7.70 | 35 | 10.42 | 0.0832 |
| Disruptive Behavior Disorder (including ADHD medications) | 1872 | 61.62 | 1663 | 61.55 | 209 | 62.20 | 0.8158 |
| Mood Disorder (including Antidepressants) | 1910 | 62.87 | 1670 | 61.81 | 240 | 71.43 | 0.0006 |
| Antianxiety and sedative/ hypnotics | 140 | 4.61 | 125 | 4.63 | 15 | 4.46 | 0.8938 |
| Pervasive developmental disorder | 221 | 7.27 | 191 | 7.07 | 30 | 8.93 | 0.2158 |
| Other mental disorder | 912 | 30.02 | 803 | 29.72 | 109 | 32.44 | 0.3046 |
| Mood stabilizer | 514 | 16.92 | 438 | 16.21 | 76 | 22.62 | 0.0031 |
| **Number of different categories of psychotropic medications taken** | | | | | | | |
| 0 | 762 | 25.08 | 676 | 25.02 | 86 | 25.60 | 0.8181 |
| 1 | 1371 | 45.13 | 1238 | 45.82 | 133 | 39.58 | 0.0303 |
| >=2 | 905 | 29.79 | 788 | 29.16 | 117 | 34.82 | 0.0325 |
| **Number of different categories of psychiatric disorders diagnosed** | | | | | | | |
| 0 | 636 | 20.93 | 569 | 21.06 | 67 | 19.94 | 0.6348 |
| 1 | 11<br>17 | 36.77 | 1005 | 37.19 | 112 | 33.33 | 0.1662 |
| 2 | 828 | 27.25 | 740 | 27.39 | 88 | 26.19 | 0.6422 |
| 3 | 376 | 12.38 | 320 | 11.84 | 56 | 16.67 | 0.0113 |
| >=4 | 81 | 2.67 | 68 | 2.52 | 13 | 3.87 | 0.1467 |
| **Charlson comorbidity score** | | | | | | | |
| 0 | 2741 | 90.22 | 2440 | 90.30 | 301 | 89.58 | 0.6751 |
| 1 | 273 | 8.99 | 243 | 8.99 | 30 | 8.93 | 0.9688 |
| >=2 | 24 | 0.79 | 19 | 0.70 | 5 | 1.49 | 0.1254 |

**Table 2:** Average exposure time and average daily dose of antipsychotics

| Exposure time* | Average Exposure Days | Average Daily Dose (mg/day) |
|---|---|---|
| Monotherapy time (N=3,035) | 173 | 147 |
| Monotherapy low-dose time (N=2,970) | 159 | 114 |
| Monotherapy high-dose time (N=770) | 14 | 516 |
| Polypharmacy time (N=336) | 4 | 385 |
| Polypharmacy low-dose time (N=236) | 2 | 206 |
| Polypharmacy high-dose time (N=161) | 2 | 620 |

*Monotherapy time included the antipsychotic exposure time of polypharmacy users before initiation of polypharmacy. The number of patients contributing to monotherapy low-dose (n=2,970) and high-dose time (n=770) did not add up to the number of patients contributing to overall monotherapy time (n=3,035) because patients may have exposure time of both high and low dose use. This also explains the discrepancy between the number of patients contributing to polypharmacy low-dose and high-dose time respectively and the total patients contributing to overall polypharmacy time.

**Table 3:** Incidence Rate Ratio for Metabolic adverse events

| | Monotherapy | | | Polypharmacy | | | Incidence Rate Ratio (IRR) | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Adverse Events** | No. of New Cases | Time in Person-Years | Incidence Rate Per 1000 Person Per Year | No. of New Cases | Time In Person-Years | Incidence Rate Per 1000 Person Per Year | | |
| **Metabolic** | 162 | 2730.44 | 59.33 | 15 | 215.01 | 69.76 | 1.18 | 0.65-1.70 |

For Non-Cases:- Monotherapy Time= (Polypharmacy Initiation Date - Index Date); Polypharmacy Time=(Follow Up End Date – Polypharmacy Initiation Date)
For Cases Occurring Before Polypharmacy Initiation:- Monotherapy Time = (Event Date – Index Date); Polypharmacy Time=0;
For Cases Occurring After Polypharmacy Initiation:- Monotherapy Time = (Polypharmacy Initiation Date – Index Date); Polypharmacy Time=(Event Date - Polypharmacy Initiation Date);

**Table 4:** Incidence Rate Ratio for Metabolic adverse events

| | |
|---|---|
| **Time invariant Antipsychotic Exposure Definition (Logistic)** | |
| **Exposure (Ref: Monotherapy only)** | **AOR (95% CI)** |
| Any Polypharmacy | 1.20 (0.76-1.90) |
| **Time invariant Antipsychotic Exposure Definition (Cox)** | |
| **Exposure (Ref: Monotherapy only)** | **AHR (95% CI)** |
| Any Polypharmacy | 1.18 (0.76-1.82) |
| **Time Varying Antipsychotic Exposure Definition (Cox)** | |
| **Exposure (Ref: No Use)** | **AHR (95% CI)** |
| Monotherapy | 1.22 (0.87-1.73) |
| Polypharmacy | 1.72 (0.73-4.04) |
| **Time Varying Antipsychotic Dose Definition (Cox)** | |
| **Dose (Ref: No Use)** | **AHR (95% CI)** |
| Low Dose | 1.21 (0.87-1.69) |
| High Dose | 2.42 (1.35-4.32) |
| **Time Varying Antipsychotic Exposure-Dose Definition (Cox)** | |
| **Exposure Dose (Ref: No Use)** | **AHR (95% CI)** |
| Monotherapy Low Dose | 1.20 (0.86-1.68) |
| Monotherapy High Dose | 2.34 (1.26-4.36) |
| Polypharmacy Any Dose | 2.34 (0.85-6.46) |
| **Time Varying Antipsychotic Type Definition (Cox)** | |
| **Type (Ref: No Use)** | **AHR (95% CI)** |
| Any FGA (Alone/With SGA) | 0.89 (0.12-6.45) |
| SGA Only | 1.33 (0.96-1.83) |

AOR=Adjusted Odds Ratio; AHR=Adjusted Hazard Ratio; Ref=Reference group
*All models were adjusted for various patient characteristics.

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