Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study

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This is a study of the metabolic and distal cardiovascular/cerebrovascular outcomes associated with the use of second-generation antipsychotics (SGAs) compared to antidepressants (ADs) in adults aged 18-65 years, based on data from Thomson Reuters MarketScan® Research Databases 2006-2010, a commercial U.S. claims database. Interventions included clinicians' choice treatment with SGAs (allowing any comedications) versus ADs (not allowing SGAs). The primary outcomes of interest were time to inpatient or outpatient claims for the following diagnoses within one year of SGA or AD discontinuation: hypertension, ischemic and hypertensive heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidemia, and obesity. Secondary outcomes included the same diagnoses at last follow-up time point, i.e., not censoring observations at 365 days after SGA or AD discontinuation. Cox regression models, adjusted for age, gender, diagnosis of schizophrenia and mood disorders, and number of medical comorbidities, were run. Among 284,234 individuals, those within one year of exposure to SGAs versus ADs showed a higher risk of essential hypertension (adjusted hazard ratio, AHR=1.16, 95% CI: 1.12-1.21, p<0.0001), diabetes mellitus (AHR=1.43, CI: 1.33-1.53, p<0.0001), hypertensive heart disease (AHR=1.34, CI: 1.10-1.63, p<0.01), stroke (AHR=1.46, CI: 1.22-1.75, p<0.0001), coronary artery disease (AHR=1.17, CI: 1.05-1.30, p<0.01), and hyperlipidemia (AHR=1.12, CI: 1.07-1.17, p<0.0001). Unrestricted follow-up results were consistent with within one-year post-exposure results. Increased risk for stroke with SGAs has previously only been demonstrated in elderly patients, usually with dementia. This study documents, for the first time, a significantly increased risk for stroke and coronary artery disease in a non-elderly adult sample with SGA use. We also confirm a significant risk for adverse metabolic outcomes. These findings raise concerns about the longer-term safety of SGAs, given their widespread and chronic use.

Key words: Second-generation antipsychotics, essential hypertension, diabetes mellitus, hypertensive heart disease, stroke, coronary heart disease, hyperlipidemia

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Second-generation antipsychotics (SGAs) were introduced approximately 20 years ago as supposedly safer and better-tolerated alternatives to first-generation antipsychotics for the treatment of schizophrenia and related disorders (1-3). They have proven to be effective for schizophrenia (4,5), but their use has extended to major mood disorders (6,7) and a broad range of other psychiatric illness (8,9).

The initial optimism about safety was refuted by the well-documented adverse metabolic effects of these drugs (10-13). U.S. Food and Drug Administration (FDA)'s warnings about severe metabolic side effects were followed by the establishment of guidelines for cardiometabolic monitoring in patients prescribed antipsychotics (14). Clinically relevant, unfavorable cardiometabolic effects, including obesity, diabetes mellitus, hypertension, and abnormal blood lipids, were commonly reported across the lifespan, from children and adolescents to the elderly (10,15-18).

However, despite well-documented proximal cardiometabolic side effects that are established risk factors for future cardiovascular and cerebrovascular events, data on the potential adverse cardiovascular and cerebrovascular consequences of SGA use are scarce and, even for high-metabolic risk agents, contradictory (19). Limited and often inconclusive documentation of such adverse events has largely been confined to studies of the elderly, who are closer to experiencing such events but also have a high medication-independent risk profile for myocardial infarction and stroke (20-38).

As the majority of patients receiving SGAs are younger adults, and even children and adolescents (39), we sought to examine the potential detrimental metabolic, cardiovascular, and cerebrovascular effects in a non-elderly adult population. Given that these adverse consequences are very clinically significant but relatively uncommon and require longer-term follow-up, we studied a large sample using a healthcare claims database.

METHODS

Database

We obtained the study data from the Thomson Reuters MarketScan® Research Databases, a commercial U.S. claims

database, for years 2006-2010. This database contains individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. Data for individual patients are integrated from all providers of care, maintaining all healthcare utilization and cost record connections at the patient level.

Patients were excluded from the database for the following reasons: a) no enrollment in 2006; b) enrolled in a health plan that did not capture medication claims nor mental health and substance abuse claims; c) unavailable person level enrollment data, making it impossible to differentiate patients from other enrollees, as well as identify subjects with no claims data; d) age <18 or >65, as the primary sample of interest was non-elderly adults; e) claims in 2006 for any of the medical diagnoses used as outcomes; f) claims for any of the medical diagnoses used as outcomes prior to first observed SGA exposure or antidepressant (AD) treatment; g) follow-up <6 months in 2007-2010; and h) no exposure to SGA or AD treatment in 2007-2010.

The start date for the study was defined as the first exposure to SGA or AD in 2007-2010. The rationale for choosing a minimum of 6-month follow-up from the start date was to allow sufficient time for an outcome of interest to be observed after starting SGAs or ADs. The study end date was defined as a subject's last known date of enrollment in a health plan that captured drug and mental health claims or 365 days after the last exposure to SGA or AD. Subjects were followed through their study end, which allowed different event types to be observed within a subject.

Subjects not enrolled consecutively in a health plan during a year were assumed to have been enrolled for all months prior to their final month of enrollment. Any month skipped between the first and last month of enrollment was assumed to be either an error or that having an outcome of interest during that month was unlikely. Subjects not enrolled in a drug prescription or mental health/substance abuse claims program for consecutive years had their end date defined to be the last date of enrollment in a health plan that captured both drug claims and mental health/substance abuse claims. These observations were censored because we did not know if any outcomes of interest occurred during these periods. Subjects with this pattern of sporadic enrollment in a health plan that captures drug and mental health or substance abuse claims accounted for <1% of the entire sample.

SGA inception cohort

The SGA inception cohort included subjects aged 18-65 years without SGA use and without medical diagnosis claim of any of the outcomes of interest in 2006, i.e., within 12 months prior to the study period (2007-2010), or any point prior to the start of SGAs, and initiating continuous SGA treatment for at least 4 weeks during 2007-2010.

Continuous use was defined as no more than 1 week without use of an SGA (i.e., not having an SGA prescription refilled when the supply of the previous prescription runs out). This assumption was based on the last prescription fill date and the days' supply, which was used to calculate when a prescription should have been refilled. Medication claims for a SGA supply <1 week or >180 days were excluded, as this was deemed either an inappropriate trial or clinically implausible. The use of other concurrent medications, including ADs, was allowed, but not accounted for in this cohort.

Comparison cohort

The comparison cohort included the remaining subjects aged 18-65 years without SGA use, AD use, or a medical diagnosis claim of any of the outcomes of interest in 2006, i.e., within 12 months prior to the study period (2007-2010), or any point prior to the start of ADs. Additionally, patients initiated continuous AD treatment for at least 4 weeks during the study period. Medication claims for an AD supply <1 week or >180 days were excluded. Unlike the SGA cohort, which may have been exposed to ADs, the AD cohort was not exposed to SGAs during the entire study period. The use of other concurrent medications, excluding SGAs, was allowed, but not accounted for in this cohort.

We chose an AD initiator cohort as the comparison group in order to balance background risk factors present in SGA initiators that are based on mental illness and unhealthy lifestyle behaviors, including smoking, which are related to a higher risk for the studied outcomes, all of which have been associated with depression and even AD treatment too (40-42). Moreover, using defined initiation time point in both cohorts allowed us to control for severity of mental disorder, while having a time point of discontinuation allowed us to use the same rule for right-censoring in both groups in the primary analysis.

Outcomes

Primary outcomes of interest were times to inpatient and outpatient claims for the following diagnoses within one year of treatment discontinuation (ICD-9 codes in parentheses): hypertension (401, 402), ischemic and hypertensive heart disease (410, 413, 414), cerebrovascular disease (434, 435), diabetes mellitus (250), hyperlipidemia (272), and obesity (278). Secondary outcomes included the same diagnoses at last follow-up time point, i.e., not censoring the observations at 365 days after the last exposure to either SGAs or ADs, in order to examine the robustness of our findings and allow for longer-term carry over effects.

Statistical analysis

Cox (proportional hazards) regression analysis, censoring patients without an event of interest at 365 days after

Table 1 Sample characteristics

	Total	SGA exposed cohort	AD exposed cohort	p
N	284,234	31,207	253,027	
Age, years±SD	44.46±10.74	44.91±11.16	44.40±10.69	<0.0001
Males, N (%)	83,606 (29.41)	10,224 (32.76)	73,382 (29.00)	<0.0001
Number of medical disorders at baseline, median (Q1, Q3)	5.00 (2.00, 9.00)	7.00 (3.00, 12.00)	5.00 (2.00, 9.00)	
Patient years of follow-up censoring patients 365 days after treatment discontinuation, median (Q1, Q3)	1.49 (1.00, 2.62)	1.55 (1.00, 2.87)	1.48 (1.00, 2.59)	<0.0001
Patient years of follow-up not censoring patients 365 days after treatment discontinuation, median (Q1, Q3)	2.55 (1.62, 3.36)	2.63 (1.62, 3.55)	2.54 (1.62, 3.34)	0.0001
Patient days of treatment exposure, median (Q1, Q3)	180 (60, 480)	150 (60, 420)	180 (60, 480)	<0.0001
Mood disorders diagnosis, N (%)	60,906 (21.43)	22,681 (72.68)	38,225 (15.11)	<0.0001
Schizophrenia diagnosis, N (%)	2,027 (0.71)	1,842 (5.90)	185 (0.07)	<0.0001
SGAs prescribed during the study, N (%)				
Aripiprazole		7,316 (2.57)		
Asenapine		8 (0.00)		
Clozapine		60 (0.02)		
Olanzapine		2,901 (1.02)		
Quetiapine		12,094 (4.25)		
Risperidone		3,362 (1.18)		
Ziprasidone		1,469 (0.52)		
Mixed SGA group (see text)		3,997 (1.41)		

SGA – second-generation antipsychotic, AD – antidepressant, Q1 – quartile 1, Q3 – quartile 3

last exposure to the studied medication or last date of health plan enrollment, was used to separately model each outcome of interest as a function of exposure group (i.e., SGA versus AD). The proportional hazards assumption was evaluated by plotting the log negative log of the survival function by the log of time.

Adverse outcomes that were significantly associated with SGA exposure in the univariable Cox regression analysis were further explored using multivariable Cox regression analysis. The multivariable models included treatment group, age, gender, diagnosis of schizophrenia, diagnosis of mood disorder, and a medical morbidity count. Schizophrenia and mood disorders were identified by inpatient and outpatient claims. The medical morbidity count was generated by summing the number of unique medical diagnoses recorded for each subject in 2006, which was used as a covariate in order to adjust for potential differences between the SGA and AD groups regarding overall medical morbidity, (related) lifestyle behaviors, and/or medical service utilization that could increase the risk for the studied outcomes. By definition, medical comorbidities excluded those used as outcomes, as patients had to be without these diagnoses in 2006 and prior to starting SGAs or ADs.

The above analyses were repeated without censoring subjects 365 days after their last SGA or AD exposure, respectively. In these analyses, the study end was redefined to be the date the respective outcome of interest occurred or the last date of enrollment in a health plan. Again, subjects were only censored for the specific outcome of interest that occurred, being followed for all other outcomes that had not occurred until last date of enrollment in a health plan.

Since individual SGAs differ regarding their short- and medium-term cardiometabolic adverse effect profile (11,13, 15,17,18), we also performed subgroup analyses to evaluate the intermediate metabolic and distal cardiovascular and cerebrovascular risks of the five most frequently used SGAs, i.e., aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Unfortunately, the clozapine and asenapine groups were too small to perform reliable analyses. Whenever more than one SGA was used, a subject was classified based on the SGA that was received for the majority of the study period (i.e., more than two-thirds of a subject's "exposure" to a specific SGA). If no single SGA was received for >67% of the study period, a subject was classified as belonging to the "mixed SGA" group.

RESULTS

The sample (N=284,234) included 83,606 men and 200,628 women, with a mean age of 44.46±10.74 years. Details of the sample are provided in Table 1.

In univariable Cox regression analyses, SGA exposure was associated with a significantly increased risk for all the outcomes of interest (Table 2). In addition to the well-established proximal metabolic risks of SGAs, such as essential

Table 2 Univariable metabolic and cardiovascular risk associated with SGA exposure at one year

Outcome: claims diagnosis	Hazard ratio (95% CI) for SGA users vs. AD users	Chi square	p
Essential hypertension	1.27 (1.23-1.31)	208.1066	<0.0001
Diabetes mellitus	1.73 (1.63-1.83)	335.1633	<0.0001
Obesity	1.24 (1.18-1.32)	56.1796	<0.0001
Stroke	2.12 (1.83-2.45)	99.5837	<0.0001
Hypertensive heart disease	1.56 (1.33-1.84)	28.9700	<0.0001
Myocardial infarction	1.40 (1.13-1.72)	9.8147	0.0017
Angina	1.32 (1.15-1.51)	15.4601	<0.0001
Coronary artery disease	1.52 (1.39-1.67)	82.8166	<0.0001
Transient ischemic attack	1.70 (1.48-1.95)	57.3919	<0.0001
Hyperlipidemia	1.28 (1.24-1.33)	175.9416	<0.0001

SGA – second-generation antipsychotic, AD – antidepressant

hypertension, diabetes mellitus, obesity, and hyperlipidemia, there was a significantly increased risk for myocardial infarction (hazard ratio, HR=1.40, CI: 1.13-1.72), stroke (HR=2.12, CI: 1.83-2.45), angina (HR=1.32, CI: 1.15-1.51), hypertensive heart disease (HR=1.56, CI: 1.33-1.84), coronary artery disease (HR=1.52, CI: 1.39-1.67), and transient ischemic attack (HR=1.70, CI: 1.48-1.95).

In multivariable Cox regression analyses, adjusting for gender, age, schizophrenia, mood disorders, and medical morbidity count, the risk for stroke, hypertensive heart disease and coronary heart disease remained significantly higher in the SGA exposure group (Table 3).

Table 4 presents univariable and multivariable Cox regression analyses for outcomes of interest when participants were not censored at one year, serving as a sensitivity analysis for our primary analyses of outcomes at one year after SGA or AD discontinuation. The univariable analyses were consistent with the results within one year of discontinuation. The multivariable results for the uncensored data (Table 4) were also consistent with the primary results restricting follow-up to 365 days post exposure (Table 3).

Results from the multivariable analyses comparing AD users with clinicians' choice SGA treatment groups are shown in Table 5. Individual antipsychotic groups differed considerably in size, resulting in differences in power to detect significant differences in outcomes compared to AD users. Even despite this confound, patients exposed to olanzapine, quetiapine and mixed antipsychotic use had a higher number of adverse metabolic and cardiovascular outcomes (i.e., 6, 8 and 7 out of the ten examined outcomes) compared to risperidone, aripiprazole and ziprasidone (i.e., 2, 4 and 5 out of ten examined outcomes) (Table 5).

In addition to the risk data presented, the actual incidence rates per 1000 person-years for the outcomes of interest are presented in Table 6.

DISCUSSION

We used a commercial claims database with broad coverage of health insured non-elderly adults in the U.S. to examine the risks associated with SGA use compared to AD use within one year of exposure and without restriction of follow-up after discontinuation during a 4-year period, 2007-2010. Despite exclusion of the elderly, we observed a statistically and clinically significant increased risk with SGA use vs. AD use for proximal cardiometabolic risk factors and outcomes, such as essential hypertension, dyslipidemia, and diabetes mellitus, confirming prior reports (10-16). However, importantly, we also observed an increased risk for distal and generally difficult-to-study cardiovascular (i.e., coronary artery disease) and cerebrovascular (i.e., stroke) outcomes, both with and without restriction of the follow-up period after

Table 3 Multivariable Cox hazard ratios for significant adverse outcomes of interest at one year

Outcome: claims diagnosis	Hazard ratio (95% CI) for SGA users vs. AD users[a]	Hazard ratio (95% CI) for age (10 year increments)	Hazard ratio (95% CI) for gender (male vs. female)	Hazard ratio (95% CI) for medical morbidity count	Hazard ratio (95% CI) for mood disorder	Hazard ratio (95% CI) for schizophrenia
Essential hypertension	1.16 (1.12-1.21)***	1.60 (1.59-1.62)***	1.35 (1.32-1.39)***	1.01 (1.01-1.01)***	0.98 (0.95-1.01)	1.24 (1.12-1.38)***
Diabetes mellitus	1.43 (1.33-1.53)***	1.53 (1.49-1.56)***	1.20 (1.14-1.26)***	1.00 (1.00–1.01)***	1.12 (1.06-1.19)***	1.74 (1.48-2.04)***
Obesity	0.96 (0.89-1.02)	0.92 (0.91-0.94)***	0.56 (0.52-0.58)***	1.01 (1.00–1.01)***	1.51 (1.44-1.58)***	1.46 (1.24-1.72)***
Stroke	1.46 (1.22-1.75)***	1.71 (1.60-1.82)***	1.21 (1.06-1.39)**	1.04 (1.03-1.05)***	1.25 (1.07-1.45)**	1.43 (0.94-2.18)
Hypertensive heart disease	1.34 (1.10-1.63)**	1.70 (1.60-1.81)***	1.58 (1.39-1.80)***	1.02 (1.01-1.03)***	0.98 (0.84-1.16)	1.37 (0.85-2.20)
Myocardial infarction	1.04 (0.82-1.33)	2.15 (1.98-2.35)***	2.72 (2.33-3.18)***	1.03 (1.02-1.04)***	1.20 (0.99-1.45)	0.81 (0.38-1.75)
Angina	1.03 (0.87-1.21)	1.90 (1.80-2.00)***	1.43 (1.29-1.58)***	1.04 (1.03-1.04)***	1.06 (0.93-1.20)	1.00 (0.63-1.60)
Coronary artery disease	1.17 (1.05-1.30)**	2.24 (2.15-2.32)***	2.24 (2.09-2.40)***	1.03 (1.02-1.03)***	1.06 (0.97-1.16)	1.38 (1.06-1.81)*
Transient ischemic attack	1.17 (0.99-1.38)	1.76 (1.66-1.86)***	1.14 (1.01-1.29)*	1.04 (1.04-1.05)***	1.19 (1.04-1.37)*	1.46 (0.98-2.17)
Hyperlipidemia	1.12 (1.07-1.17)***	1.58 (1.56-1.61)***	1.42 (1.38-1.46)***	1.01 (1.01-1.02)***	1.03 (1.00–1.07)	1.21 (1.08-1.36)**

SGA – second-generation antipsychotic, AD – antidepressant
[a]adjusted for gender, age, psychiatric diagnosis and medical morbidity count, *p<0.05, **p<0.01, ***p<0.0001

Table 4 Univariable and multivariable Cox hazard ratios when participants are not censored one year after last medication exposure

Outcome: claims diagnosis	Univariable hazard ratio (95% CI) for SGA users vs. AD users	Multivariable[a] hazard ratio (95% CI) for SGA users vs. AD users
Essential hypertension	1.29 (1.25-1.33)***	1.18 (1.14-1.22)***
Diabetes mellitus	1.67 (1.59-1.76)***	1.39 (1.30-1.48)***
Obesity	1.25 (1.18-1.31)***	0.94 (0.88-0.99)*
Stroke	2.17 (1.90-2.48)***	1.49 (1.26-1.75)***
Hypertensive heart disease	1.60 (1.38-1.85)***	1.39 (1.17-1.66)**
Myocardial infarction	1.49 (1.19-1.81)**	1.01 (0.79-1.29)
Angina	1.34 (1.19-1.51)***	1.05 (0.91-1.21)
Coronary artery disease	1.54 (1.42-1.67)***	1.18 (1.07-1.31)**
Transient ischemic attack	1.80 (1.59-2.04)***	1.25 (1.08-1.46)**
Hyperlipidemia	1.27 (1.23-1.32)***	1.11 (1.06-1.15)***

SGA – second-generation antipsychotic, AD – antidepressant
[a]adjusted for gender, age, psychiatric diagnosis and medical morbidity count, *p <0.05, **p<0.01, ***p<0.0001

medication discontinuation. Each of these findings was confirmed and consistent even when age, gender, and medical morbidity were taken into account.

The risk for stroke in subjects on SGAs has received substantial attention (22-38). Most, but not all, studies documented an increased risk for stroke in SGA users; however, without exception, these studies included elderly subjects (generally ≥65 years) (22-38), and most focused on patients with dementia (22-38). To the best of our knowledge, the present study is the first documentation of a clinically significant increase in stroke risk, as well as coronary artery disease risk, in a younger population (mean age=44.46 years) receiving SGAs. While increasing age, male gender and medical morbidity also significantly contributed to the risk for stroke and coronary artery disease, these additional risk factors did not detract from the risk increase associated with SGA exposure.

Our examination of long-term adverse outcomes by individual SGA or mixed SGA group has to be considered very preliminary and interpreted with caution. Reasons for this include the vastly different sample sizes of the individual SGA groups, making it more likely to show a significant difference compared to AD users the larger the sample size per subgroup was. In this context, it is notable that olanzapine (N=2,901) and mixed SGAs (N=3,997), which were among the smallest groups, were also among the three treatments with the highest number of adverse metabolic and cardiovascular effects. Conversely, although aripiprazole (N=7,316) was prescribed to the second highest number of patients, it was in the lower risk group, together with risperidone (N=3,362) and ziprasidone (N=1,469), for which power was much lower and may have been insufficient to detect a significant difference compared to AD users. However, the non-random treatment assignment is an even larger confounding factor. Clinician's choice treatment with SGAs is vulnerable to a channeling bias, i.e., the preferential use of lower risk agents in higher risk patients and vice versa. In any case, these data underscore the need to establish which antipsychotics may possess lower short- and, particularly, long-term cardiovascular and cerebrovascular risk. Such studies need to be sufficiently large and avoid or control for channeling bias.

The strength of a healthcare claims database is the ability to study large numbers of subjects who are not restricted to those consenting to participate in research over a relatively long duration of time. This may have allowed for our observation of increased cardiovascular and cerebrovascular risk in this younger population, which may not be evident in smaller clinical samples.

Table 5 Multivariable Cox hazard ratios for significant adverse outcomes of interest by SGA risk group

Outcome: claims diagnosis	Hazard ratio (95% CI) for aripiprazole (N=7,316) vs. ADs	Hazard ratio (95% CI) for olanzapine (N=2,901) vs. ADs	Hazard ratio (95% CI) for quetiapine (N=12,094) vs. ADs	Hazard ratio (95% CI) for risperidone (N=3,362) vs. ADs	Hazard ratio (95% CI) for ziprasidone (N=1,469) vs. ADs	Hazard ratio (95% CI) for mixed SGAs (N=3,997) vs. ADs
Stroke	0.95 (0.65-1.39)	1.60 (1.06-2.41)*	1.60 (1.26-2.01)***	1.71 (1.15-2.54)**	1.05 (0.54-2.05)	1.64 (1.16-2.32)**
Obesity	1.14 (1.01-1.28)*	0.80 (0.66-0.97)*	0.86 (0.78-0.94)**	0.86 (0.71-1.02)	1.08 (0.88-1.34)	1.09 (0.95-1.24)
Diabetes mellitus	1.22 (1.06-1.40)**	1.38 (1.16-1.60)**	1.36 (1.23-1.50)***	1.61 (1.37-1.89)***	1.78 (1.44-2.20)***	1.73 (1.51-1.98)***
Essential hypertension	1.00 (0.93-1.08)	1.17 (1.06-1.28)**	1.24 (1.18-1.31)***	1.05 (0.95-1.15)	1.25 (1.10-1.43)**	1.25 (1.15-1.35)***
Hyperlipidemia	1.09 (1.01-1.19)*	1.20 (1.08-1.33)**	1.08 (1.02-1.15)*	1.01 (0.90-1.13)	1.27 (1.10-1.46)**	1.23 (1.12-1.35)***
Hypertensive heart disease	1.12 (0.76-1.66)	1.18 (0.72-1.93)	1.39 (1.07-1.81)*	0.90 (0.52-1.58)	1.74 (0.97-3.12)	1.92 (1.34-2.75)**
Angina	0.51 (0.34-0.77)**	1.05 (0.70-1.56)	1.24 (1.01-1.53)*	0.61 (0.36-1.02)	2.02 (1.34-3.05)**	1.09 (0.78-1.54)
Myocardial infarction	0.84 (0.51-1.41)	1.67 (1.04-2.68)*	1.15 (0.83-1.59)	0.63 (0.30-1.34)	0.40 (0.10-1.61)	1.03 (0.60-1.76)
Coronary artery disease	0.88 (0.70-1.11)	1.20 (0.94-1.55)	1.27 (1.10-1.46)*	1.03 (0.78-1.35)	1.36 (0.96-1.92)	1.30 (1.04-1.63)*
Transient ischemic attack	0.80 (0.56-1.14)	1.13 (0.75-1.71)	1.21 (0.97-1.51)	1.13 (0.75-1.71)	1.64 (1.02-2.61)*	1.47 (1.07-2.00)**

SGA – second-generation antipsychotic, ADs – antidepressants, *p <0.05, **p<0.01, ***p<0.0001

Table 6 Incidence of events per 1000 person-years

Outcome	SGA users (cases per 1,000 person-years)	AD users (cases per 1,000 person-years)
Essential hypertension	79.2	62.7
Diabetes mellitus	23.4	13.5
Obesity	23.2	18.5
Stroke	3.7	1.8
Hypertensive heart disease	2.9	1.8
Myocardial infarction	1.7	1.2
Angina	4.0	3.0
Coronary artery disease	9.3	6.1
Transient ischemic attack	4.1	2.4
Hyperlipidemia	59.1	46.0

SGA – second-generation antipsychotic, AD – antidepressant

Nevertheless, database studies also have limitations. These include the non-randomized treatment groups, naturalistic treatment setting and lack of information about unhealthy lifestyle behaviors, including smoking. In order to reduce the effect of unhealthy lifestyle behaviors and other background risk factors that we were unable to measure, we used a psychiatric control group in an inception cohort design, choosing AD use as our control. We made this choice because both depression and ADs have been associated with metabolic syndrome and its components as well as with distal adverse cardiovascular and cerebrovascular outcomes (40-42). However, since patients receiving SGAs and ADs may differ in specific risk factors for the outcomes under investigation, we used covariates in the Cox regression analyses to adjust for potentially relevant differences. Covariates included traditional risk factors, such as gender and age. In addition, we adjusted the analyses for a primary diagnosis of schizophrenia or mood disorder as well as for a medical comorbidity count. Notably, while each of these covariates was significantly related to the outcomes of interest, the higher risk in SGA users persisted even when adjusting for these variables.

Another limitation is lacking information about the duration and severity of the current illness episode. However, to mitigate against this problem, we used the inception cohort design focusing on patients with illness severity prompting clinicians to initiate treatment with an SGA or AD. Additionally, while the treatment was clinician and patient driven, the naturalistic database approach ensures greater generalizability of the findings than in controlled trials, that ordinarily also have higher attrition rates.

Further, we did not have body mass index and laboratory data available, so that the diagnoses, particularly of more proximal cardiometabolic risk factors and metabolic outcomes, may be an underestimate. In this context, we cannot fully rule out a surveillance bias in that SGA treated patients may have had more measurements of body weight and laboratory parameters than AD treated patients. However, although monitoring guidelines exist for SGAs (14,43), they are notoriously seldom followed, and several studies failed to observe any change in monitoring after the warning about metabolic effects of SGAs by the FDA and guideline development and promulgation (44). Nevertheless, even if a surveillance bias may have led to a greater detection of cardiovascular risk factors and metabolic outcomes, the cardiovascular and cerebrovascular outcomes are much less dependent on detection bias and diagnoses are not made by laboratory testing, which strengthens our results.

A further limitation is that data were only available from 2006 to 2010, and that 2006 through the first date of SGA or AD exposure was used as a "baseline period". Therefore, we do not have any details of medical history on subjects included in our study prior to 2006. We used an absence of drug claims for SGAs and ADs in 2006 as a proxy for no past SGA and AD use. Although it is possible that our study subjects could have used SGAs prior to 2006, this fact would only bias towards the null hypothesis, as the AD group could have had carry over effects from prior SGA use. Further, although we "only" had a 2-year median follow-up, even this still relatively short observation period was sufficient to demonstrate significant elevations of risk for both proximal and more distal cardiovascular and cerebrovascular risk factors and endpoints, which adds to the concern regarding the widespread use of SGAs, especially for off-label conditions (8,9).

Cigarette smoking is a risk factor for both cardiovascular and cerebrovascular disease. It is also more common in people with a psychiatric diagnosis and who are on psychotropic medicines (45). Moreover, smoking rates are generally reported to be higher in schizophrenia than in subjects with mood disorders (46). Our database did not allow us to obtain smoking information by subject, so that the effect of cigarette smoking as a confounding factor cannot be definitively excluded. However, the fact that the risk for SGAs versus ADs held even when the diagnoses of schizophrenia and mood disorders were entered as covariates into the analyses, strengthens our results as not likely being attributable to a differential frequency of cigarette smoking.

In the U.S., increased use of SGAs over the last 20 years has been clearly documented (8,39). SGAs are effective for psychotic and mood disorders (4-7); however, they are also widely used for numerous off-label conditions (8,9,39), and an ever-increasing number of patients is being prescribed this class of psychotropic agents without appropriate monitoring (44). Our data suggest that the risks associated with SGA use extend beyond the adverse metabolic risks that are well-known (10-18). It is highly likely that the increased risk for major cerebrovascular and cardiovascular events we observed is a downstream consequence of these well-documented metabolic risks (13,15). Greater care should be exercised in monitoring and mitigating the adverse metabolic consequences of SGAs, even in a younger population, and these medications should be used with greater caution, especially in conditions for which a sufficient evidence base for efficacy and safety is missing.

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The first two authors contributed equally to this work.

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