Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Antipsychotics and stroke risk

Lockwood G. Taylor, PhD, MPH

Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
FDA

August 28, 2017

Disclosure

- No relationships to disclose

- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Background

2 Classes of Antipsychotics (APs)

Typical Antipsychotic Drugs (APs)

1. Compazine (prochlorperazine)
2. Haldol (haloperidol)
3. Loxitane (loxapine)
4. Mellaril (thioridazine)
5. Moban (molindone)
6. Navane (thiothixene)
7. Orap (pimozide)
8. Prolixin (fluphenazine)
9. Stelazine (trifluoperazine)
10. Thorazine (chlorpromazine)
11. Trilafon (perphenazine)

Atypical Antipsychotic Drugs (APs)

1. Aripiprazole (Abilify)
2. Asenapine Maleate (Saphris)
3. Clozapine (Clozaril)
4. Iloperidone (Fanapt)
5. Lurasidone (Latuda)
6. Olanzapine (Zyprexa)
7. Olanzapine/Fluoxetine (Symbyax)
8. Paliperidone (Invega)
9. Quetiapine (Seroquel)
10. Risperidone (Risperdal)
11. Ziprasidone (Geodon)

https://www.fda.gov/Drugs/DrugSafety/ucm124830.htm
https://www.fda.gov/Drugs/DrugSafety/ucm094303.htm

Background

Labels of 3 atypical APs have a warning for stroke in elderly demented patients based on RCTs; no stroke warnings for typical or other atypical APs

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Background

Evidence from epi studies conducted in the elderly suggests users of typical APs may have higher stroke risk than users of atypical APs[1-3*]; increased risk specifically for haloperidol in some studies[2,4*]

Particularly among elderly or patients with dementia

*See references slide

Regulatory questions

- Do non-elderly/non-demented users of typical APs have a higher risk of stroke compared to users of atypical APs?

- Does the increased risk of stroke observed in RCTs of atypical APs (in elderly dementia patients) also exist in the non-elderly and non-demented?

Objectives

1. Evaluate stroke risk among new users of typical APs compared to new users of atypical APs
2. Assess stroke risk among SSRI users initiating atypical APs compared to SSRI users initiating z-hypnotics*

* Z-hypnotics: non-benzodiazepine hypnotics zolpidem, eszoplicone, zaleplon used in treatment of insomnia

Objectives

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* Z-hypnotics: non-benzodiazepine hypnotics zolpidem, eszoplicone, zaleplon used in treatment of insomnia

Design Overview

Design	• Retrospective new user cohort • 13 Sentinel Data Partners, Jan 2001-Sep 2015
Exposure	• New users of typical APs vs. new users of atypical APs
Outcome	• Ischemic or hemorrhagic stroke • Primary inpatient diagnosis
Inclusion	• 18-64 years old • 6 months prior continuous insurance eligibility
Exclusion	• Use of any APs in previous 183 days, history of dementia, cancer, or past stroke

Analysis

Follow-up

- Duration of exposure episode (30-day gap)

Censoring

- First occurrence of outcome, Rx for comparator, disenrollment, death, or end of query period

Analysis

- Cox proportional hazards
- 1:1 propensity score matching
- Included patient demographics, medical history/comorbidity variables, medication use history, and health service utilization variables
- **Secondary analyses: 1-15 days, 16-90 days, haloperidol only**

Baseline Characteristics
Unmatched & Matched Cohorts

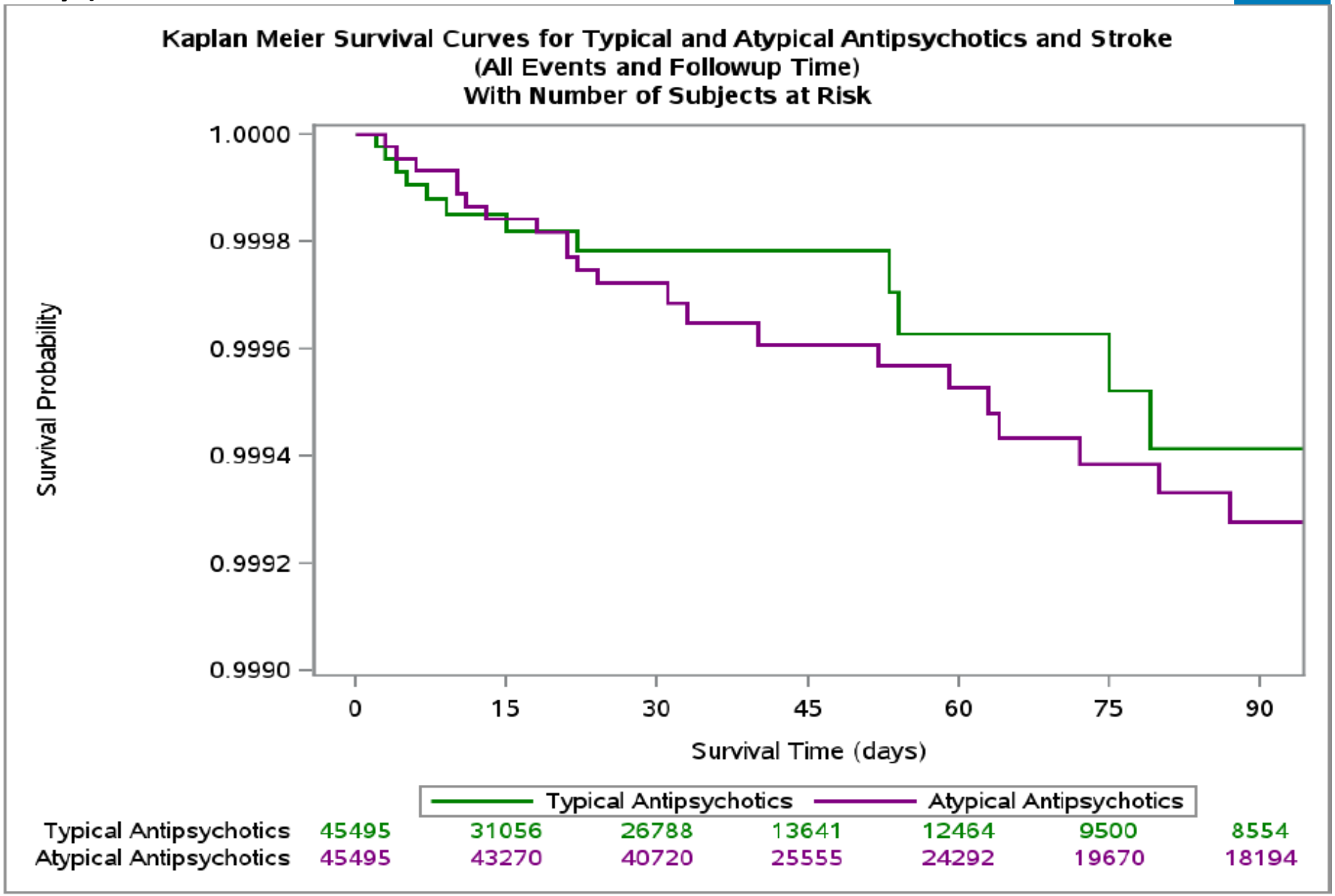
	Unmatched			Matched		
Selected characteristics	**Typical AP N (%/SD*)**	**Atypical AP N (%/ SD*)**	**Std Diff**	**Typical AP N (%/ SD*)**	**Atypical AP N (%/ SD*)**	**Std Diff**
Total	45,576	806,611		45,495	45,495	
Mean age	44.0 (12.6*)	39.9 (12.8*)	0.324	44.0 (12.6*)	44.2 (12.7*)	-0.020
Female	21,206 (46.5)	489,469 (60.7)	-0.287	21,194 (46.6)	20,987 (46.1)	0.009
Afib/flutter	648 (1.4)	4,745 (0.6)	0.084	620 (1.4)	660 (1.5)	-0.007
AMI	899 (2.0)	7,789 (1.0)	0.084	879 (1.9)	928 (2.0)	-0.008
Diabetes	5,226 (11.5)	52,950 (6.6%)	0.172	5,182 (11.4)	5,393 (11.9)	-0.014
HTN	9,800 (21.5)	120,258 (14.9)	0.171	9,754 (21.4)	9,886 (21.7)	-0.007
Renal failure	1,869 (4.1)	11,495 (1.4)	0.164	1,817 (4.0)	1,855 (4.1)	-0.004
Depression	10,603 (23.3)	324,387 (40.2)	-0.370	10,586 (23.3)	10,860 (23.9)	-0.014
Schizophrenia	5,687 (12.5)	56,550 (7.0)	0.185	5,676 (12.5)	5,998 (13.2)	-0.021
ACE-inhibitor	6,152 (13.5)	75,035 (9.3)	0.132	6,125 (13.5)	6,228 (13.7)	-0.007
Beta-blockers	5,786 (12.7)	76,471 (9.5)	0.103	5,753 (12.6)	5,857 (12.9)	-0.007
Oral anti-coagulants	1,025 (2.2)	9,540 (1.2)	0.082	993 (2.2)	981 (2.2)	0.002
Statins	6,787 (14.9)	91,915 (11.4)	0.104	6,762 (14.9)	6,928 (15.2)	-0.010
Mean #AMB encounter	8.7 (11.1*)	9.5 (10.4*)	-0.071	8.7 (11.1*)	8.7 (10.7*)	-0.005
Mean # IP encounter	0.4 (1.0*)	0.3 (0.7*)	0.149	0.4 (1.0*)	0.4 (1.1*)	0.003

Stroke Risk for Antipsychotics (AP):

Overall, 1-15 days, 16-90 days, Haloperidol only

	Unmatched (site adjusted-only)				1:1 matched			
	# Exposed	Person years	# Events	HR (95% CI)	# Exposed	Person years	# Events	HR (95% CI)
Overall								
Typical AP	45,576	10,125.82	25	1.75 (1.17-2.63)	45,495	10,113.92	25	**0.87 (0.54-1.41)**
Atypical AP	806,611	338,987.22	396	1 (Ref)	45,495	20,646.19	53	1 (Ref)
1-15 days after exposure								
Typical AP	45,576	1,534.75	7	3.06 (1.37-6.83)	45,495	1,532.82	7	**1.16 (0.41-3.32)**
Atypical AP	806,611	32,431.81	42	1 (Ref)	45,495	1,829.06	7	1 (Ref)
16-90 days after exposure								
Typical AP	30,204	3,109.76	6	1.23 (0.54-2.80)	30,186	3,107.76	6	**0.52 (0.20-1.36)**
Atypical AP	757,812	96,228.27	124	1 (Ref)	30,186	3,885.00	14	1 (Ref)
Haloperidol only								
Haloperidol	13,882	3,369.51	9	1.80 (0.93-3.48)	13,841	3,366.33	9	**1.31 (0.54-3.21)**
Atypical AP	801,275	336,212.38	397	1 (Ref)	13,841	6,482.65	11	1 (Ref)

Figure 1. Kaplan Meier survival curves for propensity score-matched analysis (90 days)



Objectives

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2. Assess stroke risk among SSRI users initiating atypical APs compared to SSRI users initiating z-hypnotics*

* Z-hypnotics: non-benzodiazepine hypnotics zolpidem, eszoplicone, zaleplon used in treatment of insomnia

Design Overview

Design	• Retrospective cohort • 13 Sentinel Data Partners, Jan 2001-Sep 2015
Exposure	• Prevalent SSRI users who add an atypical AP vs. prevalent SSRI users adding z-hypnotic
Outcome	• Ischemic or hemorrhagic stroke • Primary inpatient diagnosis
Inclusion	• Baseline SSRI users 18-64 years old • 6 months prior continuous insurance eligibility
Exclusion	• Use of antipsychotics or z-hypnotics in previous 183 days, history of dementia or past stroke

Analysis

Follow-up	• Duration of exposure episode (30-day gap)
Censoring	• First occurrence of outcome, Rx for comparator, disenrollment, death, or end of query period
Analysis	• Cox proportional hazards • 1:1 propensity score matching • Included patient demographics, medical history/comorbidity variables, medication use history, health service utilization variables, pre-index SSRI use (1-60, 61-120, 121-183 days) • Included SSRI duration variable separately in regression model • **Secondary analyses: 1-15 days, 16-90 days, specific atypical APs**

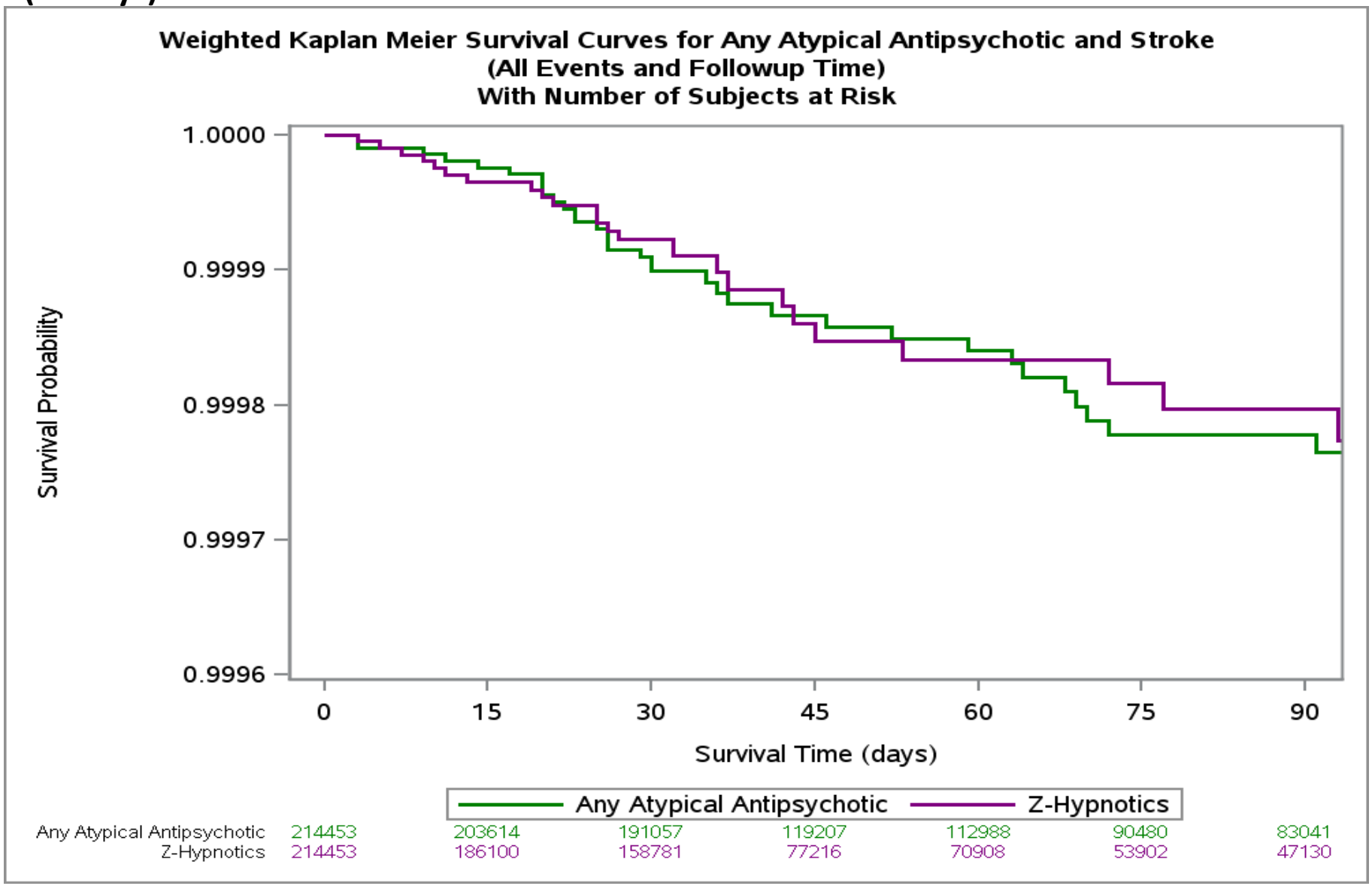
Baseline Characteristics
Unmatched & Matched Cohorts

	Unmatched			Matched		
Selected characteristics	**Atypical AP + SSRI, N(%/ SD*)**	**Z-hypnotic + SSRI, N(%/ SD*)**	**Std Diff**	**Atypical AP + SSRI, N(%/SD*)**	**Z-hypnotic + SSRI, N(%/SD*)**	**Std Diff**
Total	303,428	516,456		214,453	214,453	
Mean age	39.7 (12.8*)	44.5 (11.7*)	-0.394	41.2 (12.7*)	41 (11.9*)	0.014
Female	193,290 (63.7)	366,656 (71.0)	-0.156	142,088 (66.3)	140,843 (65.7)	0.012
Afib/flutter	1,777 (0.6)	4,196 (0.8)	-0.027	1,342 (0.6)	1,371 (0.6)	-0.002
AMI	3,132 (1.0)	5,898 (1.1)	-0.011	2,252 (1.1)	2,279 (1.1)	-0.001
Diabetes	20,860 (6.9)	36,123 (7.0)	-0.005	15,066 (7.0)	15,106 (7.0)	-0.001
HTN	46,214 (15.2)	77,703 (15.0)	0.005	32,026 (14.9)	31,913 (14.9)	0.001
Renal failure	4,283 (1.4)	7,639 (1.5)	-0.006	3,010 (1.4)	3,094 (1.4)	-0.003
Depression	148,561 (49.0)	122,338 (23.7)	0.545	86,010 (40.1)	89,428 (41.7)	-0.032
Schizophrenia	16,995 (5.6)	2,236 (0.4)	0.306	3,186 (1.5)	2,195 (1.0)	0.042
ACE-inhibitor	30,016 (9.9)	59,992 (11.6)	-0.056	22,966 (10.7)	22,776 (10.6)	0.003
Beta-blockers	30,197 (10.0)	54,968 (10.6)	-0.023	22,287 (10.4)	22,308 (10.4)	0
Oral anti-coagulants	3,697 (1.2)	9,650 (1.9)	-0.053	2,974 (1.4)	3,053 (1.4)	-0.003
Statins	36,564 (12.1)	86,498 (16.7)	-0.134	29,409 (13.7)	29,137 (13.6)	0.004
Mean #AMB encounter	9.9 (10.6*)	8.2 (8.9*)	0.176	9.2 (9.7*)	9.3 (9.3*)	-0.009
Mean # IP encounter	0.3 (0.8*)	0.2 (0.6*)	0.261	0.2 (0.7*)	0.2 (0.6*)	0.007

Stroke Risk for Atypical Antipsychotics (APs) vs. z-hypnotics, adjusted for duration of SSRI use

	Unmatched (site-adjusted only)				1:1 matched			
	# Exposed	Person years	# Events	HR (95% CI)	# Exposed	Person years	# Events	HR (95% CI)
Overall								
Atypical AP + SSRI	303,428	121,662.27	147	0.89 (0.70-1.13)	214,453	85,129.30	112	**1.31 (0.93-1.84)**
Z-hyp + SSRI	516,456	131,308.61	144	1 (Ref)	214,453	52,090.92	49	1 (Ref)
1-15 days								
Atypical AP + SSRI	303,428	12,156.06	11	0.74 (0.35-1.56)	214,453	8,600.55	5	**0.71 (0.23-2.25)**
Z-hyp + SSRI	516,456	20,055.07	20	1 (Ref)	214,453	8,297.13	7	1 (Ref)
16-90 days								
Atypical AP + SSRI	286,586	36,596.09	45	0.88 (0.58-1.32)	192,817	24,316.00	32	**1.33 (0.76-2.33)**
Z-hyp + SSRI	438,894	43,234.33	51	1 (Ref)	192,817	19,349.82	20	1 (Ref)

Figure 2. Kaplan Meier survival curves for propensity score-matched analysis (90 days)



Stroke Risk by Specific Atypical Antipsychotic vs. z-hypnotics, adjusted for duration of SSRI use

	1:1 matched			
	# Exposed	**PY**	**# Events**	**HR (95% CI)**
Olanzapine + SSRI	43,701	13,659.80	30	**1.70 (0.90-3.23)**
Z-hypnotic + SSRI	43,701	10,241.36	14	1 (Ref)
Quetiapine + SSRI	104,686	35,899.06	45	**1.24 (0.76-2.03)**
Z-hypnotic + SSRI	104,686	24,527.88	25	1 (Ref)
Risperidone + SSRI	52,179	17,583.98	28	**1.10 (0.59-2.05)**
Z-hypnotic + SSRI	52,179	12,033.37	16	1 (Ref)
Aripiprazole + SSRI	67,052	21,427.12	20	**1.45 (0.69-3.06)**
Z-hypnotic + SSRI	67,052	15,761.67	11	1 (Ref)
Olanzapine + fluoxetine	12,197	3,716.62	7	**2.07 (0.51-8.44)**
Z-hypnotic + fluoxetine	12,197	2,858.66	3	1 (Ref)

Discussion

- No significant associations found in either analysis
  - Typical vs atypical APs: crude increased HR adjusted away with 1:1 propensity-score matching
  - Atypical vs z-hypnotics: modestly, but non-significant, increased HRs
  - Increased risk not ruled out completely
- Event rates low in non-elderly population
- 1:1 propensity-score matching reduced sample size and precision of estimates
  - Trade-off with improved confounding adjustment
- Did not assess subgroup risk by age group, dose

Discussion

- From regulatory perspective, study results do not warrant labeling stroke risk for non-elderly/non-demented patients taking APs

- Discussions on implications of study results on epidemiologic studies of stroke risk in elderly and/or demented AP users are ongoing

Conclusion

- Results from two studies of antipsychotic users informed regulatory question regarding labeling by suggesting that the increased stroke risk previously observed in the elderly/demented may not exist in the non-elderly/non-demented population

- FDA benefited from Sentinel studies, which allowed for assessment of rare outcome in specific population

References

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2. Hsieh P, Hsiao F, Gau S, et al. Use of antipsychotics and risk of cerebrovascular events in schizophrenic patients: A nested case-control study. J Clin Psychopharmacol. 2013; 33(3): 299-305.
3. Wang S, Schneeweiss S, Setoguchi S, et al. Ventricular arrhythmias and cerebrovascular events in the elderly using conventional and atypical antipsychotic medications. J of Clin Psychopharmacol. 2007; 27: 707-710.
4. Shin JY, Choi NK, Lee J, Park MJ, Lee SH, Park BJ. A comparison of risperidone and haloperidol for the risk of ischemic stroke in the elderly: a propensity score-matched cohort analysis. J Psychopharmacol. 2015;29:903-9.

Acknowledgements

FDA

- Andy Mosholder
- Michael Nguyen

Sentinel

- Jane Huang
- Megan Reidy
- Genna Panucci
- Darren Toh

Many thanks are due to the Data Partners who provided the data used in this analysis

Backup slides

Typical vs atypical APs

Typical APs

- CHLORPROMAZINE HCL
- FLUPHENAZINE
- HALOPERIDOL
- LOXAPINE
- MOLINDONE
- PERPHENAZINE
- PERPHENAZINE/AMITRIPTYLINE
- THIORIDAZINE
- THIOTHIXENE
- TRIFLUOPERAZINE

Atypical APs

- ARIPIPRAZOLE
- ASENAPINE
- BREXPIPRAZOLE
- CARIPRAZINE
- CLOZAPINE
- ILOPERIDONE
- LURASIDONE
- OLANZAPINE
- OLANZEPINE/FLUOXETINE
- PALIPERIDONE
- QUETIAPINE
- RISPERIDONE
- ZIPRASIDONE

Existing antipsychotic labeling for stroke

Aripiprazole

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis [see also BOXED WARNING].

Olanzapine

Cerebrovascular Adverse Events (CVAE), Including Stroke— Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Patient Counseling Information (17.2)].

Risperidone

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL ® is not approved for the treatment of patients with dementia-related psychosis.[See also Boxed Warnings and Warnings and Precautions (5.1)]

SSRI and Z-hypnotics

Z-hypnotics

- ESZOPICLONE
- ZALEPLON
- ZOLPIDEM

SSRIs

- CITALOPRAM
- ESCITALOPRAM
- FLUOXETINE
- FLUVOXAMINE
- PAROXETINE
- SERTRALINE
- VILAZODONE
- VORTIOXETINE

Stroke codes

- 433.01 Diagnosis ICD-9-CM Occlusion and stenosis of basilar artery with cerebral infarction
- 433.11 Diagnosis ICD-9-CM Occlusion and stenosis of carotid artery with cerebral infarction
- 433.21 Diagnosis ICD-9-CM Occlusion and stenosis of vertebral artery with cerebral infarction
- 433.31 Diagnosis ICD-9-CM Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
- 433.81 Diagnosis ICD-9-CM Occlusion and stenosis of other specified precerebral artery with cerebral infarction
- 433.91 Diagnosis ICD-9-CM Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
- 434.01 Diagnosis ICD-9-CM Cerebral thrombosis with cerebral infarction
- 434.11 Diagnosis ICD-9-CM Cerebral embolism with cerebral infarction
- 434.91 Diagnosis ICD-9-CM Cerebral artery occlusion, unspecified, with cerebral infarction
- 436 Diagnosis ICD-9-CM Acute, but ill-defined, cerebrovascular disease
- 430 Diagnosis ICD-9-CM Subarachnoid hemorrhage
- 431 Diagnosis ICD-9-CM Intracerebral hemorrhage

P-score variables for typical vs atypical APs

The following covariates were assessed during the baseline period and were included in the propensity score:

age, year, sex, comorbidity score, health service utilization, drug utilization, the following medical conditions: acute myocardial infarction, diabetes, heart failure, hypercholesterolemia, hypertension, kidney failure (acute or chronic), obesity, transient ischemic attack, atrial fibrillation or atrial flutter, peripheral vascular disease, coagulation defects, and cardiovascular disease, the following psychiatric conditions: anxiety, bipolar disorder, depression, posttraumatic stress disorder, schizophrenia/psychotic disorder, and substance abuse, and use of the following drugs: angiotensin-converting-enzyme (ACE) inhibitor, antiarrhythmic, beta-blocker, statin, oral anticoagulant, non-oral anticoagulant, angiotensin receptor blocker, antiplatelet, and diuretic.

Table 1b. Cohort of New Initiators of Typical Antipsychotics and Atypical Antipsychotics (Matched, Aggregated), Ratio = F, Caliper = 0.05

Characteristic	Medical Product				Covariate Balance	
	Typical Antipsychotics		Atypical Antipsychotics			
	N/Mean	%/Std Dev[1]	N/Mean	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients (N)	45,495	99.8%	45,495	5.6%	-	-
Patient Characteristics						
Mean age	44.0	12.6	44.2	12.7	-0.255	-0.020
Age: 18-64	45,495	100.0%	45,495	100.0%	0	-
Gender (Ambiguous)	-	0.0%	-	0.0%	0	-
Gender (Female)	21,194	46.6%	20,987	46.1%	0.455	0.009
Gender (Male)	24,299	53.4%	24,503	53.9%	-0.448	-0.009
Gender (Unknown)	2	0.0%	5	0.0%	-0.007	-0.008
Recorded history of:						
Prior Combined Comorbidity Raw Score	0.9	1.5	0.9	1.5	-0.014	-0.010
Atrial Fibrillation and Flutter	620	1.4%	660	1.5%	-0.088	-0.007
Acute Myocardial Infarction	879	1.9%	928	2.0%	-0.108	-0.008
Coagulation Defects	287	0.6%	279	0.6%	0.018	0.002
Diabetes	5,182	11.4%	5,393	11.9%	-0.464	-0.014
Heart Failure	1,131	2.5%	1,160	2.5%	-0.064	-0.004
Hypercholesterolemia	5,689	12.5%	5,856	12.9%	-0.367	-0.011
Hypertension	9,754	21.4%	9,886	21.7%	-0.290	-0.007
Kidney Failure	1,817	4.0%	1,855	4.1%	-0.084	-0.004
Obesity	2,499	5.5%	2,582	5.7%	-0.182	-0.008
Other Cardiovascular Disease	889	2.0%	882	1.9%	0.015	0.001
Peripheral Vascular Disease	831	1.8%	831	1.8%	0.000	0.000
Transient Ischemic Attack	121	0.3%	116	0.3%	0.011	0.002
Anxiety	7,763	17.1%	8,033	17.7%	-0.593	-0.016
Bipolar	6,215	13.7%	6,427	14.1%	-0.466	-0.013
Depression	10,586	23.3%	10,860	23.9%	-0.602	-0.014
Posttraumatic Stress Disorder	1,355	3.0%	1,472	3.2%	-0.257	-0.015
Schizophrenia	5,676	12.5%	5,998	13.2%	-0.708	-0.021
Substance Abuse	6,468	14.2%	6,652	14.6%	-0.404	-0.012
History of use:						
ACE-inhibitors	6,125	13.5%	6,228	13.7%	-0.226	-0.007
Antiarrhythmics	357	0.8%	385	0.8%	-0.062	-0.007
Non-oral Anticoagulant	579	1.3%	576	1.3%	0.007	0.001
Oral Anticoagulant	993	2.2%	981	2.2%	0.026	0.002
Antiplatelets	991	2.2%	1,068	2.3%	-0.169	-0.011
Angiotensin Receptor Blockers	2,062	4.5%	2,149	4.7%	-0.191	-0.009
Beta Blockers	5,753	12.6%	5,857	12.9%	-0.229	-0.007
Diuretics	5,331	11.7%	5,414	11.9%	-0.182	-0.006
Statins	6,762	14.9%	6,928	15.2%	-0.365	-0.010
Health Service Utilization Intensity:						
Mean number of ambulatory encounters (AV)	8.7	11.1	8.7	10.7	-0.057	-0.005
Mean number of emergency room encounters (ED)	0.9	1.9	0.9	2.3	0.010	0.005
Mean number of inpatient hospital encounters (IP)	0.4	1.0	0.4	1.1	0.003	0.003
Mean number of non-acute institutional encounters (IS)	0.1	0.6	0.1	0.5	0.002	0.004
Mean number of other ambulatory encounters (OA)	2.0	5.1	2.0	5.3	-0.004	-0.001
Mean number of filled RX	16.6	18.8	16.7	17.5	-0.092	-0.005
Mean number of generics	6.8	6.2	6.9	5.9	-0.036	-0.006
Mean number of unique drug classes	6.1	5.3	6.2	5.0	-0.081	-0.016

[1]Value represents standard deviation where no % follows the value

P-score variables for atypical APs + SSRI vs Z-hypnotics + SSRI

The following covariates were assessed during the baseline period and were included in the propensity score:

Age, year, sex, comorbidity score, health service utilization, drug utilization, the following medical conditions: acute myocardial infarction, diabetes, heart failure, hypercholesterolemia, hypertension, kidney failure (acute or chronic), obesity, transient ischemic attack, atrial fibrillation or atrial flutter, cancer (excluding non-melanoma cancer), peripheral vascular disease, coagulation defects, and cardiovascular disease, the following psychiatric conditions: anxiety, bipolar disorder, depression, posttraumatic stress disorder, schizophrenia/psychotic disorder, and substance abuse, and use of the following drugs: angiotensin-converting-enzyme (ACE) inhibitor, antiarrhythmic, beta-blocker, statin, oral anticoagulant, non-oral anticoagulant, angiotensin receptor blocker, antiplatelet, diuretic, and pre-index SSRI/Fluoxetine use categorized into 3 levels of duration (1-60 days, 61-120 days, 121-184 days).

Table 1a. Cohort of New Initiators of Any Atypical Antipsychotics and Z-hypnotic with Pre-Index SSRI Use (Unmatched, Aggregated), Ratio: 1:1, Caliper: 0.05[1]

Characteristic	Medical Product				Covariate Balance	
	Any Atypical Antipsychotics + SSRI		Z-hypnotic + SSRI			
	N/Mean	%/Std Dev[2]	N/Mean	%/Std Dev[2]	Absolute Difference	Standardized Difference
Patients (N)	303,428	100.0%	516,456	100.0%	-	-
Demographics						
Mean age	39.7	12.8	44.5	11.7	-4.829	-0.394
Age: 18-64	303,428	100.0%	516,456	100.0%	0	-
Gender (Ambiguous)	1	0.0%	-	0.0%	0	-
Gender (Female)	193,290	63.7%	366,656	71.0%	-7.293	-0.156
Gender (Male)	110,117	36.3%	149,765	29.0%	7.292	0.156
Gender (Unknown)	20	0.0%	35	0.0%	0	0
Pre-index SSRI Use:						
SSRI Day Supply: 1-60 days	109,801	36.2%	184,607	35.7%	0.442	0.009
SSRI Day Supply: 61-120 days	46,690	15.4%	82,190	15.9%	-0.527	-0.014
SSRI Day Supply: 121-184 days	146,937	48.4%	249,659	48.3%	0.085	0.002
Combined comorbidity index, CCI[3]:						
Prior Combined Comorbidity Raw Score	1	1.3	0.5	1.3	0.443	0.338
Recorded history of medical conditions[4]:						
Atrial Fibrillation and Flutter	1,777	0.6%	4,196	0.8%	-0.227	-0.027
Acute Myocardial Infarction	3,132	1.0%	5,898	1.1%	-0.110	-0.011
Cancer	4,829	1.6%	18,053	3.5%	-1.904	-0.121
Coagulation Defects	913	0.3%	1,782	0.3%	-0.044	-0.008
Diabetes	20,860	6.9%	36,123	7.0%	-0.120	-0.005
Heart Failure	3,334	1.1%	6,358	1.2%	-0.132	-0.012
Hypercholesterolemia	28,153	9.3%	57,550	11.1%	-1.865	-0.062
Hypertension	46,214	15.2%	77,703	15.0%	0.185	0.005
Kidney Failure	4,283	1.4%	7,639	1.5%	-0.068	-0.006
Obesity	13,749	4.5%	21,766	4.2%	0.317	0.015
Other Cardiovascular Disease	3,066	1.0%	6,659	1.3%	-0.279	-0.026
Peripheral Vascular Disease	2,354	0.8%	4,501	0.9%	-0.096	-0.011
Transient Ischemic Attack	571	0.2%	916	0.2%	0.011	0.003
Anxiety	98,819	32.6%	81,372	15.8%	16.812	0.401
Bipolar	54,743	18.0%	14,101	2.7%	15.311	0.518
Depression	148,561	49.0%	122,338	23.7%	25.273	0.545
Posttraumatic Stress Disorder	15,805	5.2%	6,603	1.3%	3.930	0.223
Schizophrenia	16,995	5.6%	2,236	0.4%	5.168	0.306
Substance Abuse	53,029	17.5%	20,854	4.0%	13.439	0.444
History of use[5]:						
ACE-Inhibitors	30,016	9.9%	59,992	11.6%	-1.724	-0.056
Angiotensin Receptor Blockers	10,412	3.4%	28,556	5.5%	-2.098	-0.102
Antiarrhythmics	1,201	0.4%	3,037	0.6%	-0.192	-0.027
Antiplatelets	3,935	1.3%	8,859	1.7%	-0.418	-0.034
Beta Blockers	30,197	10.0%	54,968	10.6%	-0.691	-0.023
Diuretics	26,669	8.8%	55,544	10.8%	-1.966	-0.066
Non-oral Anticoagulant	1,993	0.7%	5,542	1.1%	-0.416	-0.045
Oral Anticoagulant	3,697	1.2%	9,650	1.9%	-0.650	-0.053
Statins	36,564	12.1%	86,498	16.7%	-4.698	-0.134
Health Service Utilization Intensity:						
Mean number of ambulatory encounters (AV)	9.9	10.6	8.2	8.9	1.712	0.176
Mean number of emergency room encounters (ED)	0.7	1.6	0.4	1.1	0.359	0.261
Mean number of inpatient hospital encounters (IP)	0.3	0.8	0.2	0.6	0.147	0.216
Mean number of non-acute institutional encounters (IS)	0.1	0.5	0	0.4	0.049	0.119
Mean number of other ambulatory encounters (OA)	1.8	4.1	1.8	4.1	-0.012	-0.003
Mean number of filled RX	18	17.0	16.7	15.4	1.267	0.078
Mean number of generics	7.2	5.4	6.9	5.0	0.363	0.069
Mean number of unique drug classes	6.5	4.6	6.3	4.3	0.280	0.063

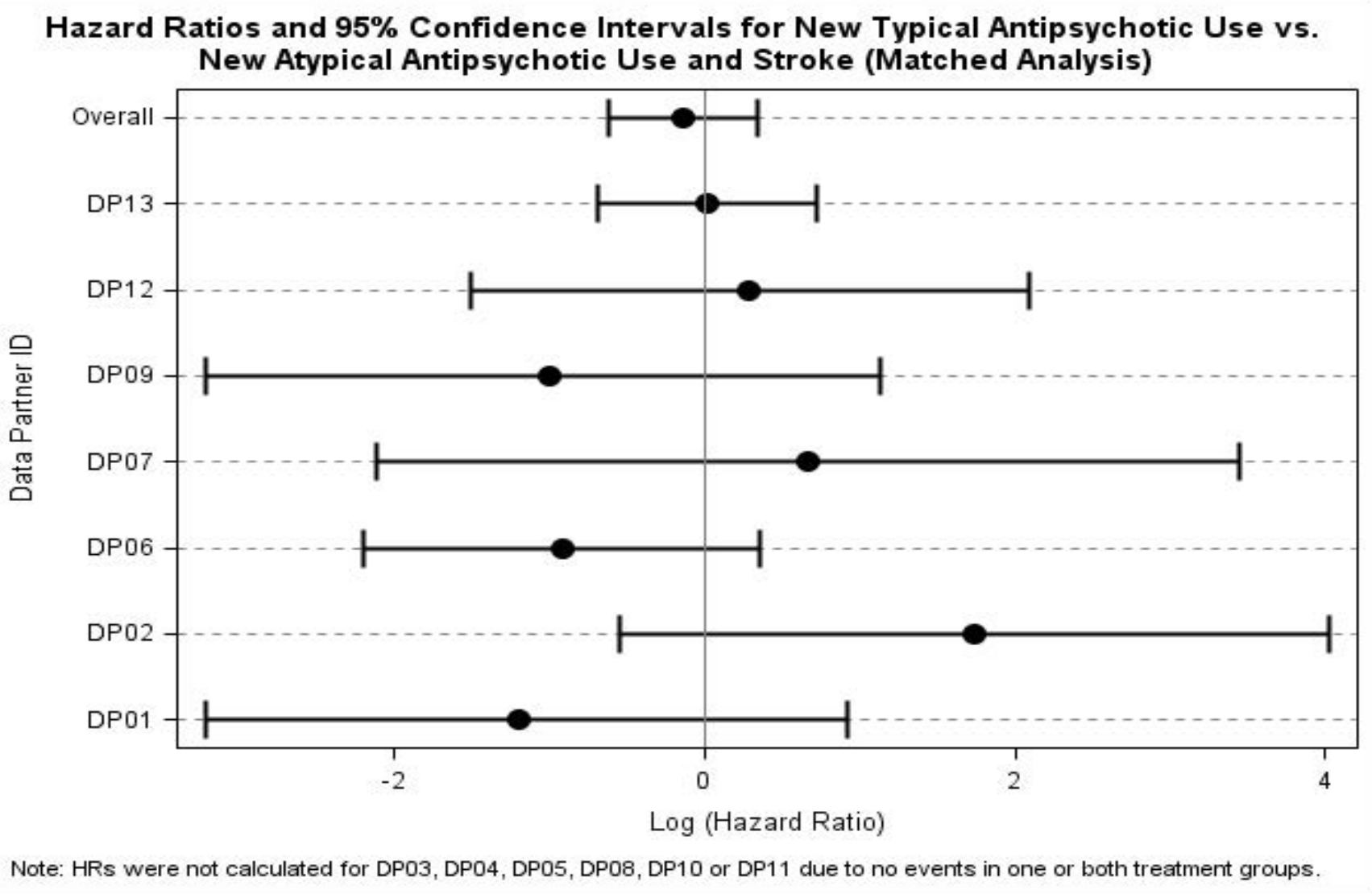
[1]Cohort for sensitivity analysis with risk window = 1-15 days is same as that for primary analysis of all atypical antipsychotics

[2]Value represents standard deviation where no % follows the value

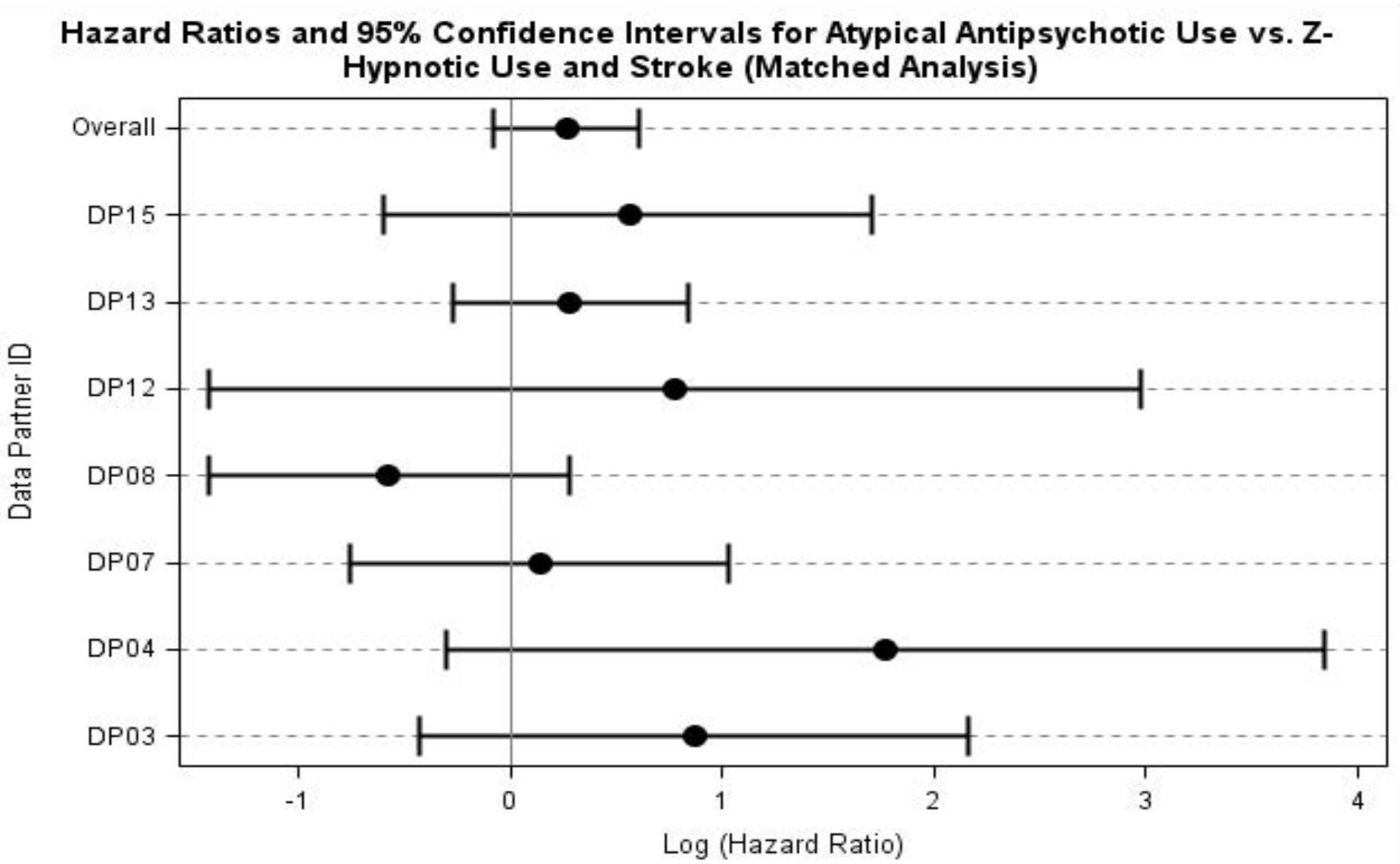
[3]See https://www.ncbi.nlm.nih.gov/pubmed/21208778

[4]Medical Conditions, including psychiatric conditions, are defined as >= 1 procedure/diagonsis code in IP, ED, or IS setting or >=2 procedure/diagonsis codes (on separate dates) in AV or OA settings in previous 183 days.

[5]Drug Use defined as at least 1 dispensing in the previous 183 days. Additional diagnostic and procedural codes (from any care setting) were used to identify anticoagulant use.



Note: HRs were not calculated for DP03, DP04, DP05, DP08, DP10 or DP11 due to no events in one or both treatment groups.



Note: HRs were not calculated for DP01, DP02, DP05, DP06, DP09, DP10, DP11, or DP14 due to no events in one or both treatment groups.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