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Original Study

Antipsychotics and the Risk of Cerebrovascular Accident: A Systematic Review and Meta-Analysis of Observational Studies

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A B S T R A C T

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stroke
dementia

Background: Studies investigating the association between antipsychotic use and the risk of cerebrovascular accident (CVA) showed inconsistent results.

Aim: Conduct a systematic review and meta-analysis to evaluate whether use of antipsychotics is associated with increased risk of CVA.

Methods: Major electronic databases were searched from 1970 to October 2016 for observational studies investigating the risk of CVA among users of antipsychotics. Pooled estimates of odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by random effects meta-analysis.

Results: Of 1171 citations identified, 10 studies were considered eligible. Significant increase in risk of CVA was associated with first-generation antipsychotics (OR 1.49; 95% CI 1.24–1.77) but not with second-generation antipsychotics (OR 1.31; 95% CI 0.74–2.30). Use of any antipsychotics in patients with dementia was associated with a low risk of CVA (OR 1.17; 95% CI 1.08–1.26).

Conclusions: The available evidence suggests use of with first-generation antipsychotics as opposed to second-generation antipsychotics significantly increased the risk of CVA.

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Use of antipsychotics among the public continues to rise around the world.^{1–5} Increases in national antipsychotic utilization were seen in the United States from 1995 to 2008 and in England from 1998 to 2010.^{1,4} Throughout much of the world, the prescribing indication for antipsychotics is principally for schizophrenia, but these medications are commonly prescribed for a broad range of diseases other than

schizophrenia. Such diseases include psychotic and affective disorders, personality and anxiety disorders, and agitation in dementia.^{5,6} The rise in the use of antipsychotics is alarming as several life-threatening adverse effects have been reported with their use.

Studies have linked the use of antipsychotic medications to adverse metabolic events, adverse cardiovascular events, and even death.^{6–13} In addition, the use of antipsychotics has been associated with an increased risk of cerebrovascular accidents (CVAs) in a number of studies and systematic reviews; however, with conflicting evidence in the literature, this association remains controversial.^{14,15} Until recently, the positive correlation between antipsychotic use and risk of CVA was primarily seen in elderly adults, particularly those with dementia.^{16–19} It is unclear whether use of antipsychotics in the general population is also associated with increased risk of cerebrovascular events. In addition, the risk of CVA reported in the literature varies considerably depending on the type of antipsychotic used. A

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number of studies have shown a higher risk of CVA associated with typical or first-generation antipsychotics (FGAs) compared with atypical or second-generation antipsychotics (SGAs),^{6,16,20} others have suggesting the opposite,^{21,22} and some studies have even indicated no difference between the 2 classes.^{23–25} Despite the controversy in the available evidence, the US Food and Drug Administration issued a boxed warning on the increased risk of death and cerebrovascular events when FGAs are used for the off-label indication of dementia.²⁶

Given the contradicting nature of the evidence, we conducted a systematic review and meta-analysis to determine whether use of antipsychotics is associated with an increased risk of CVA.

Methods

Search Strategy

We performed this study in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Ethical Committee approval was not required for the meta-analysis. We searched PubMed and EMBASE for published studies from 1970 to October 2016 that explored the risk of CVA associated with use of antipsychotic medications. The search terms included “antipsychotic,” “anti psychotic,” “antipsychotic drugs,” “Chlorpromazine,” “Haloperidol,” “Bromperidol,” “Fluphenazine,” “Zuclopenthixol,” “Pentixol,” “Flupentixol,” “Levopromazine,” “Perphenazine,” “Pimozide,” “Penfluridol,” “Sulpiride,” “Amisulpride,” “Amoxapine,” “Asenapine,” “Aripiprazole,” “Blonanserine,” “Clozapine,” “Iloperidone,” “Melperone,” “Olanzapine,” “Risperidone,” “Paliperidone,” “Quetiapine,” “Sertindole,” “Lurasidone,” “Ziprasidone,” “cerebrovascular accidents,” “cerebrovascular disorders,” “ischemic stroke,” “hemorrhagic stroke,” “transient ischemic attack,” and “stroke.” Antipsychotics include FGAs and SGAs based on the US Food and Drug Administration drug classification.^{27–29} We used “cerebrovascular disorders,” “ischemic stroke,” “transient ischemic attack,” “TIA,” “hemorrhagic stroke,” “stroke,” and “brain infarction” as the search terms for the outcomes of interests. We did not set restrictions on geography or language, and we did not seek unpublished investigations. Two investigators (W. H., C. L.) independently examined all titles and abstracts and obtained full texts of potentially relevant articles. Following the database search, a review of the abstracts was conducted to rule out the studies that involved case reports, case series, reviews, editorials, clinical trials, systematic reviews, meta-analyses, or clinical guidelines. To be eligible for inclusion, studies must have met the following criteria: (1) observational study with a control group, (2) nonuse of any antipsychotic served as a reference group, (3) reported data on CVA outcomes, and (4) offered sufficient data to construct risk estimates. The same cohort reported in different articles was evaluated to include the most recent publication. Publications by the same author or group of authors were also carefully investigated to exclude overlapping cohorts or results. The most recent study results were included for further meta-analysis. We abstracted data from full-text articles using structured review forms, and disagreements were resolved by consensus meetings.

Data Extraction and Quality Assessment

For all studies, we extracted information on the first author's surname, year of publication, country, study design, sources of database, sociodemographics, sample sizes, case numbers, duration of study, exposure, outcomes of interests, crude and adjusted effect sizes as available, and matching and confounding factors. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of included studies.³⁰ Studies awarded more than 6 stars were considered high quality, and 9 stars represented the highest quality.

Data Synthesis

Our primary measure of interest was the pooled odds ratio (OR) of CVA related to the exposure of any antipsychotics. Secondary measures of interest were exposure to FGAs or SGAs compared with nonusers. Subgroup analyses were conducted for the following subgroups: elderly population, population with dementia, case-control study design, and population-based study design. Pooled ORs were estimated by the Mantel-Haenszel method.³¹ Publication bias was assessed using the Begg adjusted rank correlation test and the Egger regression asymmetry test. The Begg adjusted rank correlation test was used to measure the correlation between estimates of treatment effect and variances. Similarly, the Egger asymmetry test is a regression of the standardized treatment effects on the standard errors. For both methods, a significant result suggests correlation between effect size and estimates of precision which would be evidence of publication bias. Visual assessment was conducted by constructing funnel plots. A funnel plot is a scatter plot of the effect measure estimate on the horizontal axis vs the standard error of the effect estimate on the vertical axis. The plot should form a pyramid in the absence of bias.^{32,33} To assess consistency and evaluate heterogeneity, we calculated the I^2 statistic. A fixed-effect model was used for I^2 less than 50%, whereas random-effects model was used for studies with I^2 greater than 50%.^{34,35} All meta-analyses were performed using Stata statistical software v 12 (StataCorp, College Station, TX).

Results

Study Selection and Characteristics

The number of articles excluded and the reasons for exclusion of each individual article are reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1). Our search strategy yielded 1171 references, 23 of which were considered eligible for full-text review. Of these, we excluded 9 studies for the reasons reported in the Figure 1. Finally, 10 articles met the inclusion criteria and were included in the meta-analysis. These 10 studies^{16,19,25,36–42} included 16,993 CVA cases from 5 case-control studies,^{16,19,36–38} 1 case-case-time-control,⁴⁰ 1 self-control case series study,⁴¹ 1 cross-sectional study,²⁵ and 2 cohort studies.^{39,42} Nine of the studies identified patients from administrative

Fig. 1. PRISMA flow-diagram for selection of articles for meta-analysis.

databases,^{16,19,36–42} whereas 1 study used an electronic health record (Table 1).²⁵ All studies included adult participants, 8 of which focused on elderly patients,^{16,19,36–39,41,42} and 5 of which included patients with dementia.^{16,19,38,41,42} Characteristics of individual studies are summarized in Table 1.

Study Quality

Quality evaluation by the NOS is summarized in Table 2. All included studies used appropriate design. The studies varied with respect to their exposure and case definitions. Current use of FGAs or SGAs was the most frequent measure of exposure, whereas other studies further classified drug use into recent or past users, high-dose or low-dose users, and short-term or long-term users. All 10 included studies used the definition of CVA provided by the *International Classification of Diseases, Ninth Revision, Clinical Modification* or *International Classification of Diseases, Tenth Revision, Clinical Modification* as their main outcome. Only 1 study performed CVA diagnosis validation from reviewed medical records.⁴² The studies also varied in

the adjusted covariates. All studies comprehensively adjusted for potential confounders in their analysis. In terms of overall quality, 5 studies received 9 stars and 4 studies received 8 stars when evaluated using NOS, indicating low risk of bias (Table 2).

Antipsychotics and Risk of CVA

Nine out of 10 studies examined the pooled use of both FGAs and SGAs (Table 3). Combining FGAs and SGAs, use of any antipsychotics was associated with an increased risk of CVA [OR 1.45; 95% confidence interval (CI) 1.24–1.70; $I^2 = 91.0\%$]^{16,19,25,36–38,40–42} (Figure 2A). Restricting the analysis to only population-based studies, use of any antipsychotics was still associated with an increased CVA risk (OR 1.51; 95% CI 1.20–1.91; $I^2 = 93.3\%$).^{16,19,25,36,37,40} Seven studies investigated the use of any antipsychotics in the elderly population, and a similar increase in CVA risk was observed (OR 1.49; 95% CI 1.25–1.77; $I^2 = 89.1\%$).^{16,19,36–38,41,42} However, only 4 studies evaluated the use of any antipsychotics in dementia patients and the results showed a low risk of CVA (OR 1.17; 95% CI 1.08–1.26; $I^2 = 0\%$).^{16,19,38,42} Five studies

Table 1
Characteristics of Included Studies

Authors (Location, Year)	Setting and Study Population	Sample Size	Exposure	Outcome Definition and Case Ascertainment	Adjustment in Multivariate Analysis
Liperoti et al ³⁸ (USA, 2005)	SAGE database, age older than 65 years	4788 (case 1130)	FGAs and SGAs	Hospital claim for ischemic stroke and transient ischemic attack identified by ICD-9-CM	Comorbidity, age, sex, ethnicity, concomitant medications, body mass index, activities of daily living scale score, Cognitive Performance Scale score, behavior index score
Douglas et al ⁴¹ (UK, 2008)	UK-based General practice research database	6790	FGAs and SGAs	Diagnosis of stroke in the database identified by ICD-10-CM	Self-control case series
Sacchetti E et al ³⁹ (Italy, 2008)	HSD, age older than 65 years	74,162 (case 2507)	FGAs and SGAs except aripiprazole and ziprasidone	Hospital claim for stroke identified by ICD-9-CM; stroke, hemiparesis or hemiplegia registered in the HSD during the follow-up	Comorbidity, chronic disease score, age, sex, indication of use for an antipsychotic, use of drugs during follow-up
Kleijer et al ³⁶ (The Netherlands, 2009)	PHARMO (The PHARMCO Institute, Utrecht, The Netherlands), PRISMANT (previously known as the Dutch Centre for Healthcare Information [LMR database]) database, age older than 50 years	26,157 (case 518)	FGAs and SGAs, current, recent past and past use	Hospital claim for ischemic or hemorrhagic stroke identified by ICD-9-CM	Comorbidity, medications, age, sex, type of antipsychotics (high- or low-central α 1-adrenoreceptor affinity, high- or low-central α 1-adrenoreceptor affinity)
Chan et al ⁴² (Hong Kong, 2010)	Hospital-based database, age older than 65 years	1089 (case 107)	FGAs and SGAs	Cerebrovascular adverse events validated by medical records	Comorbidity, age, sex, medications (benzodiazepine, antidepressants)
Laredo et al ¹⁶ (UK, 2011)	UK-based General Practice Research Database, age older than 65 years	18,762 (case 3149)	FGAs and SGAs	Hospital claim for cerebrovascular accident identified by ICD-9-CM	Sociodemographics (age, sex), myocardial infarction, mitral stenosis, atrial fibrillation, heart failure, diabetes mellitus, hyperlipidemia, hypertension, obesity, anticoagulants, platelet inhibitors, lipid-lowering drugs, oral hypoglycemic agents, insulin, and antihypertensive drugs
Wang et al ⁴⁰ (USA, 2012)	Veterans Health Administration Database	14,671 (case 511)	FGAs and SGAs	Ischemic stroke identified by ICD-9-CM, validated by Reker et al's high specificity stroke diagnostic code algorithm	Unmeasured time-invariant confounders, exposure-time trends, medications
Hsieh et al ³⁷ (Taiwan, 2013)	National Health Insurance Research Database of Taiwan	9715 (case 386)	FGAs and SGAs, current, recent and past use	Hemorrhagic stroke, ischemic stroke, or transient ischemic attack identified by ICD-9-CM	Comorbidity, medications
Liu et al ¹⁹ (Taiwan, 2013)	National Health Insurance Research Database, aged older than 65 years	2243 (case 811)	FGAs and SGAs	Hospital claim for stroke identified by ICD-9-CM	Age, sex, monthly income, geographic region, hypertension, diabetes
Mundet-Tudurí et al ²⁵ (Spain, 2013)	Electronic health record from 51 primary care centers in Barcelona, aged between 18 and 95 years old	27,811 (case 1084)	FGAs and SGAs	Diagnosis of stroke in the database identified by ICD-10-CM	Sociodemographics (age, sex), clinical characteristics (comorbidity, co-medications), smoking, BMI, blood pressure, blood sugar, HDL cholesterol, LDL cholesterol, triglycerides

BMI, body mass index; HDL, high-density lipoprotein; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification; LDL, low-density lipoprotein; UK, United Kingdom; HSD, Health Search Database; SAGE, Systematic assessment of geriatric drug use via epidemiology.

Table 2
Quality Assessment of Included Studies Based on the NOS

Authors (Location, Year)	Selection (Design)	Comparability	Exposure	Outcome	Total NOS Stars
Liperoti et al ³⁸ (USA, 2005)	★★★	★★	★★★		8 High quality study
Sacchetti et al ³⁹ (Italy, 2008)	★★★	★★		★★★	8 High quality study
Kleijer et al ³⁶ (The Netherlands 2009)	★★★★	★★	★★★		9 High quality study
Chan et al ⁴² (Hong Kong, 2010)	★★★★	★★		★★★	9 High quality study
Laredoet al ¹⁶ (UK, 2011)	★★★★	★★	★★★		9 High quality study
Wang et al ⁴⁰ (USA, 2012)	★★★★	★★	★★★		9 High quality study
Hsieh PH et al ³⁷ (Taiwan, 2013)	★★★	★★	★★★		8 High quality study
Liu et al ¹⁹ (Taiwan, 2013)	★★★★	★★	★★★		9 High quality study

used case-control design and the remaining studies used other designs.^{16,19,36–38} Restricting analysis to case-control studies showed an attenuated but significant risk of CVA with antipsychotic use (OR 1.28; 95% CI 1.12–1.47; $I^2 = 59.0\%$).

In addition, studies were evaluated to determine whether CVA risk differs between FGAs and SGAs (Figure 2B and C). Use of FGAs was associated with a significant increase in risk of CVA (OR 1.48; 95% CI 1.24–1.77; $I^2 = 85.2\%$), but use of SGAs had an attenuated and nonsignificant risk of CVA (OR 1.31; 95% CI 0.74–2.30; $I^2 = 94.8\%$). Excluding studies that used hospital patients as their control showed an increased risk of CVA with FGAs (OR 1.95; 95% CI 1.12–3.37; $I^2 = 38.2\%$)^{16,36,37} but not with SGAs (OR 1.15; 95% CI 0.46–2.87; $I^2 = 97.6\%$).^{16,37,39} The subgroup analyses that evaluated all studies without dementia patients showed increased risk of CVA for both FGAs (OR 1.97; 95% CI 1.42–2.73; $I^2 = 38.2\%$) and SGAs (OR 1.69; 95% CI 0.79–3.63; $I^2 = 97.8\%$).^{25,36,37,39–41}

Publication Bias

The test for publication bias did not yield significant results in 3 main medication categories. The results of the Egger test indicated no evidence of publication bias in both FGA and SGA users ($P = .72$), which was consistent with the Begg test ($P = .76$). Among FGA users, no significant evidence of potential publication bias was noted using the Begg test ($P = .46$) and Egger test ($P = .63$). The Begg test of SGAs suggested no significant evidence of potential publication bias ($P = 1.00$) (Table 4). Funnel plots of the 3 main exposure categories are

shown in Figure 3. These plots present no clear asymmetry and support the results of the aforementioned tests.

Discussion

We reviewed the literature and quantitatively summarized the existing observational studies that evaluated the association between antipsychotic use and CVA risk. A total of 186,188 antipsychotic users and roughly 17,000 CVA cases were identified, which is by far the largest systematic review conducted to date. Our meta-analysis showed that use of antipsychotics increases CVA risk, regardless of patient age or study design. Compared with nonusers, users of antipsychotic medications have an approximately 1.5-fold increased risk of developing CVA. Heterogeneity of strengths of association may reflect true pharmacologic differences in type of antipsychotics, differences in study methodology, and the distribution of effect modifiers such as patient age or presence of dementia. Greater risk was seen among the elderly population, whereas risk of CVA in dementia patients was not as pronounced. In the subgroup analysis, FGAs and SGAs showed differences in CVA risk. Use of FGAs was associated with a nearly 1.5-fold increased risk of CVA, whereas use of SGAs was associated with an attenuated (1.3-fold) and nonsignificant increase in CVA risk.

Our overall findings are consistent with the results reported in 2 previous systematic reviews, which suggest antipsychotics may trigger cerebrovascular events.^{43,44} The review by Sacchetti et al⁴³ included both randomized clinical trials and observational studies,

Table 3
Summary of Subgroup Analysis

Categories	Number of Studies	Summary Estimate (95% CI)	I^2
Exposure to overall antipsychotics			
All studies	9	1.45 (1.24–1.70)	91.0%
Elderly population	7	1.49 (1.25–1.77)	89.1%
Dementia population	4	1.17 (1.08–1.26)	0%
Population-based study	6	1.51 (1.20–1.91)	93.3%
Case-control design	5	1.28 (1.12–1.47)	59.0%
Exposure to FGAs			
All studies	6	1.48 (1.24–1.77)	85.2%
Exclusion of studies using hospital controls	3	1.95 (1.12–3.37)	72.9%
Exclusion of studies using dementia population	3	1.97 (1.42–2.73)	38.2%
Exposure to SGAs			
All studies	6	1.31 (0.74–2.30)	94.8%
Exclusion of studies using hospital controls	3	1.15 (0.46–2.87)	97.6%
Exclusion of studies using dementia population	3	1.69 (0.79–3.63)	97.8%

Fig. 2. Forest plot of risk of CVA-associated with (A) any antipsychotics, (B) FGAs, and (C) SGA.

while the Pratt et al⁴⁴ review evaluated only observational studies. Neither review, however, performed meta-analyses to provide summary estimates. The review by Sacchetti et al showed that incidence of CVA was consistently increased in the antipsychotic arm, but the small sample size of each trial prevented a conclusive outcome. The Pratt et al review was also descriptive but noted that the results may have been greatly influenced by the study design.⁴⁴

Moreover, the 2 reviews suggested a low risk of CVA associated with antipsychotic use among people with dementia, but a high CVA risk associated with antipsychotic use in the elderly population. Unlike the aforementioned reviews, our updated review computed pooled summary estimates across different subgroups, determined sources of heterogeneity, and included 5 additional eligible studies. Our quantitative analysis confirmed the

Fig. 2. (continued).

observation that elderly users of antipsychotics had a moderate risk of CVA but users with dementia did not have a low risk of CVA as previously observed. All but 4 studies used case-control design so a subgroup analysis could not be performed for other study designs. Some studies used hospital patients as their control, which could attenuate the risk of CVA.

The large number of antipsychotic users is a main strength of this study, allowing for analysis of CVA risk differences between FGA users and SGA users. Users of FGAs were found to have a 1.5-fold greater risk of CVA when compared with nonusers. In contrast to findings of previous meta-analyses, this study shows a nonsignificant association between use of SGAs and risk of CVA (OR 1.31; 95% CI 0.74–2.30; $I^2 = 94.8\%$). It should be noted that the CI is wide and the measure for statistical heterogeneity (I^2) is high. Two of the eligible studies reported an increased CVA risk among SGA users,^{39,41} whereas 4 studies reported no increased risk.^{16,37,38,42} The heterogeneity in the observed risk of CVA can be partly attributed to differences in study design. For study design, 5 studies were case-control,^{16,19,36–38} 1 case-case-time-control study,⁴⁰ 1 self-control case series study,⁴¹ 1 cross-sectional study,²⁵ and 2 cohort studies.^{39,42} Heterogeneity in CVA risk may also be attributed to differences in patient selection as demonstrated in Table 1. Five studies evaluated elderly dementia patients,^{16,19,38,41,42} 1 study evaluated schizophrenia patients,³⁷ and 6 studies evaluated general or hospitalized elderly patients.^{25,36–40} Use of SGAs in patients without dementia resulted in an increased risk of CVA (OR 1.69, 95% CI 0.79–3.63), but the results remained nonsignificant and heterogeneous. To confirm the potential risk of CVA with

SGAs, more high quality population-based observational studies are required that employ appropriate study designs.

A few meta-analyses have examined the association between antipsychotics and cerebrovascular events in the population with dementia. However, the prevalence of dementia is rather low in the general population, ranging from 38 to 421 per 100,000 persons.⁴⁵ Given the low prevalence of dementia, it is important to determine whether the risk of CVA differs among general users of antipsychotics compared with the population with dementia. To the best of our knowledge, this is the first meta-analysis to investigate the association between use of any antipsychotics and the risk of CVA in population-based studies. Our results suggest a high risk of CVA (51%) in general users of antipsychotics and a low risk of CVA (17%) in dementia patients.

Although we have performed a very thorough literature review and meta-analysis, our research is not without limitations. First, included studies were heterogeneous in terms of study design, timing of antipsychotic exposure, and diagnostic outcomes. In addition, despite the fact that the majority of studies were adjusted for many confounders with high quality results of NOS assessment, we cannot exclude the possibility of residual confounding for observational studies, especially being that the effect estimates differed greatly between a self-control case series design and traditional case control or cohort designs. Finally, this meta-analysis was limited in its ability to substantiate potential mechanisms linking antipsychotic use and risk of CVA, such as direct vascular toxicity, coagulation dysfunction, or weight gain.

To conclude, our study suggests that overall antipsychotic exposure is associated with an increased risk of CVA. In addition, subgroup analysis suggests that elderly patients have a higher risk of CVA than the population with dementia. Antipsychotic treatments should still be prescribed based on elderly patients' individual benefits and risks especially for behavioral and psychological symptoms of dementia. These associations may be causal but the possibility of residual confounding cannot be excluded. It is unlikely that more detailed information on a large population of

Table 4
Tests for Publication Bias

Exposure	Begg P Value	Egger P Value
Overall	.76	.72
FGAs	.46	.63
SGAs	1.00	.63

Fig. 3. Funnel plot of effect estimate of CVA risk in users of (A) any antipsychotics, (B) FGAs, and (C) SGAs relative to nonusers. The studies were plotted with the estimated effect on the horizontal axis and the reciprocal of standard error of the estimated effect on the vertical axis (ie, a measure of precision). Studies with less estimated precision scatter more widely at the bottom of the graph, whereas studies with more precision should scatter less at the top. The shapes produced do not contradict the results of the Begg and Egger tests.

antipsychotic users will become available in the immediate future. Clinicians should be aware of the higher risk of CVA among patients using antipsychotics, particularly in FGA users and the elderly population.

References

- Alexander GC, Gallagher SA, Mascola A, et al. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiol Drug Saf* 2011;20:177–184.
- Comer JS, Mojtabai R, Olfson M. National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. *Am J Psychiatry* 2011;168:1057–1065.
- Harrison JN, Cluxton-Keller F, Gross D. Antipsychotic medication prescribing trends in children and adolescents. *J Pediatr Health Care* 2012;26:139–145.
- Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998–2010. *Br J Psychiatry* 2012;200:393–398.
- Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry* 2006;63:679–685.
- Jackson JW, VanderWeele TJ, Viswanathan A, et al. The explanatory role of stroke as a mediator of the mortality risk difference between older adults who initiate first-versus second-generation antipsychotic drugs. *Am J Epidemiol* 2014;180:847–852.
- Lin ST, Chen CC, Tsang HY, et al. Association between antipsychotic use and risk of acute myocardial infarction: A nationwide case-crossover study. *Circulation* 2014;130:235–243.
- Jones ME, Campbell G, Patel D, et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in users of olanzapine and other antipsychotics: A study with the General Practice Research Database. *Cardiovasc Psychiatry Neurol* 2013;2013:647476.
- Langballe EM, Engdahl B, Nordeng H, et al. Short- and long-term mortality risk associated with the use of antipsychotics among 26,940 dementia outpatients: A population-based study. *Am J Geriatr Psychiatry* 2014;22:321–331.
- Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009;360:225–235.
- Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. *N Engl J Med* 2005;353:2335–2341.
- Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934–1943.
- Trifiro G, Verhamme K, Ziere G, et al. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. *Pharmacoepidemiol Drug Safety* 2007;16:538–544.
- van Iersel MB, Zuidema SU, Koopmans RT, et al. Antipsychotics for behavioural and psychological problems in elderly people with dementia. *Drugs Aging* 2005;22:845–858.
- Jackson JW, Schneeweiss S, VanderWeele TJ, et al. Quantifying the role of adverse events in the mortality difference between first and second-generation antipsychotics in older adults: Systematic review and meta-synthesis. *PLoS One* 2014;9:e105376.
- Laredo L, Vargas E, Blasco AJ, et al. Risk of cerebrovascular accident associated with use of antipsychotics: Population-based case-control study. *J Am Geriatr Soc* 2011;59:1182–1187.
- Wu CS, Wang SC, Gau SS, et al. Association of stroke with the receptor-binding profiles of antipsychotics—A case-crossover study. *Biol Psychiatry* 2013;73:414–421.
- Shin JY, Choi NK, Jung SY, et al. Risk of ischemic stroke with the use of risperidone, quetiapine and olanzapine in elderly patients: A population-based, case-crossover study. *J Psychopharmacol* 2013;27:638–644.
- Liu ME, Tsai SJ, Chang WC, et al. Population-based 5-year follow-up study in Taiwan of dementia and risk of stroke. *PLoS One* 2013;8:e61771.

20. Pratt NL, Roughead EE, Ramsay E, et al. Risk of hospitalization for stroke associated with antipsychotic use in the elderly. *Drugs Aging* 2010;27:885–893.
21. Correll CU, Joffe BI, Rosen LM, et al. Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a nonelderly adult sample: Results from a claims-based inception cohort study. *World Psychiatry* 2015;14:56–63.
22. Percudani M, Barbui C, Fortino I, et al. Second-generation antipsychotics and risk of cerebrovascular accidents in the elderly. *J Clin Psychopharmacol* 2005;25:468–470.
23. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: Population-based retrospective cohort study. *BMJ* 2005;330:445.
24. Herrmann N, Mamdani M, Lanctôt KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004;161:1113–1115.
25. Mundet-Tuduri X, Iglesias-Rodal M, Olmos-Dominguez C, et al. Cardiovascular risk factors in chronic treatment with antipsychotic agents used in primary care. *Rev Neurol* 2013;57:495–503.
26. US F. FDA requests Boxed Warnings on conventional antipsychotics. Secondary FDA requests Boxed Warnings on conventional antipsychotics 2008. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116912.htm>. Accessed November 1, 2016.
27. Hartling L, Abou-Setta AM, Dursun S, et al. Antipsychotics in adults with schizophrenia: Comparative effectiveness of first-generation versus second-generation medications: A systematic review and meta-analysis. *Ann Intern Med* 2012;157:498–511.
28. U.S. F. Information on Conventional Antipsychotics. Secondary Information on Conventional Antipsychotics 2008. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107211.htm>. Accessed November 1, 2016.
29. FDA US. Atypical Antipsychotic Drugs Information. Secondary Atypical Antipsychotic Drugs Information. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm>. Accessed November 1, 2016.
30. Wells GA, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Secondary The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed XXX.
31. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies. *J Natl Cancer Inst* 1959;22:719–748.
32. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–1101.
33. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
34. Borenstein M, Hedges LV, Higgins J, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97–111.
35. Bown M, Sutton A. Quality control in systematic reviews and meta-analyses. *Eur J Vasc Endovasc Surg* 2010;40:669–677.
36. Kleijer B, Van Marum R, Egberts A, et al. Risk of cerebrovascular events in elderly users of antipsychotics. *J Psychopharmacol* 2009;23:909–914.
37. Hsieh PH, Hsiao FY, Gau SS, et al. Use of antipsychotics and risk of cerebrovascular events in schizophrenic patients: A nested case-control study. *J Clin Psychopharmacol* 2013;33:299–305.
38. Liperoti R, Gambassi G, Lapane KL, et al. Cerebrovascular events among elderly nursing home patients treated with conventional or atypical antipsychotics. *J Clin Psychiatry* 2005;66:1090–1096.
39. Sacchetti E, Trifirò G, Caputi A, et al. Risk of stroke with typical and atypical anti-psychotics: A retrospective cohort study including unexposed subjects. *J Psychopharmacol* 2008;22:39–46.
40. Wang S, Linkletter C, Dore D, et al. Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. *Stroke* 2012;43:28–31.
41. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: Self-controlled case series study. *BMJ* 2008;337:a1227.
42. Chan MC, Chong CS, Wu AY, et al. Antipsychotics and risk of cerebrovascular events in treatment of behavioural and psychological symptoms of dementia in Hong Kong: A hospital-based, retrospective, cohort study. *Int J Geriatr Psychiatry* 2010;25:362–370.
43. Sacchetti E, Turrina C, Valsecchi P. Cerebrovascular accidents in elderly people treated with antipsychotic drugs. *Drug Safety* 2010;33:273–288.
44. Pratt N, Roughead EE, Salter A, et al. Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: A systematic review. *BMC Med Res Methodol* 2012;12:1.
45. Lambert M, Bickel H, Prince M, et al. Estimating the burden of early onset dementia; Systematic review of disease prevalence. *Eur J Neurol* 2014;21:563–569.