Meta-analysis of population-based studies comparing risk of cerebrovascular accident associated with first- and second-generation antipsychotic prescribing in dementia

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SHORT TITLE: Meta-analysis: risk of CVA with atypical antipsychotics use

ABSTRACT:

Background: Second-generation (atypical) antipsychotics are often prescribed in the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD), however, their use has been discouraged in light of clinical trials suggesting that they cause an increased risk of cerebrovascular accidents (CVA).

OBJECTIVE: Aim of the study was to assess relative risk of CVA in dementia patients prescribed second-generation (atypical) antipsychotics rather than first-generation (typical) antipsychotics, through meta-analysis of population-based studies.

METHODS: A literature search was conducted using several relevant databases. Five studies were included in the review and data were pooled to conduct meta-analysis using the inverse variance method.

RESULTS: Amongst a total of 79910 patients treated with SGAs, including risperidone, quetiapine and olanzapine, and a total number of 1287 cases of CVA were reported. In the comparison group, which consisted of 48135 patients treated with FGAs, a total of 511 cases of CVA were reported. The relative risk (RR) of CVA was 1.02 (95% CI, 0.56-1.84) for the SGA group. There was no significant difference in the risk of stroke ($p < 001$) between groups, but significant heterogeneity was found among the results of included studies ($p < 0.001$).

CONCLUSION: Meta-analysis of population-based data suggest that the use of second-generation as opposed to first-generation antipsychotics to control BPSD is not associated with significantly increased risk of CVA . Despite the large numbers of participants, only four studies were included in this meta-analysis, and our results are therefore best interpreted as suggestive of no difference in risk between the two classes of antipsychotic, rather furthering a definitive conclusion to this effect.

DECLARATION OF INTEREST: Ahsan Rao and Amna Suliman are PhD fellows at Faculty of Medicine, Imperial college, London. Sabine Vuik is a PhD fellow at the Institute of Global Health Innovation, Imperial college, London. Giles Story is a trainee in Psychiatry. Professor Paul Aylin is a professor of epidemiology and public health as well as the co-director at Dr. Foster Unit, Imperial college, London. Professor Ara Darzi holds the Paul Hamlyn Chair of Surgery at Imperial College London, the Royal Marsden Hospital and the Institute of Cancer Research. He is director of the Institute of Global Health Innovation at Imperial College London and Chair of Imperial College Health Partners. He is an Honorary Consultant Surgeon at Imperial College Hospital NHS Trust.

ETHICAL APPROVAL: This article is a review of previous studies, and therefore no ethical approval was required.

Introduction

Dementia is a clinical syndrome of deterioration in cognitive function, which goes beyond what would be expected from normal aging and is associated with impairment in a person's everyday functioning[1]. It affects 6% to 8% of adults over 65 years of age and approximately 20% of adults over the age of 80[2]. Dementia imposes a considerable emotional and physical challenge for patients and their families[3]. Irrespective of the underlying pathology, the syndrome necessitates a multifaceted management approach[5]. Pharmaceutical interventions form part of this, and are the focus of this review. Acetylcholinesterase (AchE) inhibitors, namely donezapil, rivastigmine and galantamine, are currently recommended in the UK to improve cognitive function in mild to moderate Alzheimer's disease, while the *N*-methyl-d-aspartate (NMDA) receptor antagonist, memantine, is recommended for patients unable to tolerate AChE inhibitors or for the same indication in severe Alzheimer's disease[5]. However, addressing non-cognitive symptoms such as agitation, anxiety, delusions, hallucinations and associated aggressive behavior forms a substantial component of the global management of dementia[6]. These symptoms, commonly termed Behavioral and Psychological Symptoms of Dementia (BPSD), occur with high frequency, particularly in Alzheimer's disease, where their estimated prevalence is as high as 90%. BPSD also present a major challenge for those who provide care for people with dementia[6].

Non-pharmacological interventions, such as treating undetected sources of pain or improving the patient's environment, remain first line management for both acute and chronic BPSD[7]. Antipsychotic medication is recommended by NICE

(National Institute for Health and Care Excellence) only if the patient remains in severe distress despite these interventions, and/or poses a risk of harm to themselves or others. Indeed, the Banerjee Report, an independent review of the use of antipsychotics in elderly people with dementia commissioned by the UK government, concluded that antipsychotics were overused to treat BPSD, given the associated risks of these drugs and their relatively limited clinical benefit[8]. In this review we focus on the increased risk of cerebrovascular accident (CVA) which has been associated in particular with the prescribing of second-generation antipsychotics (SGAs, also known as atypical antipsychotics) for people with dementia. This risk came to light following a series of clinical trials from 2002 onwards[9,10].

A recent Cochrane review based on five randomized controlled trials of SGA use in Alzheimer's disease (also incorporating data published by the Committee for the Safety of Medicines) found that patients treated with risperidone were significantly more likely than placebo-treated controls to experience serious adverse cerebrovascular events (37/1175 vs 8/779, OR 3.64, 95% CI 1.72 to 7.69, P = 0.0007)[8]. However, the Cochrane review did not comment on CVA risk associated with other second-generation drugs, nor were individuals prescribed SGAs directly compared with those prescribed the older, first-generation antipsychotics (FGAs, also known as typical antipsychotics) to assess their relative risk of CVA.

Population-based administrative data has become an advantageous alternative tool for research of clinical outcomes[11]. It is primarily collected for billing purposes from providers and in many countries is gathered on a national

scale[12]. Such data includes a large number of patients with relevant clinical indicators. Administrative data has recently been used to directly compare risk of CVA between risperidone, a SGA, and other antipsychotics[13]. Here we aim to establish the excess CVA risk associated with SGA, as compared to FGA by performing a systematic review and meta-analysis of existing population-based studies.

Methods

PRISMA guidelines were followed to conduct the systematic review[6]. The following inclusion criteria were used:

1. Participants: population over the age of 60.
2. Intervention: individuals treated with only one class of antipsychotic, giving rise to FGA and SGA groups.
3. Method: Direct comparison of FGA and SGA groups with CVA as one of the outcomes of the study.
4. Outcome: incidence of any type of CVA among participants.
5. Study design: studies based on retrospective population-based administrative data to assess risk or incidence of any type of cerebrovascular accident (CVA) in dementia patients.

The following exclusion criteria were used:

1. Studies that used clinical data from controlled trials, local hospitals or single-centres, and case series.

2. Studies that evaluated the use of antipsychotics and risk of CVA in populations diagnosed with medical conditions other than dementia.

Search and study selection

The literature search was conducted from 15th March to 15th May 2015. The following literature databases were used: Embase (1947-2015), Medline (1946-2015), Web of Science (1950-2015), Current Contents Connect, SciELO citation index. Various search terms were used to identify studies that discussed risk of CVA in patients with the use of antipsychotics *(Table 1).* Search terms for stroke, dementia and antipsychotics were 'exploded' to include all relevant terms. All the subheadings were included in the search. Similarly, '$' was used to include both singular and plural forms of the search term. Boolean terms, such as 'AND' and 'OR', were used to combine search terms to search for relevant titles. Further studies were identified through cross-referencing of studies reviewed initially. Two independent researchers, AR and AS, reviewed the selected studies separately.

Data collection

The data was collected from 01 May 2015 to 30th May 2015 by Authors AR and AS independently. The following information was extracted from the included studies: primary authors, year of publication, the place where study was conducted, administrative database used, type of CVA, follow-up period, duration of exposure of anti-psychotics, number of patients in each group, types of antipsychotics used, and incidence of CVA in each group.

Assessment of bias

The Newcastle-Ottawa scale was used to assess bias in the studies[14]. The scale uses star ranking based on thee major criteria: selection of participants, comparability and definition of outcome. A maximum of eight star ranking can be obtained by a study. The scale has been validated and recommended by Cochrane review methodological guidelines for non-randomised cohort studies.

Statistical methods

Statistical software Review Manager, version 5.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom) was used to perform the analysis[14]. The Risk Ratio (RR) was used to analyse differences in dichotomous variables, and 95% confidence intervals (CI) were reported for each derived statistic. An inverse-variance method of meta-analysis was used, since this method assigns more weight to studies with larger cohorts and smaller standard errors, than to those with small groups of patients and large standard errors. This method was used within a random-effect model so that it can evaluate any heterogeneity between the studies.

We illustrated the relative strength of treatment effects using a forest plot[14], where the measure of the treatment effect for each study is shown in terms of the odds ratio for categorical variables, with horizontal lines showing confidence intervals. The overall treatment effect is shown as a diamond. The vertical line in the graph is the line of no effect. If the confidence interval horizontal line of a particular study overlaps this line, then the size of the treatment effect of the individual study is not significant (no-effect). Similarly, if the lateral points of the diamond, indicating the overall effect, intersect the vertical line of no effect, there is no difference between overall treatment sizes of the two groups. The chi-squared test

(α=0.05) was included in the forest plot to assess heterogeneity of intervention's effect, that is variation in the outcome beyond chance. Inconsistency across the studies was quantified by I^2 method.

We also used a funnel plot, in which the individual treatment effect of each study is plotted against its study size, to illustrate the extent of publication bias[14]. A symmetrical funnel shape of the scattered plot of studies is likely to indicate no publication bias, heterogeneity between studies, and a "small study effect", where small studies in the analysis show larger treatment effects.

Results

Characteristics of studies

The search strategy for the selection of studies was based on the PRISMA protocol for the conduction of systematic reviews (*figure 1*). Initially, 648, 690 titles were identified from the search, however this number was reduced to 565 when the terms were combined together with Boolean terms and duplicate titles excluded. On screening of the titles, 55 were considered relevant and had their abstracts reviewed. In total, 16 full-text articles were reviewed, and five studies were included in the meta-analysis based on the inclusion criteria mentioned above. Excluded studies with their reasons for exclusion from the review are outlined in *Table 2*.

A total of five studies were included in the review, most of which were conducted in US and Canada (*Table 3*). All studies identified two cohorts of patients: dementia patients prescribed FGAs and dementia patients prescribed SGAs. Two studies had additional control groups: patients not taking any antipsychotics[15] and patients taking benzodiazepines[13]. The follow-up duration ranged from 3 months to 5 years. Most studies included all elderly patients over the age of 65 using antipsychotics, while two studies only focused on patients with confirmed diagnosis of dementia[13, 15].

Risk of CVA with the use of SGAs

Four studies did not find any significant difference between patients treated with second- and first-generation antipsychotics. However, in one study, the risk of CVA was higher with the use of FGAs (haloperidol and prochlormazine) as compared to SGA (risperidone). Cerebrovascular accidents included all types of

haemorrhagic stroke (subarachnoid, intracerebral or cranial haemorrhage) and ischaemic stroke (cerebral occlusion, stenosis, or thrombosis) as well as other cerebrovascular events like transient ischaemic attack, cerebral artery spasm and ill-defined cerebrovascular disease, however, Gill *et al* and Shin *et al* only included incidence of ischaemic stroke outcomes.

Barnett *et al* examined risk of inpatient admission for CVA associated with antipsychotic prescribing in 14029 adults over the age of 65 receiving care for dementia, using patient information from the Veterans Administration (VA) and Medicare Provider and Analysis Review Part A (MEDPAR-A) data files. Slightly over a quarter of their sample (27%, n = 3725) were diagnosed with vascular-type dementia, while the remaining 73% (n = 10,304) had a diagnosis of Alzheimer's dementia. Amongst those prescribed anitpsychotics, a larger proportion (n=1585) had been newly prescribed second-generation drugs, including risperidone (5.8%), quetiapine (2.9%) and olanzapine (2.5%), whereas only 1.3% of the sample (187) were found to be newly started on an FGA, of which haloperidol formed the largest component (1.2%). On average, patients received olanzapine, risperidone and quetiapine for 116.4 +/- 126.2, 107.9 +/- 112.9 and 128.1 +/- 127.3 days respectively, compared to haloperidol (79.6 +/- 99.6 days).

The authors showed that the risk of admission for CVA was not significantly raised in patients treated with antipsychotics, whether second-generation (n=1585, relative risk [RR]=1.20; 95% CI, 0.83-1.73) or first-generation (n=187, RR=1.29; 95% CI, 0.48-3.47), as compared to those not receiving antipsychotics (n=12257)[15]. In an analysis of all subtypes of dementia, the authors found no significant

difference in the risk of CVA between individual SGAs (risperidone [RR=0.49; 95% CI, 0.21-1.12], olanzapine [RR=0.62; 95% CI, 0.25-1.53], quetiapine [RR=0.70; 95% CI, 0.30-1.65]) and haloperidol. However, in a subgroup analysis of the patients with vascular dementia, the risk of CVA was higher with the use of either SGAs (RR=1.47; 95% CI, 0.76-2.84) and FGAs (RR=2.57; 95% CI, 0.60-11.06) compared to no use of antipsychotics. In the vascular subgroup however, the authors note a significantly decreased risk of CVA in patients receiving risperidone, relative to those prescribed haloperidol (RR=0.13; 95% CI, 0.03-0.63).

In an analysis of Medicaid data, Finkel *et al* compared the risk of inpatient admission for CVA in patients over the age of 60 who were receiving treatment for dementia, and who had been newly prescribed either SGAs (n=8285), FGAs (n=1260) or benzodiazepines (n=9442), following a period of six months or more of no use of these medicines[13]. The authors adopted benzodiazepines as a control group since benzodiazepines are among the most widely used non-antipsychotic treatments for BPSD. The FGA group in this study only included patients prescribed haloperidol, which the authors justified on the basis that haloperidol use represented 80% of the FGA prescribing within the cohort. The patients were followed up for maximum of 3 months after the initiation of antipsychotic or until the event of acute inpatient admission with stroke.

In the first multivariate analysis, the authors compared the risk of CVA for a reference group prescribed risperidone (n=4137) with CVA risk for patients prescribed olanzapine (n=2928), quetiapine (n=710), haloperidol (typical anti-psychotic [n=1260]) or benzodiazepines (n=9442). No significant difference in the

incidence of CVA was found between risperidone and either olanzapine or quetiapine. However, haloperidol (P<0.05) and benzodiazepines (P<0.001) were associated with significantly *greater* odds of CVA than risperidone. In a second multivariate analysis, benzodiazepines were taken as a reference group. All SGAs (P<0.001), olanzapine (P<0.005), risperidone (P<0.001) and quetiapine (P<0.05) had significantly lower odds of CVA than benzodiazepines. The authors depicted odds ratios graphically and their numeric values were not stated in the study text.

Vasilyeva *et al* examined administrative health care database in Manitoba, Canada to compare CVA risk in patients over the age of 65 prescribed SGAs (n=7779) with that associated with FGAs (n=4655)[17]. The most common SGA was risperidone (66.6%) followed by olanzapine (22.5%) and quetiapine (11%). Common FGAs were prochlorperazine (52.7%) followed by haloperidol (19.9%), methotrimeprazine (9%), loxapine (7.7%), and chlorpromazine (6.9%). Patients were followed up until the occurrence of cerebrovascular event and maximum upto 1 year. The cummulative incidence of all SGAs were compared with FGAs. The total incidence of stroke was 809 and 197 in SGAs and FGAs respectively. There was no significant difference in the incidences of stroke between the groups. The hazard ratio (HR) was 1.136 (CI 0.961-1.344).

Gill *et al* examined administrative healthcare databases in Ontario, Canada, so as to compare two cohorts of adults over aged 65 with dementia: those who had been newly prescribed SGAs (risperidone, olanzapine, and quetiapine) and those who had been newly prescribed FGAs (haloperidol, fluphenazine, thiothixene, pimozide, trifluoperazine, flupenthixol, zuclopenthixol, thioproperazine,

chlorpromazine, thioridazine, mesoridazine, loxapine, perphenazine, promazine, pericyazine, and chlorprothixane). Their primary outcome of interest was hospital admission with a primary diagnosis of ischaemic stroke. Patients were observed for at least 30 days after they were prescribed antipsychotics. The follow-up period lasted for maximum of 4 years and ended with the events of stroke, death, switch to another antipsychotic or discontinuation of medication. The authors found an incidence of ischaemic stroke of 284 amongst patients prescribed SGAs (n=17,845), by comparison to 227 in the FGA group (n=14,865)[16], amounting to a non-significant difference in relative risk (1.01, 95% CI, 0.81-1.26). Similarly, the risk of stroke amongst patients prescribed risperidone (adjusted hazard ratio [HR] 1.04; 95% CI, 0.82-1.31), olanzapine (HR 0.91; 95% CI, 0.62-1.32) or quetiapine (HR 0.78; 95% CI, 0.38-1.57) was not significantly greater than that amongst those prescribed FGAs.

Shin *et al* examined administrative healthcare databases in Korea, so as to compare two cohorts of adults over aged 65: those who had been newly prescribed SGAs and FGAs. The patients on SGAs were prescribed risperidone (n=24668), quetiapine (n=15860), and olanzapine (n=3888), whereas patients on FGAs were prescribed haloperidol (n=19564) and chlorpromazine (n=7604). Their primary outcome of interest was hospital admission with a primary diagnosis of ischaemic stroke. Patients were observed for maximum period of 3 years after they were prescribed antipsychotics. The follow-up period ended with the events of stroke, death, switch to another antipsychotic or discontinuation of medication. The average follow-up period was 150.9 days (SD 172.6) and 130.3 days for SGAs and

FGAs respectively. Overall, the incidence rate was 62 and 64 for SGAs (n=44416) and FGAs (n=27168) respectively. The incidence of stroke was specific antipsychotics were as following: risperidone (n=31/24668), quetiapine (n=36/15860), olanzapine (n=5/3888), haloperidol (n=43/19564), and chlorpromazine (n=21/7604). There was higher risk of stroke associated with FGAs compared to SGAs (adjusted HR 2.71; 95% CI, 2.01-3.52). Similarly, the risk of stroke in patients prescribed haloperidol (adjusted HR 2.64; 95% CI, 1.27-3.26) and chlorpromazine (adjusted HR 3.50; 95% CI, 2.17-5.65) compared to risperidone.

Meta-analysis

Amongst a total of 79910 patients treated with SGAs, including risperidone, quetiapine and olanzapine, and a total number of 1287 cases of CVA were reported. In the comparison group, which consisted of 48135 patients treated with FGAs, a total of 511 cases of CVA were reported. The relative risk (RR) of CVA was 1.02 (95% CI, 0.56-1.84) for the SGA group. There was no significant difference in the risk of stroke (p 0.96), however, this was associated with significant heterogeneity among the results of included studies ($p < 0.001$) (*Figure 2*).

Two studies also compared risk of CVA in dementia patients using SGAs with those not taking any antipsychotics[13, 15]. The incidence of CVA in those prescribed an SGA was 126/9870 as compared to those not taking any antipsychotics (n=493/21699). The relative risk (RR) of CVA was 0.95 (95% CI, 0.78-1.17) for the atypical antipsychotic group, which was not significantly different from non-users (p= 0.66) with non-significant heterogeneity between the studies (p= 0.21).

Risk of publication bias

All studies included in the review had a rating of 5 or above on the NOS scale indicating that each study was deemed to have a low risk of bias due to the selection of patients, adequate follow-up and clearly defined outcome measures, and that the comparison groups were adequately matched for co-morbidities and social demographics[15, 16, 17].

Discussion

The results from the meta-analysis conducted on five studies using population administrative data find no significant difference in the rate of CVA amongst dementia patients prescribed newer second-generation (atypical) anti-psychotics as compared to those receiving older, first-generation (typical) anti-psychotics.

A biological explanation for the link between CVA and use of anti-psychotic medication remains obscure[16]. Antipsychotics, in particular the second-generation drugs, have been linked to changes in the metabolism of lipids and glucose, however, these changes are likely to manifest over a long timescale and would not appear to explain why most CVA events occur within 6-12 weeks of commencing medication. A further possibility is that the high risk of CVA may be related to the anti-cholinergic properties of first-generation antipsychotics, resulting in hypotension, changes in heart rate and blood pressure, which in turn cause microinfarcts in the brain[21]. Paradoxically however, the use of risperidone, a second-generation antipsychotic, is associated with inhibition of platelet aggregation, which is most likely to cause decreased risk of ischaemic stroke[16]

Our meta-analysis suggested that there was significant heterogeneity between the studies to account for any risk of CVA associated with type of antipsychotics. Three studies included in the review did not find significant risk of CVA associated with SGAs compared to FGAs[13, 15, 16]. Vasilyeva et al. demonstrated higher incidence rate of CVA in SGAs group but the risk was similar to FGAs when adjusted for patients' characteristics and past medical history[29]. On the other hand,

the risk of CVA was significantly higher in FGAs group (haloperidol and chlorpromazine) as compared to SGAs (risperidone)[9]. Two studies included in the review also compared risk of CVA in patients prescribed second-generation antipsychotics to those not taking any antipsychotics[13, 15]. The analysis from these studies found that use of a second-generation antipsychotic did not significantly increase risk of CVA relative to the non-user group. On the other hand, previous clinical trials have found that risperidone was associated with increased risk of CVA as compared to a placebo group. However, these trials did not comprehensively assess the risk of CVA associated with the use of other second-generation antipsychotics in dementia patients[13,17]. Nor did they take into account confounding risk factors that could contribute to increased risk of CVA, such as previous stroke, diabetes, hypertension, atrial fibrillation and hyperlipidaemia. Furthermore these studies had a short follow-up period and did not show any significant difference in other serious medical events (drug reaction, hospitalisation, disability, and death) between second-generation antipsychotics and placebo[13]. After the published data from the clinical trials, the use of second-generation antipsychotics in local communities did not decrease, but government agencies issued warnings about the association of these drugs with risk of CVA[13].

The use of population-based administrative data for research has several advantages. It consists of large patient cohorts and different quality metrics[11]. Data is collected for different types of healthcare providers, such as primary care, hospital care, and pharmacy data[10]. These databases can be linked together to study trends in outcomes and patients can be followed up for a long period of time. By

means of hospital administrative data, when a patient is admitted to hospital, the cost for the whole cycle of care can be assessed, which includes diagnosis, investigations, management, length of stay and discharge plan[22]. Administrative data has also been used to assess other clinically relevant factors that impact outcomes of dementia[23].

It was important and relevant to clinical decision-making to conduct meta-analysis that directly compared risk of CVA between first- and second-generation antipsychotic prescribing in dementia. The use of typical antipsychotics had not been associated with risk of CVA contrary to atypical antipsychotics[13]. The review has suggested that the use of atypical antipsychotics is as safe as typical antipsychotics. Previous incidence of CVA mentioned in clinical trials was very low[15]. The pooling of data from population-based studies provided significant number of cases of CVA in antipsychotic users to compare risk in different antipsychotic groups in a hope to prevent sampling bias. Since there was very limited number of population-based studies that directly compared risk of CVA between atypical antipsychotic users and those not taking any antipsychotics[13, 15], the systematic review was primarily focused on comparing atypical and typical antipsychotic groups. Once more data is available, more research is warranted into comparison of risk of CVA in atypical antipsychotic group and non-users.

The studies included in the review have several limitations. There is still paucity of data to directly compare different groups of antipsychotics. Our meta-analysis was based on data collected from only 5 studies. The studies were potentially prone to selection bias because patients using multiple antipsychotics

and those who died during follow-up were excluded from the studies. Analyses included all kinds of dementia, while the adverse effect of antipsychotics may vary according to the type of dementia. The risk of CVA is further related to other lifesytle health behaviours like smoking, BMI, and physical activity; none of those variables were recorded in the administrative databases, and so could not be explicitly controlled for[31]. It was also difficult to ascertain the duration and dose of antipsychotics used, as previous studies have shown that the adverse events of the medications were dose dependent[10]. Results from the analysis cannot be used to identify association between antipsychotics and specific type of stroke as most studies pooled all types of stroke – ischaemic and haemorrhagic – when comparing adverse events of different kinds of antipsychotics. However, Barnett *et al* performed subgroup analysis on different kinds of dementia and found atypical antipsychotics to have relatively low risk of CVA compared to typical antipsychotics in vascular dementia patients.

In conclusion, the results from meta-analysis suggest that the use of atypical antipsychotics was not associated with significant increased risk of CVA compared to typical antipsychotics based on population-based data. Future research should evaluate direct comparison of other adverse events between atypical and typical antipsychotics.

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