REVIEW ARTICLE

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Cerebrovascular Accidents in Elderly People Treated with Antipsychotic Drugs

A Systematic Review

Emilio Sacchetti,[1,2,3,4] *Cesare Turrina*[1,2,3] and *Paolo Valsecchi*[3]

1 Department of Psychiatry, Brescia University School of Medicine, Brescia, Italy
2 University Psychiatric Unit, Brescia University School of Medicine and Brescia Spedali Civili, Brescia, Italy
3 Department of Mental Health, Brescia Spedali Civili, Brescia, Italy
4 Centre of Behavioural and Neurodegenerative Disorders, Brescia University and EULO, Brescia, Italy

Contents

Abstract

After 2002, an association between stroke and antipsychotic use was reported in clinical trials and large database studies. This review considers previous quantitative reviews, newly published clinical trials, and recent observational cohort and case-control studies, and focuses on the clinical significance of the risk for stroke, the difference between typical and atypical antipsychotics, the possible at-risk patient profile and the timing of stroke after exposure. A search of MEDLINE covering the period from 1966 to June 2009 was carried out using selected keywords. Inclusion criteria were (i) quantitative reviews on stroke and antipsychotics; (ii) double-blind, placebo-controlled clinical trials involving patients with dementia treated with antipsychotics; and (iii) observational database cohort studies and observational case-control studies investigating the association between stroke and antipsychotics. Clinical trials were excluded if they were single-blind or if patients were affected by dementia and/or other neurological illnesses.

Four reviews with aggregate data, 2 meta-analyses, 13 randomized, double-blind, controlled trials, 7 observational cohort studies and 4 observational case-control studies were selected and analysed. The incidence of

cerebrovascular accidents (CVAs) was found to be very low in aggregate reviews and meta-analyses (2–4%). When the number collected was sufficiently high, or different drug treatments were grouped together, the higher rate in subjects exposed to antipsychotics was statistically significant. Inspection of other randomized controlled clinical trials, not included in aggregate reviews and meta-analyses, reported similar rates of CVAs. The majority of observational cohort studies compared typical and atypical antipsychotics and no significant class differences were found. A comparison with non-users was carried out in some cohort studies. In case-control studies, the probability of CVAs in users compared with non-users was in the range of 1.3- to 2-fold greater. Preliminary data also indicate that the highest risk of stroke is related to the first weeks of treatment, and a risk profile for stroke is emerging, such as older age, cognitive impairment and vascular illness. Different pathophysiological pathways may be involved, ranging from the facilitation of thrombosis, pre-existing cardiovascular factors, sedation and a common diathesis for stroke of dementia, schizophrenia and affective illness.

Before prescribing an antipsychotic, clinicians should weigh all the risk factors for a given patient and consider not only the indications as provided by the regulatory agencies, but also the overall effectiveness of typical and atypical antipsychotics.

On 11 October 2002, Janssen-Ortho Inc., Canada, released a Dear Healthcare Professional Letter regarding Risperdal® (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials.[1] This represented a response to a *post hoc* analysis of controlled clinical trials of risperidone in elderly patients with dementia that reported higher rates of cerebrovascular accidents (CVAs) in subjects randomized to the active treatment arm versus individuals in the placebo group. Similar warnings involving risperidone and other atypical antipsychotics followed in different countries.[2-7]

First-generation (conventional) antipsychotics were excluded from official restriction because of the lack of dedicated placebo-controlled clinical trials. Therefore, there was renewed clinical interest in the use of the older antipsychotics in patients with dementia; however, this return to past practice reveals a number of relevant shortcomings. First, the absence of specific information is not proof that conventional antipsychotics are devoid of cerebrovascular risk. Second, the atypical antipsychotics may be considered more benign than conventional antipsychotics on the clinical hallmark of dementia, the cognitive deficit.[3,4,8,9] Third, people with dementia are especially prone to movement disorders,[10] and the conventional antipsychotics are disadvantaged compared with the atypical antipsychotics with respect to this adverse drug reaction.[3,9,11-13] Fourth, although doubts persist about the convenience of treating patients with dementia with antipsychotics in general,[14-15] current evidence is insufficient to conclude in favour of the superiority of second-generation antipsychotics,[5,16] and these medications can be considered at least as effective as first-generation antipsychotics.[12,17]

Consequently, warnings from health organizations may have encouraged many physicians to revise their treatment plans for patients with dementia who are in need of therapy with antipsychotic drugs by substituting atypical antipsychotics with conventional antipsychotics, even though there is no evidence to suggest that the conventional antipsychotics are more benign in terms of cerebrovascular risk and are not detrimental with respect to cognitive impairment and movement disorders. Patients with dementia have been reported to be the front runners for the prescription of antipsychotics for people over the age of 65 years.[18] A recent report on the effect of

regulatory warnings on antipsychotic prescription rates in elderly patients with dementia has shown only a slight decrease (between 3.2% and 5%) in the use of atypical antipsychotic drugs and a slowdown in the decrease in the use of conventional agents.[19]

The current literature on cerebrovascular risk in patients treated with antipsychotics has been enriched by a number of retrospective, observational, cohort and case-control studies, mostly in large databases. These studies have been mainly carried out to answer questions, not covered by controlled clinical trials, on differences between first- and second-generation antipsychotics with regard to the emergence of CVAs. A number of observational studies have also tested the possibility that, in elderly people, the relationship between stroke and related events and antipsychotics is not confined exclusively to patients with dementia but includes patients with different psychiatric diagnoses.

Given the theoretical and practical implications of increased cerebrovascular risk in elderly patients treated with antipsychotics, and the proliferation of dedicated experimental research, some reviews and meta-analyses have also been produced in recent years in an attempt to organize the available data in a unitary perspective and generate more solid hypotheses. It is known that reviews and meta-analyses can be short lived. Indeed, systematic reviews have a mean survival time of 5.5 years, and one-quarter require updating after 2 years.[20]

This systematic review considers previous quantitative reviews, newly published clinical trials and recent observational cohort and case-control studies, and focuses on the clinical significance of the risk for stroke, the difference between conventional and atypical antipsychotics, the possible at-risk patient profile and the timing of stroke after exposure.

1. Literature Selection

To identify studies pertinent to the relationship between the use of antipsychotics and stroke or related CVAs, MEDLINE citations (from 1966 to June 2009) were surveyed on the National Library of Medicine's PubMed online search engine, using the key words 'stroke', 'CV accident', and 'CV event' in combination with 'neuroleptic', 'antipsychotic', 'first-generation antipsychotic', 'typical antipsychotic', 'second-generation antipsychotic', 'atypical antipsychotic', 'risperidone', 'olanzapine', 'quetiapine', 'aripiprazole', 'ziprasidone', 'clozapine', 'amisulpride', 'haloperidol', 'chlorpromazine' and 'perphenazine'. The search was restricted to articles written in English on human clinical studies, observational studies, reviews and meta-analyses.

For randomized controlled clinical trials (RCTs), the selection criteria were a diagnosis of dementia in admitted or ambulatory patients; treatment with an atypical or typical antipsychotic; randomization of patients in a double-blind, placebo-controlled trial; and an active comparator when the placebo arm was not considered. Papers already included in other quantitative reviews were not re-analysed. Clinical trials were excluded if they were single-blind or included patients with dementia complicated by other neurological illnesses.

For observational studies, the criteria for selection were database, cohort studies that defined two or more groups according to exposure to an antipsychotic or a class of antipsychotics; a comparison group of unexposed subjects or a comparison group of subjects exposed to another drug or class of drugs; and a cerebrovascular event as the outcome variable. For case-control studies, cases were defined by the presence of stroke and related CVAs, and controls were defined by no illnesses or illnesses other than stroke. The diagnosis of dementia was not an entry criterion, since we were also interested in cerebrovascular events in patients with other diagnoses.

Supplementary literature on the effects of antipsychotics in experimental models of stroke and cerebral ischaemia, and a large series of candidate predisposing factors for CVAs in people with dementia, schizophrenia and mood disorders were also identified using PubMed (from 1966 to June 2009) and manual searches, using the previous keywords in addition to 'aetiology', 'risk-factor', 'thrombosis', and 'thromboembolism'.

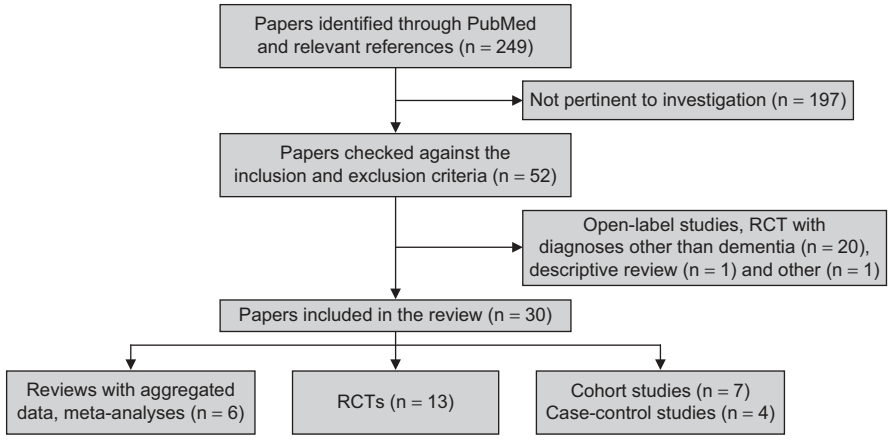

Fig. 1. Search strategy used to identify relevant studies from the literature. **RCT** = randomized controlled trial.

The abstract of each extracted article was screened to select those of potential interest. A manual search of the references cited in the various papers was also performed to identify additional publications.

Our literature search identified 249 studies and reviews, 30 of which were included in our review and 219 were excluded. A flow diagram outlining the selection process is presented in figure 1.

2. Evidence from Randomized Controlled Clinical Trials (RCTs)

2.1 Pooled and Meta-Analyses of RCTs

A number of pooled- and meta-analyses[2,4,21-24] (table I) have already reviewed many placebo-controlled RCTs. Only two initial pooled analyses[21,22] and one meta-analysis[2] focused explicitly on cerebrovascular events, two studies focused on both efficacy and safety,[4,23] and one study focused on treatment-emergent adverse events.[24]

The first warnings came after the publication of two reports[21,22] in which data for risperidone and olanzapine were aggregated. It was found that the rate of cerebrovascular events was 3.8% (29/764) in subjects exposed to risperidone and 1.5% (7/466) in those taking placebo. The rate of cerebrovascular events in patients treated with olanzapine was 1.3% (15/1178) and 0.4% (2/478) in patients taking placebo. The results were descriptive and no statistical significance was reported.

In a pooled analysis of three risperidone trials[23] it was found that cerebrovascular adverse events were 'less common' than other adverse events. Their incidence did not appear to be dose-dependent and when the analysis was restricted to serious cerebrovascular events, only 1.6% of the 722 patients administered risperidone experienced a cerebrovascular event compared with 0.7% of the 428 patients in the placebo arm. The authors reported that all subjects who experienced cerebrovascular events had one or several pre-existing risk factors. The statistical significance of these data was not given.

Another study on pooled data for both risperidone and olanzapine[2] analysed 11 clinical trials. In the six studies that included patients taking risperidone (1009 risperidone, 712 placebo), 3.3% compared with 1.1% had some type of cerebrovascular event ($p = 0.004$). When only serious adverse events were considered, the rates dropped to 1.5% versus 0.6% and the difference was not statistically significant. In the same study, the analysis of aggregate data from five studies (1178 olanzapine, 478 placebo) found a rate of 1.3% versus 0.4%, which also was not significant. The authors concluded that the association between atypical antipsychotics and cerebrovascular adverse events requires further clarification.

In a meta-analysis of six studies considering olanzapine and other comparators,[24] the rate of CVAs was found to be 3-fold higher in patients treated with olanzapine (1.3% [15/1178]) compared with patients treated with placebo (0.4% [2/478]), but these pooled data were also not significantly different. The comparison of olanzapine with typical antipsychotics reported comparable rates of CVAs. However, in a meta-analysis on the efficacy and adverse effects of atypical antipsychotics for patients with dementia,[4] cerebrovascular adverse events were significantly higher compared with controls: 1.9% versus 0.9% (data pooled for aripiprazole, olanzapine, quetiapine and risperidone). The analysis included 3327 patients on atypical antipsychotics and 1728 on placebo.

2.2 RCTs

Other controlled clinical trials have been published that were not included in the reviews described above but are included in this study. In the 13 studies that were extracted (table II), 7 were placebo-controlled, 3 had an active comparator and 3 had both.[9,25-36]

In line with previous trials, none of the new studies was designed to explicitly test the risk of cerebrovascular events during treatment with antipsychotics, or was sufficiently powered to permit conclusions about eventual differences between treatment arms for this relatively uncommon event. Assuming an increased difference of 2% between treated patients and controls, the sample size required to detect a significant difference can be computed. Taking an 80% chance of detecting the difference and testing significance at $p = 0.05$, it would be necessary to have 1240 patients in each arm of the study, as shown by previous aggregate studies and meta-analyses.

In two studies[30,32] the eventual emergence of CVAs was not mentioned, even though the topic is well known in the medical community. Furthermore, with few exceptions,[31,33,34] the type of events included under the label 'cerebrovascular events' was not specified. The studies were short-term trials with the exception of one,[9] and they recruited heterogeneously from in- and outpatients, or both. One trial[9] with a relatively prolonged period of observation (up to 36 weeks) reported that patients randomized to olanzapine,

Table I. Rates of cerebrovascular events in pooled- and meta-analyses of randomized, double-blind, placebo-controlled trials of second-generation antipsychotics in patients with dementia

Study (y)	No. of trials	Antipsychotic drug	Cerebrovascular event rate (%)
Wooltorton[21] (2002)	4	RIS	RIS: 4 PL: 2
Wooltorton[22] (2004)	5	OLA	OLA: 1.3 PL: 0.4
De Deyn et al.[23] (2005)	3	RIS	*All events:* RIS: 3.9 PL: 1.6 *Serious events:* RIS: 1.6 PL: 0.7
Herrmann and Lanctôt[2] (2005)	11	RIS, OLA	*All events:* RIS: RR 3.2 vs PL[a] OLA: RR 1.8 vs PL[a] *Serious events:* RIS: RR 2.3 vs PL[a]
Kryzhanovskaya et al.[24] (2006)	5	OLA	OLA: 1.3 PL: 0.4
Schneider et al.[4] (2006)	15	ARI, OLA, RIS, QUE	Pooled: 1.9 PL: 0.9

a RRs are reported rather than a rate.

ARI = aripiprazole; **OLA** = olanzapine; **PL** = placebo; **QUE** = quetiapine; **RIS** = risperidone; **RR** = relative risk.

Table II. Cerebrovascular events in recent, randomized, double-blind, controlled trials of antipsychotics in patients with dementia

Study (y)	Diagnosis	Duration (wk)	Treatment arm (no. of patients)	Cerebrovascular event rate (%)
Brodaty et al.[25] (2005)	Psychosis of AD and mixed dementia	12	RIS (46) PL (47)	RIS: 8.7 PL: 2.1
Deberdt et al.[26] (2005)	Dementia with psychosis	10	OLA (204) RIS (196) PL (94)	OLA: 2.5 RIS: 2 PL: 0
De Deyn et al.[27] (2005)	AD with psychosis	10	ARI (106) PL (102)	ARI: 1 TIA[a] PL: 1 TIA[a]
Mintzer et al.[28] (2006)	AD with psychosis	8	RIS (235) PL (238)	*All:* RIS: 1.7 PL: 0.4 *Stroke:* RIS: 0.4 PL: 0.4
Schneider et al.[9] (2006)	AD with psychosis, aggression and agitation	36	OLA (100) QUE (94) RIS (85) PL (142)	OLA: 2 QUE: 1 RIS: 1 PL: 1
Suh et al.[29] (2006)	BPSD	18	RIS (60) HAL (60)	Not reported
Tariot et al.[30] (2006)	AD with psychosis	10	QUE (124) HAL (128) PL (125)	QUE: 1.6 (not serious) HAL: 0.8 (not serious) PL: 2.4 (not serious)
Verhei et al.[31] (2006)	Dementia with agitation and aggression	5	OLA (30) HAL (28)	Not reported
Holmes et al.[32] (2007)	Probable AD with agitation	6	RIS (12) RVS (15)	RIS: 1 TIA[a] RVS: 0
Mintzer et al.[33] (2007)	AD with psychosis	10	ARI 2 mg (118) ARI 5 mg (122) ARI 10 mg (126) PL (121)	ARI 2 mg: 0.8 ARI 5 mg: 1.6 ARI 10 mg: 3.2 PL: 0
Naber et al.[34] (2007)	OBD with disruptive symptoms	12	RIS (612) PL (203)	RIS: 0.7 PL: 1
Zhong et al.[35] (2007)	Dementia with agitation	10	QUE 200 mg (114) QUE 100 mg (120) PL (92)	Similar among groups and <5%
Streim et al.[36] (2008)	AD with psychosis	10	ARI (130) PL (121)	ARI: 0 PL: 0.8

a Numbers of individual TIA events were reported rather than a rate.

AD = Alzheimer's disease; **ARI** = aripiprazole; **BPSD** = behavioural and psychological symptoms of dementia; **HAL** = haloperidol; **OBD** = organic brain disorder; **OLA** = olanzapine; **PL** = placebo; **QUE** = quetiapine; **RIS** = risperidone; **RVS** = rivastigmine; **TIA** = transient ischaemic attack.

quetiapine or risperidone had relatively low rates of cerebrovascular events, similar to those found in the placebo group, suggesting that prolongation of the treatment does not increase the cerebrovascular risk.

Analysis of the trials in table II supports the view that cerebrovascular events are uncommon accidents. The reported incidence in treated patients was, in most cases, between 1% and 3%, and for subjects receiving placebo the reported incidence was between 0% and 2.4%.

Most of the controlled clinical trials have common weaknesses. First, although the study of a dose relationship between CVAs and exposure to antipsychotics represents one of the bases for checking the causality of an adverse drug reaction,

this was not performed in several trials and, when analysed, was frequently negative.[20,27,28] Other relevant caveats have been well underlined, especially in a previous *ad hoc* review on cerebrovascular risk during treatment with antipsychotics.[2] In particular, it was stressed that the samples were not stratified according to cerebrovascular risk factors, a high proportion of individuals predisposed to CVAs was included, and the coding of cerebrovascular events was broad, imprecise and potentially misleading. Given the clinical impact of this difference, the proposal that serious CVAs, e.g. life threatening, requiring hospitalization or leading to permanent disability, should be considered separately from 'minor' ones[2,23,24] seems highly advisable.

3. Evidence from Observational Studies

3.1 Cohort Studies

Some data on the general population indicate the risk of stroke in dementia patients, irrespective of their exposition to antipsychotics. People with vascular dementia have been found to have the highest relative mortality rates for heart and cerebrovascular disease.[37] Pre-existing dementia was diagnosed in 12–16% of stroke patients,[38] and the recurrence of stroke, at 1-year follow-up after the patient's first stroke, was found in 28% of patients with pre-existing dementia, compared with 8% of those without dementia.[39]

Eleven observational studies with a sample size of at least 1000 individuals are included in our review. Seven were cohort database studies (table III)[6,40-45] and four were case-control studies (table IV).[7,46-48] Four studies[41,42,44,46] involved only elderly patients with dementia, and the remaining seven studies[6,7,40,43,45,47,48] included a mixed population of elderly patients with and without dementia. Among the cohort studies, only three[6,42,44] had a comparison group of subjects unexposed to antipsychotics, while four further studies[40-43] provided comparisons between different antipsychotics or classes.

The first large database study[40] (table III) considered all elderly subjects in a general population with or without dementia who were exposed to an antipsychotic. Risperidone and olanzapine were compared with the whole class of conventional antipsychotics, and no significant differences were found between newer and older medications. The crude stroke rate per 1000 person-years was 5.7 for conventional antipsychotics, 7.8 for risperidone and 5.7 for olanzapine. The adjusted risk ratios failed to detect a significant difference between atypical and conventional antipsychotics. Although the healthcare database allowed for consideration of other risk factors for stroke, such as a previous stroke, the lack of data on other important risk factors, such as obesity and smoking, was highlighted. In a similar study limited to dementia patients,[41] conventional and atypical antipsychotics were broadly considered and, again, no significant differences between the two classes of medication were found.

In a study on elderly Medicaid patients with dementia[42] that investigated hospital records for CVAs during a 3-month follow-up period, the crude incidence rates were 0.87%, 0.96%, 0.56% and 1.19% for risperidone, olanzapine, quetiapine and haloperidol, respectively. After weighting for other medical risk factors, olanzapine and quetiapine showed a risk similar to that of risperidone, while haloperidol was associated with a higher risk. Since the timeframe was selected to compare data with the average length of RCTs, it was emphasized that patients were taken from a general population, whereas patients enrolled in RCTs were subjects from nursing homes, who had greater disease severity compared with the Medicaid patients.

A postmarketing survey of general practice patients using a postal questionnaire[43] found a 6-month incidence of stroke and transient ischaemic attacks (TIAs) for risperidone, olanzapine and quetiapine of 0.30%, 0.11% and 0.35%, respectively. Compared with olanzapine, the risk ratios for risperidone and quetiapine were similar after adjusting for age, sex and dementia. Risperidone was found to have a significantly shorter time to event.

No differences were found between antipsychotic users and non-users in three cohorts of elderly patients with dementia in a Veteran Administration database.[44] The raw incidence, in

Table III. Observational studies of cerebrovascular events and exposure to first- and second-generation antipsychotics: cohort studies

Study (y)	Dataset	Indications for use	Age (y)	Outcome variable	Treatment group (no. of subjects)	Co-prescriptions of antipsychotics	Result (95% CI)
Herrmann et al.[40] (2004)	Administrative healthcare database	Mixed indications	66+	Hospital diagnosis of stroke	FGAs (1 015) RIS (6 964) OLA (3 421)	Not allowed	OLA vs FGAs: RR 1.1 (0.5, 2.3) RIS vs FGAs: RR 1.4 (0.7, 2.8)
Gill et al.[41] (2005)	Ontario Drug Benefit Database, Ontario Health Insurance Plan, Registered Persons Database	Dementia	65+	Hospital diagnosis of ischaemic stroke	SGAs (17 845) FGAs (14 865)	Allowed	SGAs vs FGAs: HR 1.01 (0.81, 1.26)
Finkel et al.[42] (2005)	Medicaid database	Dementia	60+	Any admission for cerebrovascular events	HAL (1 260) RIS (4 137) OLA (2 928) QUE (710)	Allowed for the same class	OLA vs RIS: OR 1.05 (0.63, 1.73) QUE vs RIS: OR 0.66 (0.23, 1.87) HAL vs RIS: OR 1.91 (1.02, 3.60)
Layton et al.[43] (2005)	Postmarketing, observational, postal questionnaire	Mixed indications	No limits	Cerebrovascular events, TIAs included	RIS (7 684) QUE (1 726) OLA (8 826)	Not assessed	RIS vs OLA: aRR 1.2 (0.5, 3.0) QUE vs OLA: aRR 2.1 (0.6, 7.7)
Barnett et al.[44] (2007)	Veteran Administration Database	Dementia	65+	Cerebrovascular events	No use (12 257) FGAs (187) SGAs (1 587)	Not allowed	FGAs vs no use: HR 1.29 (0.48, 3.47) SGAs vs no use: HR 1.20 (0.83, 1.74)
Sacchetti et al.[6] (2008)	Health Search Database	Mixed indications	65+	Incident stroke	No use (69 939) SGAs (599) BTF (749) PHT (907) SBA (1 968)	Not allowed	PHT vs no use: HR 5.79 (3.07, 10.9) BTF vs no use: HR 3.55 (1.56, 8.07) SBA vs no use: HR 2.20 (0.98, 4.90)

Continued next page

Table III. Contd

Study (y)	Dataset	Indications for use	Age (y)	Outcome variable	Treatment group (no. of subjects)	Co-prescriptions of antipsychotics	Result (95% CI)
							SGAs vs no use: HR 2.46 (1.07, 5.65) No use vs SGAs: HR 0.40 (0.17, 0.92) PHT vs SGAs: HR 2.34 (1.01, 5.41) BTF vs SGAs: HR 1.44 (0.55, 3.76) SBA vs SGAs: HR 0.89 (0.33, 2.38)
Sacchetti et al.[45] (2009)	Health Search Database	Mixed indications	50+	Incident stroke	No use (128 308) Users (6 180)	Not allowed	SGAs + FGAs vs no use: OR 12.4 (8.4, 18.1) [first month of treatment]

aRR = rate ratio (adjusted); **BTF** = butyrophenones; **FGAs** = first-generation antipsychotics; **HAL** = haloperidol; **HR** = hazard ratio (adjusted); **no use** = no use of antipsychotics; **OLA** = olanzapine; **OR** = odds ratio (adjusted); **PHT** = phenothiazines; **QUE** = quetiapine; **RIS** = risperidone; **RR** = relative risk; **SBA** = substituted benzamides; **SGAs** = second-generation antipsychotics; **TIA** = transient ischaemic attack.

an observational period of 18 months, was 3.2% in unexposed subjects, 4.3% in those receiving conventional antipsychotics and 3.5% in those receiving atypical antipsychotics. The weighted hazard ratio for any cerebrovascular event of subjects exposed to first- and second-generation antipsychotics was similar to controls. A higher relative risk (1.39) was found for patients with vascular dementia compared with patients with Alzheimer's disease.

A cohort study[6] based on the Health Search database, a nationwide register of data taken from the daily clinical activity of general practitioners, investigated the risk of having a first stroke in a general population, irrespective of a diagnosis of dementia. The cohorts were weighted for many illnesses and treatments, and a group of unexposed subjects was available. The annual crude incidence rates for unexposed individuals was 1.2%; the incidence rates for users of butyrophenones, phenothiazines, substituted benzamides and atypical antipsychotics were 4.7%, 7.3%, 2.1% and 4.7%, respectively. Compared with unexposed controls, the adjusted hazard ratios were 3.55 for butyrophenones, 5.79 for phenothiazines, 2.20 for substituted benzamides and 2.46 for atypical antipsychotics. When the atypical antipsychotics were used as the reference group, the adjusted hazard ratios were 0.40, 1.44, 2.34 and 0.89 for non-use of antipsychotics and use of butyrophenones, phenothiazines and benzamides, respectively. Concurrent use of anticoagulants was strongly associated with stroke.

A study focusing on the time to occurrence of stroke,[45] based on a re-analysis and an extension of a previous report,[6] found that the risk for stroke in the first month of treatment with antipsychotics was 12.4-fold greater compared with controls, and returned to normal or almost normal levels thereafter.

3.2 Case-Control Studies

A study of nursing home patients affected by dementia[46] compared the prescription of older and newer antipsychotics in cases of stroke and in a control group represented by dementia patients

Table IV. Observational studies of cerebrovascular events and exposure to first- and second-generation antipsychotics: case-control studies

Study (y)	Dataset	Indications for use	Age (y)	Linked variable	Group (no. of subjects)	Co-prescriptions of antipsychotics	Result (95% CI)
Liperoti et al.[46] (2005)	MDS and SAGE databases	Dementia	65+	Risperidone Olanzapine FGA	Stroke and TIAs, with dementia (1130) Controls with dementia (3658)	Not assessed	RIS vs no use: OR 0.87 (0.67, 1.12) OLA vs no use: OR 1.32 (0.83, 2.11) FGAs vs no use: OR 1.24 (0.95, 1.63)
Percudani et al.[47] (2005)	Hospital admission, regional database of prescriptions	Mixed indications	65+	Cerebrovascular events	No use (1 609 903) HAL (4218) OLA (2419) RIS (5539) QUE (1346)	Not allowed	FGAs + SGAs vs no use: OR 1.24 (1.16, 1.32) RIS vs HAL: OR 1.43 (1.12, 1.93) OLA vs HAL: OR 1.26 (0.92, 1.72) QUE vs HAL: OR 1.39 (0.95, 2.05)
Douglas and Smeeth[7] (2008)	General Practice Research Database	Mixed indications	No limits	Incident stroke	SGAs (905) FGAs (6334)	Allowed for the same class	SGAs + FGAs vs no use: aRR 1.73 (1.60, 1.87) FGAs vs no use: aRR 1.69 (1.55, 1.84) SGAs vs no use: aRR 2.32 (1.73, 3.10)
Kleijer et al.[48] (2009)	'PHARMO' record, Hospital discharge diagnoses	Mixed indications	50+	Stroke	Stroke (518) No stroke (2030)	Not assessed	FGAs vs SGAs: OR 2.6 (1.3, 5.0) SGAs + FGAs vs no use: OR 9.9 (5.7, 17.2) [first week of treatment]

aRR = rate ratio (adjusted); **FGAs** = first-generation antipsychotics; **HAL** = haloperidol; **no use** = no use of antipsychotics; **OLA** = olanzapine; **OR** = odds ratio (adjusted); **QUE** = quetiapine; **RIS** = risperidone; **SGAs** = second-generation antipsychotics; **TIAs** = transient ischaemic attacks.

hospitalized for septicaemia or urinary tract infection. The drug regimen was defined by the last recorded prescription before the event. The odds ratio (OR), adjusted for a number of possible risk factors, showed no significant differences between subjects exposed to risperidone (0.87), olanzapine (1.32), conventional antipsychotics (1.24) and controls. Data also suggested an interaction between previous cerebrovascular events and the use of olanzapine (table IV).

In a case-control study,[47] cases and controls were identified using information from the hospital discharge diagnoses of all subjects admitted over a 1-year period in the Lombardia region. The proportion of CVAs in individuals exposed to antipsychotics and unexposed individuals was 2.65% and 2.15%, respectively, with an OR of 1.24. Compared with patients treated with haloperidol, the group exposed to risperidone had a significantly higher OR (1.43); clozapine, olanzapine and quetiapine were not significantly different from haloperidol. No information was available concerning risk factors for the whole group, other than age, sex and prescriptions.

A study using the General Practice Research Database[7] used the same subjects before starting antipsychotic therapy as their own controls. Therapy was defined as 'at least one prescription' for an antipsychotic. A higher rate ratio was found during the treatment period with conventional (1.69) and atypical antipsychotics (2.32). The ratio was higher in the subgroups of subjects with dementia (3.50). When the analysis was restricted to patients with haemorrhagic stroke, the difference was no longer significant.

A study[48] based on a drug claim database, and the hospital discharge diagnoses of both ischaemic and haemorrhagic stroke and TIAs, sampled a group of cases with 'first admission for stroke' and controls with no history of stroke.

The adjusted OR in current users of all antipsychotic drugs was 1.6 and users of conventional antipsychotics had an increased risk of stroke compared with users of atypical antipsychotics (2.6). No differences in the risk of ischaemic or haemorrhagic stroke were observed. Agents with a high serotonergic affinity showed a protective effect (OR = 0.5). For the first time, a specific time pattern for the emergence of stroke was documented as the ratio was higher (9.9) in the first week of treatment compared with controls. In the following weeks, the ORs for the groups of treated and untreated patients substantially overlapped. Prescription of antithrombotic agents was reported in 60.2% of cases and 32.6% of controls.

3.3 Observational Studies: Strengths and Limitations

Observational studies have their own strengths and weaknesses. A strength is that subjects can be taken from community samples, which may be more representative than nursing home patients, where more physically frail subjects can be expected. Another strong point is the availability of estimates for a relatively rare event, such as a CV accident, in large numbers of exposed patients. Observational studies can test if conventional antipsychotics are associated with a different risk compared with atypicals, and if the risk is restricted to patients with dementia or the elderly population at large. A further added value of observational studies is that many possible confounders, such as previous cerebrovascular events, hypertension, diabetes, heart disease, other physical risk factors and concomitant use of large numbers of medications can be included in multivariate analyses; however, some studies considered only a few variables,[43,47] and databases are not informative about variables related to unhealthy lifestyles.

A weakness is that both ischaemic and haemorrhagic stroke were usually investigated and pooled, although the two events are different. Another weak point is that antipsychotics were frequently grouped together according to their class (conventional or atypicals) but the two labels comprise drugs with distinct chemical and biological profiles. The continuity of antipsychotic exposure is an important issue that was considered in only a few studies. For example, two Canadian studies[40,41] correctly defined the period of exposure by the regular refilling of prescriptions, and the follow-up period ended when no further prescriptions were dispensed. Similarly, a continuity of prescription was also taken into account in the Health Search Database study,[6] with a carryover time of 2 months after the last prescription. However, in another study,[47] the outcome variable (stroke) was taken from hospital discharge diagnoses in 2002, but drug prescriptions were filled in 2001. In a self-controlled case-series study,[7] the criteria for study entry was 'at least one prescription of an antipsychotic', but no clear-cut criteria were given for drug intake after the index prescription.

4. Main Findings

Evidence from controlled clinical trials and population studies leads to some important findings.

A higher rate of CVAs was constantly found in RCTs, but since CVAs were rare, the difference between patients exposed to antipsychotics and controls was significant in only some aggregate studies or meta-analyses.[2,4] The risk of CVAs in exposed patients was also found to be higher in observational studies[6,7,45,47,48] and in the elderly population at large,[6,7,45,47,48] irrespective of a diagnosis of dementia. The only cohort study[47] that did not find a higher risk of CVAs had a low number of subjects exposed to first-generation antipsychotics (187); 1587 were exposed to second-generation antipsychotics. Conventional antipsychotic drugs were found to be associated with a risk similar to that of atypical antipsychotics.[40,41]

Preliminary evidence from clinical trials and observational studies highlight a specific risk-patient profile: older age, cognitive impairment, vascular dementia, concurrent use of anticoagulants, atrial fibrillation, hypertension and a history of previous stroke. Furthermore, data from large observational cohorts indicate that

cerebrovascular risk is not confined to patients with dementia, but more generally involves elderly patients treated with antipsychotics for other illnesses.

Another important point is that the risk involves all classes of antipsychotics so that conventional antipsychotics are at least equal to atypical antipsychotics in their liability to cause stroke. The increase in the number of cerebrovascular deaths in patients with schizophrenia observed during the era of the conventional antipsychotics[49-51] is large, and independent support for the finding that the relationship between cerebrovascular events and the use of antipsychotics is not restricted to atypical antipsychotics.

Cerebrovascular accidents are over-represented during the restricted time period corresponding to the earliest phases of treatment with antipsychotics. Thereafter, a progressive decline in the risk towards normal or almost normal rates occurs. This conclusion is supported by observational studies[45,48] that found a significantly higher rate of CVAs during the first weeks of exposure. In three published, placebo-controlled clinical trials of risperidone, approximately half of the cerebrovascular events reported also occurred within the first weeks of treatment.[23,52] This peculiar temporal course could account for some discrepancy in the results obtained in placebo-controlled clinical trials and observational studies. Placebo-controlled clinical trials are mostly short-term studies and thus the difference in the cerebrovascular risk between active and placebo groups is maximized. On the contrary, since population studies cover longer periods of time, they may report smaller differences in the rates of CVAs observed in individuals exposed to antipsychotics, and non-exposed controls. The early limited time period in which antipsychotics are associated with an increased number of cerebrovascular events also clearly indicates that initial estimates, valid for patients with dementia, of the number needed to harm (NNH) for 1 year of therapy are too pessimistic because they were calculated by extrapolating the results of short-term trials and assumed that the relationship between exposure to antipsychotics and cerebrovascular risk remains constant over time. If this were the case, a 2% incidence in an RCT with an average exposition of 2 months would mean a 12% 1-year incidence. The NNH in this case would be 8.3 over 1 year; the estimated NNH in large databases, such as our study, would be 28.6.

5. Possible Pathological Pathways

The demonstration that cerebrovascular events largely occur at the start of treatment with antipsychotics undoubtedly suggests some causal involvement of the treatments even though proof of a dose-response relationship is persistently lacking.

A possible pathway by which antipsychotics may cause stroke is the facilitation of thrombosis. A 24-fold higher risk of venous thromboembolism was reported for low-potency antipsychotic drugs,[53] with a similar association also being shown for clozapine.[54] A recent study[55] has collected preliminary evidence that some second-generation antipsychotics are also associated with venous thromboembolism, while another study[56] found a slightly higher risk for novel antipsychotics, ranging from 1.87 to 2.68, but not for older antipsychotics. A review [57] hypothesized that possible mechanisms for thrombosis included drug-induced sedation, obesity, hyperleptinaemia, antiphospholipid antibodies and increased activity in the coagulation system. Some studies have suggested that cardiovascular effects may be operating, such as orthostatic hypotension and arrhythmias. In a community survey, 11 707 persons were followed up for 7.9 years; those with orthostatic hypotension at baseline had a 2-fold higher risk for stroke at follow-up.[58]

Pathological pathways may also involve susceptibilities to stroke in common with dementia, schizophrenia and affective illness per se. There is some evidence of abnormal levels of interleukin-6, a pro-inflammatory cytokine possibly involved in stroke,[59,60] in people with dementia,[61] schizophrenia[62] and major depression.[63] Similarly, increased levels of homocysteine have been reported in patients with stroke, Alzheimer's disease, Parkinson's disease and, possibly, schizophrenia and mood disorders;[64] multiple abnormalities in phospholipid metabolism have

been observed in patients with stroke, Alzheimer's disease and other degenerative diseases, schizophrenia and bipolar disorder.[65] In addition, the inhibition of histone deacetylases has been proposed as an epigenetic basis for stroke and a number of neurodegenerative and neuropsychiatric disorders.[66] Preclinical research on agonists of group two metabotropic glutamate receptors is targeting these drugs for possible therapeutic use in stroke, neurodegenerative disorders, schizophrenia and depression.[67]

Some studies have suggested that antipsychotics could have medium- to long-term neuroprotective effects that could counteract stroke. Preliminary reports of preclinical pharmacology indicate that pretreatment with very low doses of olanzapine, risperidone and haloperidol can reduce the volume of infarcts in animals with experimental focal cerebral ischaemia.[68-71]

Although dementia is a major indication for the use of antipsychotics in the elderly, a substantial number of those taking antipsychotics are affected by other severe mental illness, such as schizophrenia or affective disorders. Schizophrenia could facilitate increase in strokes and related accidents through a familial, possibly genetic, special predisposition to well established cerebrovascular risk factors such as diabetes, obesity and smoking.[72-75] In these cases, even some societal factors may be related to the incidence of stroke, such as poor interest in or stigma about mentally disabled individuals and poor funding for the prevention of risk. Distressed family carers may not give attention to the somatic problems of the patients, who cannot take care of their health and may persistently follow unhealthy lifestyles.

The specific contributions of antipsychotics and other risk factors for CVAs may be well integrated within a comprehensive model that views cerebrovascular disorders during treatment with antipsychotics as a complex outcome in which therapy plays a fast permissive role that is able to trigger stroke and related events when sufficient antecedent susceptibilities are also present. We have devised a hypothetical model to include all these factors (see figure, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A25).

6. Practical Recommendations for the Physician

While waiting for the regulatory agencies to provide new indications about the risk of stroke for conventional and atypical antipsychotics, and for diagnoses other than dementia, clinicians can follow some practical recommendations.

In general, antipsychotics, both conventional and atypicals, should be prescribed with care in elderly patients with dementia, and only when any delay to their use conflicts with the best interests of the patient and/or alternative treatment options have failed. Special caution should be taken for older patients with vascular dementia and severe cognitive impairment because these subjects are at higher risk of CVAs. Before starting therapy with an antipsychotic drug, physicians should provide adequate information to the patient, the family or the substitute decision maker to obtain explicit consent. A number of reasons force this very conservative approach; indeed, the prescription is off-label, a 'black-box' warning about the risk of death exists,[76,77] and current evidence indicates that, in a considerable proportion of this population, disabling adverse events associated with conventional and atypical antipsychotics may offset their efficacy in the control of the symptoms of psychosis, agitation and aggressive behaviour.[4,9,14,15,78]

For patients with and without dementia, the lack of current evidence of relevant drug- or class-specific differences on cerebrovascular risk implies that selection of the first-choice antipsychotic must be tailored for each individual patient, based on past experiences with antipsychotics, the specific risks for a large number of potential adverse iatrogenic health effects and the presence of specific domains of psychopathology.[79-81]

Once it is established that an elderly patient is in need of therapy with antipsychotics, and the choice of the drug customized, vigorous efforts should be made to reduce or minimize the influence of modifiable predisposing cerebrovascular risk factors. In patients with dementia, in whom individual cognitive interventions do not apply, careful monitoring of environmental factors must be undertaken by the family or substitute carers.

The emergence of stroke and related accidents is largely concentrated in the first weeks of exposure to antipsychotics; therefore, patients should be carefully monitored during this period.

This programme is clearly interdisciplinary because it implies the need to deal with problems of distinct, highly specialized branches of medicine, and thus is probably beyond the competence of one physician, even after specific and qualified training is given to cover the different areas of interest. Interventions by a multiprofessional team seem better suited to guarantee comprehensive care to elderly neuropsychiatric patients in need of treatment with antipsychotic drugs. In this way, the expertise of psychiatrists and/or, in the case of patients with dementia, neurologists, may integrate well with that of general practitioners, geriatricians and other medical specialists, nurses and case managers. An integrated medical and psychiatric care model probably represents one of the most reasonable strategies for improved management of the physical risk and co-morbidities that typically affect patients with severe mental disorders, irrespective of age.

7. Conclusion

In summary, before prescribing an antipsychotic, clinicians should weigh all the risk factors for a given patient and consider not only the indications as provided by the regulatory agencies, but also the overall effectiveness of conventional and atypical antipsychotics.

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Correspondence: Professor *Emilio Sacchetti*, Department of Psychiatry, Brescia University School of Medicine, P.le Spedali Civili 1, 25100, Brescia, Italy.
E-mail: sacchett@med.unibs.it