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Papers

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study

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Abstract

Objective To compare the incidence of admissions to hospital for stroke among older adults with dementia receiving atypical or typical antipsychotics.
Design Population based retrospective cohort study.
Setting Ontario, Canada.
Patients 32 710 older adults (≥65 years) with dementia (17 845 dispensed an atypical antipsychotic and 14 865 dispensed a typical antipsychotic).
Main outcome measures Admission to hospital with the most responsible diagnosis (single most important condition responsible for the patient's admission) of ischaemic stroke. Observation of patients until they were either admitted to hospital with ischaemic stroke, stopped taking antipsychotics, died, or the study ended.
Results After adjustment for potential confounders, participants receiving atypical antipsychotics showed no significant increase in risk of ischaemic stroke compared with those receiving typical antipsychotics (adjusted hazard ratio 1.01, 95% confidence interval 0.81 to 1.26). This finding was consistent in a series of subgroup analyses, including ones of individual atypical antipsychotic drugs (risperidone, olanzapine, and quetiapine) and selected subpopulations of the main cohorts.
Conclusion Older adults with dementia who take atypical antipsychotics have a similar risk of ischaemic stroke to those taking typical antipsychotics.

Introduction

A variety of behavioural disturbances such as physical aggression, agitation, hallucinations, and wandering commonly accompany dementia. The term behavioural and psychological symptoms of dementia—BPSD—describes this spectrum of non-cognitive manifestations of dementia.[1] The presence of BPSD can decrease quality of life for patients and caregivers, and increases the likelihood of the patient being placed in an institution.[2]

Treatment of BPSD is challenging. A variety of non-pharmacological and pharmacological approaches have been assessed.[3 4] Atypical antipsychotics are often prescribed to manage BPSD. Although such prescriptions represent off-label prescribing, this practise is widely endorsed because atypical antipsychotics are among the best studied treatments for BPSD and there is a perception that they have fewer adverse effects than typical antipsychotics.[5 6] Recently, however, concerns have been raised that atypical antipsychotics may increase the risk of cerebrovascular adverse events, including stroke, among older adults with BPSD.

In October 2002, Health Canada and Janssen-Ortho (a manufacturer of atypical antipsychotics) issued a warning to Canadian clinicians of a possible link between risperidone use and cerebrovascular adverse events.[7] This concern emerged from a clinical trial evaluating risperidone in the management of BPSD,[8] and a subsequent meta-analysis of the risperidone trials for this indication also showed more cerebrovascular adverse events among participants receiving risperidone (4%) than among participants receiving placebo (2%).[9] The US Food and Drug Administration issued a similar warning in April 2003.[10] More recently, pooled data from clinical trials evaluating olanzapine for BPSD have shown that it may also be associated with an increased risk of cerebrovascular adverse events.[11 12] These data suggest around a threefold increase in the relative risk of cerebrovascular events among people taking risperidone or olanzapine. Based on these data, the UK Committee on Safety of Medicines issued a warning in March 2004 advising that risperidone and olanzapine should no longer be used to manage BPSD, and that patients already receiving these drugs for BPSD should be switched to other treatments.[12] These warnings have led to controversy among clinicians.[13 14] To date, the warnings only extend to older adults receiving atypical antipsychotics for BPSD and not to patients receiving these drugs for schizophrenia or other indications. No warnings have been issued on the use of other atypical agents, such as quetiapine or aripiprazole, as few studies have been published on their use to manage BPSD. Recent data from a clinical trial of quetiapine to treat BPSD show no increased risk of cerebrovascular adverse events compared with placebo.[15]

The potential link between atypical antipsychotics and cerebrovascular adverse events in patients with BPSD is important, given the common use of these drugs in this patient population. If atypical antipsychotics are thought unsafe, clinicians may consider using typical antipsychotics to treat BPSD. We compared the incidence of admissions to hospitals for stroke among older adults with dementia who received atypical or typical antipsychotics.

Methods

From administrative healthcare databases in Ontario, Canada, we identified older adults with a diagnosis of dementia and with no history of antipsychotic drug use. In Ontario, a universally funded health programme covers most doctor services, drugs, and hospital services for patients aged 65 and older. We used

encrypted unique identifiers that are common between the databases to link anonymous information on personal details and use of health services for patients in our study. The linked databases included computerised pharmacy records of the Ontario Drug Benefit Database, which records prescription drugs dispensed to all Ontario residents aged 65 years or older. Records for admission to hospital for acute care were obtained from the Canadian Institute for Health Information Discharge Abstract Database, which uses nomenclature from the ICD-9 (international classification of diseases, 9th revision) to provide detailed diagnostic records for all hospital admissions. We obtained information on doctors' billing for inpatient and outpatient services from the records of the Ontario Health Insurance Plan, and basic personal information and vital statistics for each patient from the Registered Persons Database.

Cohort

We identified two cohorts within the population of older adults with dementia (Ontario Health Insurance Plan and ICD-9 codes 290, 331, and 797): those who were new users of any of three atypical antipsychotics (risperidone, olanzapine, and quetiapine) and those who were new users of either high potency typical antipsychotics or low potency typical antipsychotics. Typical antipsychotics included in this analysis were haloperidol, fluphenazine, thiothixene, pimozide, trifluoperazine, flupenthixol, zuclopenthixol, thioproperazine, chlorpromazine, thioridazine, mesoridazine, loxapine, perphenazine, promazine, pericyazine, and chlorprothixane. We excluded patients who were receiving non-oral antipsychotics (for example, injectable or depot preparations), and patients with other psychotic disorders such as schizophrenia that might affect their pattern of drug use. The atypical antipsychotic clozapine was not commonly used in Ontario during the period under study, and we therefore excluded patients who were taking this drug. Other atypical antipsychotics (including aripiprazole and ziprasidone) are not currently licensed for use in Canada. We did not include a cohort of non-antipsychotic users, as preliminary data show several important baseline differences between patients receiving antipsychotics and those not receiving antipsychotics. We did not include cohorts of patients taking other psychotropics for BPSD, such as trazadone or valproate, as these are also used for other indications.

Patient observation

We enrolled patients into the cohorts between 1 April 1997 and 31 March 2002. To restrict our cohorts to new users of antipsychotics, we looked back one year from the first date the antipsychotic was dispensed to ensure that no such drugs had been previously prescribed. We considered that exposure to the antipsychotic had stopped if no further data on a dispensed drug were recorded in the Ontario Drug Benefit Database within a period of two times the total days supplied for the initial date the drug was dispensed. This implied that patients were no longer taking the antipsychotic.

Ischaemic stroke

Our primary outcome was admission to hospital with a most responsible diagnosis of ischaemic stroke (ICD-9 codes 431, 434, and 436). Validation studies have established an accuracy rate of 90% for the diagnosis of stroke based on these codes.[16] Most responsible diagnosis refers to the single most important condition responsible for admission. It is a term used by trained abstractors who complete data collection for the Canadian Institute for Health Information to distinguish between the main reason for admission and comorbid conditions. We were therefore able to distinguish between old strokes and new outcome events.

Although the concerns surrounding atypical antipsychotics involve cerebrovascular adverse events, including both transient ischaemic attacks and stroke, we focused exclusively on the outcome of stroke for several reasons: firstly, the diagnostic accuracy for transient ischaemic attacks is relatively poor in administrative databases; secondly, comparatively few patients with transient ischaemic attacks are admitted to hospital; and, thirdly, the risk of stroke in the period immediately after a transient ischaemic attack is high, suggesting that we might capture subsequent events with the coding for stroke.[17–20]

Patients were observed until they were admitted to hospital with ischaemic stroke, stopped taking their antipsychotic, died, or the study ended (31 March 2002). Patients in the cohort receiving atypical antipsychotics were censored if they switched between atypical antipsychotics, to allow us to assess hazards associated with each of the three atypical drugs under study. Patients in the cohort receiving typical antipsychotics were censored if they switched to atypical antipsychotics. The coding accuracy of drug claims in the Ontario Drug Benefit Database is excellent, with an error rate of only 0.7%.[21]

Statistical analysis

We first calculated crude incidence rates of stroke for the cohorts, using the number of events per 1000 patient years. To examine the independent effect of use of atypical antipsychotics on developing ischaemic stroke, we conducted survival analysis using Cox proportional hazards models. The covariates in our models included factors that would influence the development or the recognition of incident ischaemic stroke.[22] These factors include age; sex; low income status; residence in long term care; frequency of medical contact (number of physician claim days per patient per year); medical conditions such as prior stroke, atrial fibrillation, diabetes mellitus, acute myocardial infarction in the past three months, congestive heart failure; and overall burden from comorbid disease. As an overall measure of comorbidity, we used the number of distinct drugs dispensed in the year before entry to the cohort,[23] a measure that performs as well as the Charlson comorbidity index in risk adjustment.[24] We also controlled for the concomitant use of drugs that might influence the risk of stroke or recognition (for example, antihypertensives, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapies). Finally, given the duration of our study and the potential for changes in patient care over this period, we controlled for year of entry to the study. Analyses were performed with SAS for UNIX, version 8.2.

We then carried out subgroup analyses on selected populations of the cohorts. This was done to examine subgroups that either were similar to patients in the trials (for example, most patients in the trials of atypical antipsychotics for managing BPSD were in long term care[25]) or were at high risk of stroke (for example, a history of prior stroke or atrial fibrillation). We also examined the risks from use of individual atypical antipsychotic drugs. Finally, we carried out a subgroup analysis of patients enrolled between 1 April 2000 and 31 March 2002. This analysis was done to address major shifts in the prescribing of atypical antipsychotics and typical antipsychotics between 1997 and 2002.

Results

We identified 32 710 older adults with dementia (17 845 dispensed atypical antipsychotics and 14 865 dispensed typical antipsychotics). The atypical antipsychotic cohort included

Table 1 Personal characteristics and details of comorbidity in cohorts of older adults (≥65 years) with dementia who received atypical antipsychotics or typical antipsychotics. Values are numbers (percentages) unless stated otherwise

Characteristics	Atypical antipsychotics cohort (n=17 845)	Typical antipsychotics cohort (n=14 865)
Mean (SD) age (years)	82.5 (7.3)	82.7 (7.4)
Men	6431 (36.0)	5727 (38.5)
Long term care	8485 (47.5)	7682 (51.7)
Low income	6688 (37.5)	5807 (39.1)
Urban residence	2807 (15.7)	2673 (18.0)
Mean (SD) frequency of medical contact (days)*	33.3 (25.4)	34.3 (26.8)
Year of entry to cohort:		
1997	598 (3.4)	5452 (36.7)
1998	1588 (8.9)	4570 (30.7)
1999	3696 (20.7)	2680 (18.0)
2000	5589 (31.3)	1321 (8.9)
2001	6374 (35.7)	842 (5.7)
Chronic users†	13792 (77.3)	9929 (66.8)
Overall comorbidity (Charlson comorbidity index score):		
No prior admission to hospital	3969 (22.2)	3068 (20.6)
0 (prior admission with no comorbidities listed)	6824 (38.2)	5173 (34.8)
1	3439 (19.3)	3080 (20.7)
2	1795 (10.1)	1615 (10.9)
≥3	1818 (10.2)	1929 (13.0)
Conditions affecting risk of stroke:		
Prior stroke	1330 (7.5)	1189 (8.0)
Atrial fibrillation	1992 (11.2)	1672 (11.2)
Hypertension	10894 (61.0)	8620 (58.0)
Diabetes mellitus	3404 (19.1)	2756 (18.5)
Acute myocardial infarction	396 (2.2)	391 (2.6)
Congestive heart failure	4582 (25.7)	4130 (27.8)
Endocarditis	2 (<0.1)	1 (<0.1)
Rheumatic heart disease	317 (1.8)	239 (1.6)
Malignant neoplasm	4771 (26.7)	4196 (28.2)
Procedures affecting risk of stroke:		
Electrical cardioversion for atrial fibrillation in past 3 months	11 (0.1)	9 (0.1)
Coronary angiography or angioplasty in past 3 months	15 (0.1)	16 (0.1)
Carotid endarterectomy in past 3 months	4 (<0.1)	1 (<0.1)
Drug history and drugs affecting risk of stroke:		
Mean (SD) total No of drugs per patient	8.7 (5.3)	8.5 (5.5)
Any psychotropic	10877 (61.0)	8731 (58.7)
Benzodiazepines	7367 (41.3)	6420 (43.2)
Warfarin	1582 (8.9)	1248 (8.4)
Antiplatelets:		
Aspirin	2799 (15.7)	2324 (15.6)
Ticlopidine	304 (1.7)	263 (1.8)
Clopidogrel	130 (0.7)	22 (0.1)
Combined dipyridamole and aspirin	14 (0.1)	2 (<0.1)
Antihypertensives:		
Diuretics	2154 (12.1)	1500 (10.1)
β blockers	2172 (12.2)	1594 (10.7)
Calcium channel blockers	3345 (18.7)	2545 (17.1)
Combination therapies	88 (0.5)	54 (0.4)
Angiotensin II receptor blockers	274 (1.5)	117 (0.8)
Angiotensin converting enzyme inhibitors	4697 (26.3)	3281 (22.1)
3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors	1324 (7.4)	563 (3.8)
Antidiabetic drugs	2099 (11.8)	1681 (11.3)
Hormone replacement therapies:		
Oestrogen	796 (4.5)	483 (3.2)
Tamoxifen	137 (0.8)	112 (0.8)
Raloxifene	8 (<0.1)	1 (<0.1)

*No of claim days to Ontario Health Insurance Plan per patient per year in year before entry to cohort.
†≥2 consecutive prescriptions for antipsychotics.
‡Claim to Ontario drug benefit programme for any cholinesterase inhibitor (donepezil, rivastigmine, or galantamine) in year before index (these drugs were first listed on programme in June 1999).

Table 2 Event rates and hazard ratios for older adults with dementia receiving atypical or typical antipsychotics

Main analysis (full cohorts)	Atypical antipsychotic cohort (n=17 845)	Typical antipsychotic cohort (n=14 865)
No (%) of new admissions for ischaemic stroke	284 (1.6)	227 (1.5)
Mean (SD) duration of follow up (days)	227.2 (264.0)	250.1 (335.4)
Crude event rate (No of events per 1000 person years)*	25.5	22.3
Unadjusted hazard ratio (95% CI)	1.06 (0.89 to 1.27)	1.00
Adjusted hazard ratio (95% CI)†	1.01 (0.81 to 1.26)	1.00

*(No of events/total No of days per 365 days)×1000.
†Adjusted for age; sex; low income status; residence in long term care; frequency of medical contact; year of entry to cohort; history of stroke in past five years; history of atrial fibrillation; hypertension; diabetes mellitus; acute myocardial infarction in past three months; congestive heart failure; number of distinct drugs; chronic use (≥2 consecutive prescriptions) of antipsychotics; and baseline use of warfarin, antiplatelet drugs, antihypertensive drugs, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapy.

13 503 (75.7%) patients receiving risperidone, 3459 (19.4%) receiving olanzapine, and 883 (4.9%) receiving quetiapine. Table 1 lists the personal characteristics and comorbidities of patients in both cohorts. In general, the cohorts had similar personal details (standardised differences for most comparisons were $<10\%$). Baseline characteristics were also similar for the subcohorts taking high potency typical antipsychotics (57.1%) and low potency typical antipsychotics (42.9%; data not shown). Between 1997 and 2002 a major shift took place towards increased prescribing of atypical antipsychotics. Traditional risk factors for ischaemic stroke, such as atrial fibrillation, hypertension, diabetes, and prior stroke, were common among older adults with dementia (table 1).

In the unadjusted and multivariate analyses, we found that the risk of ischaemic stroke in older adults with dementia receiving atypical antipsychotics was not significantly different from those receiving typical antipsychotics (unadjusted hazard ratio 1.06, 95% confidence interval 0.89 to 1.27; adjusted hazard ratio 1.01, 0.81 to 1.26; table 2).

The subgroup analyses were all consistent with the main analysis as they showed no significant differences in the development of stroke between the cohorts receiving atypical antipsychotics and those receiving typical antipsychotics (table 3). The risk of stroke for patients receiving risperidone (adjusted hazard ratio 1.04, 0.82 to 1.31), olanzapine (0.91, 0.62 to 1.32), and quetiapine (0.78, 0.38 to 1.57) was not significantly different from that of patients receiving typical antipsychotics. Patients dispensed two or more consecutive prescriptions (chronic users) of atypical antipsychotics were not at increased risk of stroke compared with chronic users of typical antipsychotics. Finally, the risk of stroke in the subgroup of patients enrolled between 1 April 2000 and 31 March 2002 was not significantly different between those receiving atypical antipsychotics and those receiving typical antipsychotics (adjusted hazard ratio 0.98, 95% confidence interval 0.65 to 1.47).

Discussion

In this population based cohort, older adults with behavioural and psychological symptoms of dementia (BPSD) who received atypical antipsychotic drugs seem to have a similar risk of admission to hospital for ischaemic stroke as those receiving typical antipsychotic drugs. These findings are important because of the frequency with which atypical antipsychotics are used to manage BPSD.[6] Our results may help to inform drug prescribing for this group of patients.

Table 3 Event rates and hazard ratios for subgroup analyses of older adults with dementia receiving atypical or typical antipsychotics

Characteristics	Atypical antipsychotics cohort	Typical antipsychotic cohort
History of stroke	**(n=1330)**	**(n=1189)**
No (%) of new admissions for ischaemic stroke	103 (7.7)	75 (6.3)
Mean (SD) duration of follow up (days)	217.1 (251.8)	235.0 (336.2)
Crude event rate (No of events per 1000 person years)*	130.4	98.2
Unadjusted hazard ratio (95% CI)	1.18 (0.88 to 1.59)	1.00
Adjusted hazard ratio (95% CI)†	0.80 (0.55 to 1.16)	1.00
Long term care resident at baseline	**(n=8485)**	**(n=7682)**
No (%) of new admissions for ischaemic stroke	124 (1.5)	98 (1.3)
Mean (SD) duration of follow up (days)	225.7 (267.2)	253.1 (336)
Crude event rate (No of events per 1000 person years)*	23.7	18.4
Unadjusted hazard ratio (95% CI)	1.18 (0.91 to 1.54)	1.00
Adjusted hazard ratio (95% CI)†	1.15 (0.82 to 1.60)	1.00
Chronic users‡	**(n=13 792)**	**(n=9929)**
No (%) of new admissions for ischaemic stroke	214 (1.6)	163 (1.6)
Mean (SD) duration of follow up (days)	280.6 (277.7)	352.7 (367.1)
Crude event rate (No of events per 1000 person years)*	20.2	17
Unadjusted hazard ratio (95% CI)	1.11 (0.91 to 1.37)	1.00
Adjusted hazard ratio (95% CI)†	0.89 (0.69 to 1.17)	1.00
History of atrial fibrillation	**(n=1992)**	**(n=1672)**
No (%) of admissions for ischaemic stroke	52 (2.6)	34 (2.0)
Mean (SD) duration of follow up (days)	195.6 (233.1)	195.6 (288.6)
Crude event rate (No of events per 1000 person years)*	48.8	38
Unadjusted hazard ratio (95% CI)	1.23 (0.79 to 1.89)	1.00
Adjusted hazard ratio (95% CI)†	1.23 (0.70 to 2.02)	1.00

*(No of events/total No of days per 365 days)×1000.
†Adjusted for age; sex; low income status; residence in long term care; frequency of medical contact; year of entry to cohort; history of stroke in past five years; history of atrial fibrillation; hypertension; diabetes mellitus; acute myocardial infarction in past 3 months; congestive heart failure; number of distinct drugs; chronic use (≥2 consecutive prescriptions) of antipsychotics; baseline use of warfarin, antiplatelet drugs, antihypertensives, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapy. Factors not included in risk adjustment when they were focus of subgroups analysis were residence in long term care, history of stroke in past five years, history of atrial fibrillation, and chronic use of antipsychotics.
‡≥2 consecutive prescriptions.

The findings from our main analysis were consistent with those for all subgroups we tested. The incidence rates for stroke corresponded well with those reported by other investigators and highlight the relatively high risk of ischaemic stroke among older adults with dementia.[26] We found higher incidence rates of stroke in those subgroups with established risk factors for stroke, such as atrial fibrillation and prior stroke, than in the main analysis. In contrast, we found no increase in risk among chronic users (two or more consecutive prescriptions) of atypical antipsychotics, suggesting the absence of an association between atypical antipsychotics and cerebrovascular events. In effect, with increasing duration of exposure there seems to be no increased risk of the outcome.

Several investigators found no association between use of atypical antipsychotics and cerebrovascular events.[27–29] In addition, recent data from a trial evaluating quetiapine for BPSD showed no increased risk of cerebrovascular adverse events compared with placebo.[15] Our large population based study supports these findings. In contrast, earlier clinical trials of risperidone and olanzapine reported a link between use of atypical antipsychotics and cerebrovascular adverse events, including ischaemic stroke.[9 11] It could be speculated that in these trials events other than transient ischaemic attacks and strokes were classified as "cerebrovascular adverse events." If atypical agents do contribute to the risk of stroke, however, a plausible biological rationale must exist. The risk seems to develop quickly (6-12 weeks in clinical trials), and thus it seems unlikely that the risk is mediated through drug effects on risk factors such as glucose or lipid metabolism. Similarly, drug induced atrial fibrillation would be an unlikely explanation for such a rapid increase in the risk of cerebrovascular adverse events. Potential mechanisms for cerebrovascular events related to atypical antipsychotics might include orthostatic hypotension in patients with pre-existing cerebrovascular disease, which might lead to "watershed" strokes,[14] and antipsychotic induced hyperprolactinaemia, which might promote platelet aggregation.[14 30] Others, however, have reported that risperidone may inhibit platelet aggregation (through serotonin receptor antagonism), rather than promote it.[31] Some observational data have shown that antipsychotics might be associated with an increased risk of venous thromboembolic disease[32]; arterial thrombosis such as stroke, however, shares few risk factors with venous thrombosis. In summary, a clear biological rationale has not yet been identified for an increased risk of stroke associated with use of atypical antipsychotics. The collection of data on "cerebrovascular adverse events" may have been influenced by patients' receipt of active drug therapy or placebo in the clinical trials. For example, it is possible that patients given antipsychotic treatment with relief of psychoses might report more symptoms than patients given placebo.[14]

Limitations of study

Our study has several potential limitations. Firstly, our study was observational, and although the baseline differences between our cohorts were minor, we may not have been able to adjust adequately for such differences. Important confounders may also have been unmeasured and unrecognised. We tried to avoid confounding by indication by specifically excluding data from the period after the first warning of cerebrovascular adverse events was issued (October 2002).[7] Before this time, the choice between typical antipsychotics and atypical antipsychotics was not affected by concerns about such adverse events. A second limitation is the possibility of ascertainment bias because some strokes may not have been captured if they did not lead to admission to hospital or if they led immediately to death. Despite the potential for ascertainment bias, we kept our primary outcome as admission to hospital for stroke given the accuracy with which this diagnosis is captured in the data we used. We believe that most strokes in this patient population would have resulted in hospital admission. Thirdly, given the limitations of the administrative data, we could not adjust for all of the important factors affecting the risk of stroke, such as smoking history, presence and severity of hypertension, lipid status, and specific valvular heart conditions.

What do these results mean for clinical practice? Clinicians managing patients with dementia who develop behavioural disturbances should initially rule out underlying medical illnesses or drugs that might predispose to delirium.[33] If BPSD is diagnosed, clinicians should initially consider non-pharmacological harm reduction strategies such as education of family members, ABC charting, and music therapy.[3] If pharmacotherapy is considered necessary, it should be tailored to the individual. Our data show that the risk of ischaemic stroke is similar for patients receiving atypical antipsychotics and those receiving typical antipsychotics. Other potential risks of antipsychotics (for example, extrapyramidal symptoms, tardive dyskinesia) should also be weighed against the benefits. A

What is already known on this topic

Atypical antipsychotics are commonly used to manage behavioural and psychological symptoms of dementia (BPSD)

Recent evidence from clinical trials suggests an association between atypical antipsychotic use and cerebrovascular events (including stroke) among older adults with BPSD

These data prompted the UK Committee on Safety of Medicines to recommend against the prescribing of atypical antipsychotics to patients with BPSD

What this study adds

Use of atypical antipsychotics by patients with dementia is not associated with a greater risk of stroke is than use of typical antipsychotics

Findings were consistent for a series of subgroup analyses including ones for patients at high baseline risk of stroke

The choice of atypical or typical antipsychotics to manage BPSD should not be based on concerns about the risk of stroke

working group of psychiatrists, general practitioners, and geriatricians in the United Kingdom has developed guidelines for the management of BPSD in people with a history of stroke or transient ischaemic attack.[34] Unfortunately, many of the alternatives to atypical antipsychotics for managing BPSD have received only limited evaluation and have their own important adverse event profiles.[4] The US National Institute of Mental Health is currently sponsoring the clinical antipsychotic trials of intervention effectiveness (CATIE) Alzheimer's disease trial, which is a 36 week study comparing three atypical antipsychotics, a selective serotonin reuptake inhibitor, and placebo to treat BPSD. Results are due in 2006.[35] This study and others[36] should shed light on the optimal management of BPSD and the risk of stroke in this patient population.

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Contributors: SSG, PAR, NH, PEL, and MM conceived the study. All authors contributed to the study design. KS, NG, and SSG performed the data analysis. SSG wrote the initial draft, and all authors critically revised the manuscript. PAR and MM were overseers of the research network. SSG will act as guarantor for the paper.

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Ethical approval: This study was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre.

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