RESEARCH ARTICLE

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Antipsychotics and risk of cerebrovascular events in treatment of behavioural and psychological symptoms of dementia in Hong Kong: a hospital-based, retrospective, cohort study

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Objective: The purpose of this study was to investigate the risk of cerebrovascular adverse events (CVAEs) in patients with behavioural and psychological symptoms of dementia (BPSD) treated with typical or atypical antipsychotics in Hong Kong

Method: This was a retrospective cohort study. Patients aged 65 or above, diagnosed with Alzheimer's disease, vascular or mixed dementia, and first attended the psychiatric service of our unit between 1st January 2000 to 30th June 2007 were studied. The patients were divided into three groups according to their antipsychotic usage. They were compared on sociodemographic and clinical characteristics. The risk of CVAEs was studied by means of Cox regression analysis.

Results: The studied cohort consisted of 1089 patients. The antipsychotic non-user, typical and atypical users groups consisted of 363, 654 and 72 patients, respectively. Incidence rate of CVAE for the three groups were 44.6/1000, 32.7/1000 and 49.6/1000 person years, respectively. The risk of developing CVAEs did not differ in typical or atypical antipsychotic user groups compared with non-user group. The adjusted hazard ratio of typical and atypical antipsychotic user groups were 0.964 (95% CI = 0.584–1.591) and 1.036 (95% CI = 0.350–3.066), respectively. Subgroup analyses of individual antipsychotic did not show a significant increase in risk of CVAEs.

Conclusion: This study showed that there was no statistical difference in risk of cerebrovascular events in treatment of BPSD with typical and atypical antipsychotics compared with non-user group. Nonetheless, given the side effects of antipsychotics, prescription of antipsychotics should be reserved for severe and distressing symptoms with careful consideration.

Key words: antipsychotics; BPSD; cerebrovascular event; dementia; stroke; typical/atypical antipsychotics
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Introduction

Dementia has become an important management problem in psychiatry, as the number of the aging population is rising in the world. The global dementia prevalence in people aged 60 or above was estimated to be 3.9%. Behavioural and Psychological Symptoms of Dementia (BPSD) occur in the majority of people with dementia (Ballard and Oyebode, 1995). BPSD can be defined as a constellation of psychological reactions, psychiatric symptoms and behaviours occurring in people with dementia of any aetiology (International Psychogeriatric Association, 1999). Management of BPSD has long been a great challenge to the psychogeriatricians. Antipsychotic drugs had long been used off-label to treat BPSD and were effective

(Katz *et al*., 1999; Schneider, 1999; Brodaty *et al*., 2003; Sink *et al*., 2005). Atypical antipsychotic drugs were favoured over older preparations to avoid anticholinergic and parkinsonian side effects, but potential risks with atypical antipsychotics included weight gain, diabetes mellitus, hyperlipidaemia, cardiac conduction abnormalities, cerebrovascular adverse events and mortality (Herrmann and Lanctot, 2006; Schneider *et al*., 2006; Ballard, 2007; Mackin *et al*., 2007; Newcomer, 2007).

The prescription habit changed since the U.S. Food and Drug Administration added warnings of increased cerebrovascular adverse events (CVAEs) to the prescribing information for atypical antipsychotics in 2003 (Valiyeva *et al*., 2008). Recent studies had shown that the use of antipsychotics had an increased likelihood of CVAEs, including stroke and transient ischaemic attack in elderly patients (Percudani *et al*., 2005; Katz *et al*., 2007; Schneider *et al*., 2006). However, there were also studies showing that the use of antipsychotics actually did not result in excessive CVAEs (Liperoti *et al*., 2005; Barnett *et al*., 2007). Moreover, there was a dearth of evidence concerning the risk of excessive CVAEs in Chinese patients who were using antipsychotics to treat BPSD.

Therefore, our study aimed to study the incidence of CVAEs in Chinese patients with dementia and compare the risk among antipsychotic non-users, typical and atypical antipsychotic users. We also explored if any particular antipsychotic medications were more likely to cause excessive CVAEs in our patient group.

Method

This is a retrospective, cohort study, carried out in the Department of Psychiatry of the Pamela Youde Nethersole Eastern Hospital (PYNEH). PYNEH is an acute regional hospital, serving a total population of 0.8 million with 0.1 million elderly people aged 65 or above which represents 10% of total elderly population in Hong Kong (http://www.censtatd.gov.hk), to incorporate a comprehensive psychiatric service including out-patient service, day-patient service, in-patient service, out-reach service and consultation service. Referrals for psychiatric assessment of all patients within the catchment area will be directed to the department, and a very high proportion of them will be seen.

Inclusion criteria for patient selection were 1) patients aged 65 or above, 2) diagnosis of dementia (including Alzheimer's disease, vascular and mixed dementia), and 3) first attended the psychiatric service of PYNEH in the study period from 1st January 2000 to 30th June 2007. All medical records of potential patients were then retrieved for screening, review and data collection. Patients who were not Chinese in ethnic origin, were diagnosed other types of dementia or other mental illnesses requiring use of antipsychotics, and received any form of antipsychotics within one year before attending our unit, were excluded from the study.

Medical records of all eligible patients were retrieved for screening, review and data collection. Written medical records in PYNEH were reviewed and supplementary medical information of the same patient from other public hospitals in Hong Kong was obtained through electronic database. Clinical data of patient, including diagnoses, case summaries, laboratory results, radiological results and drug prescription record from all public hospitals can be obtained accurately through this electronic database. Sociodemographic data, including age, sex, marital status, education level, living condition and social support condition were collected. Psychiatric medications used, including antipsychotics, antidepressants and anxiolytics were recorded. The presence of any important co-morbidity including prior stroke, atrial fibrillation, hypertension, diabetes mellitus, hypercholesterolaemia, ischaemic heart disease, congestive heart disease, rheumatic heart disease, smoking and malignant neoplasm were documented. The number of medications prescribed to manage the above conditions was examined and recorded.

Patients were divided into three major groups according to the treatment received, namely antipsychotic non-users, typical antipsychotic users and atypical antipsychotic users. The primary outcome measure was a hospital admission with a primary or principal diagnosis of CVAEs, including subarachnoid, intracerebral, or cranial haemorrhage, cerebral occlusion, stenosis, thrombosis, and others, including transient ischaemic attack. The observation period for non-user group started from the day of first psychiatric assessment for dementia, and for antipsychotic user groups, it started from the first day of antipsychotic prescription. The observation period ended when the patient was admitted for CVAEs, discontinued the initial antipsychotic, switched antipsychotic, died, or until the study ended (30th December 2007). The duration of prescription and the date of discontinuation of treatment can be obtained accurately from written medical notes and electronic database.

All statistical analysis was done by SPSS 15.0 (SPSS Inc, Chicago, IL). Descriptive statistics were performed

to describe sociodemographic data, clinical data and co-morbidities of subjects. Comparison of demographic and clinical data between different antipsychotic user groups was analysed using chi-square test for categorical variables, and independent *t*-test and Mann-Whitney U tests for parametric and non-parametric continuous variables respectively. Fisher's Exact Test was used when a large sample approximation was inappropriate. Incidence rates of CVAEs in the studied subjects were calculated. Survival analysis was applied to determine the association of developing CVAEs and antipsychotics use. Survival time was defined as the time taken to develop CVAEs. Using Kaplan-Meier method, the survival times of subjects who did not develop CVAEs, discontinued antipsychotic treatment, switched antipsychotic, or died before the end of observation were censored. One minus survival functions curves were plotted to illustrate the probability of developing CVAEs over time in different groups. Log rank test was used to assess the significance of the difference between curves. Cox's proportional hazards regression was used to determine hazard ratio of antipsychotic use in development of CVAEs compared with non-user. Hazard ratio was adjusted for age, sex, marital status, education level, residency, type of dementia, prior stroke, atrial fibrillation, hypertension, diabetes mellitus, ischaemic heart disease, congestive heart disease, rheumatic heart disease, hypercholesterolaemia, smoking, malignant neoplasm, and number of drugs prescribed. Because the underlying observation time distribution is rarely normal or comparable between groups, standard statistical techniques cannot be applied usually, and survival analysis and Cox's proportional hazards regression model, which were designed to analyse this type of data, were used in this study (Bewick *et al.*, 2004).

The study was approved by the Ethics Committee of Hong Kong East Cluster.

Results

A total of 1741 patients were identified to suffer from dementia in our unit, and 1693 (97%) medical records were successfully traced and reviewed. After further screening according to the inclusion and exclusion criteria, 1089 patients were included in this study. For the excluded patients, 230 patients had antipsychotic prescription before the study period, 193 patients had diagnoses with other indications for antipsychotics, 127 patients were diagnosed to have other types of dementia, and 54 patients were non-Chinese.

For the included patients, the mean age was 81.04 ± 6.805 and ranged from 65 to 103, and 65.7% of them were female. For education level, 63.5% of the patients had less than primary education level. Near 30% of the patients were institutionalised. For types of dementia, 51.7% of patients were diagnosed to have AD, 37% VaD, and 11.3% mixed type dementia, with an overall mean MMSE score of 12.56 ± 6.184.

Antipsychotic non-user group (non-user group) consisted of 363 patients, typical antipsychotic user group (typical group) consisted of 654 patients and atypical antipsychotic user group (atypical group) consisted of 72 patients. Comparison of the demographic and clinical variables is shown in Table 1. Patients in three groups did not differ with respect to age, sex and marital status. Patients in non-user group were more likely to have higher education level than typical group, secondary level 19.4% *versus* 10.3% ($p < 0.001$) and tertiary level 7.3% *versus* 3.8% ($p = 0.019$), respectively. Patients in typical group were more likely to live in institute than non-user group, 34.4% *versus* 21.7% ($p = 0.032$). Patients in non-user group and typical group were more likely to be suffering from AD than atypical group, 56.2% ($p < 0.001$) and 50.0% ($p = 0.001$) *versus* 44.4%, respectively.

Differences in prescription pattern of psychiatric medications other than antipsychotics were noted between groups. Patients in typical group and atypical group were more likely to have prescription of benzodiazepine than in non-user group (50.6 and 54.2% *versus* 20.4%, $p < 0.001$). It is more likely to be prescribed serotonin-selective reuptake inhibitors in non-user group than typical group ($p = 0.046$), and more likely to have prescription of tricyclic antidepressants in typical group than atypical group ($p = 0.031$).

There was no significant difference in the distribution of different comorbidities between groups, nor was significant difference in smoking status and number of medications prescribed for medical illnesses.

There was a higher proportion of patients in non-user group to develop CVAEs (13.5%) compared with typical group (7.8%, $p = 0.004$). There was no statistically significant difference between typical and atypical groups, or between atypical and non-user groups. Incidence rate of CVAE in the whole cohort was 38.2 per 1000 person years. Incidence rates of CVAE for the non-user group, typical group and atypical group were was 44.6 per 1000 person years, 32.7 per 1000 person years, and 49.6 per 1000 person

Table 1 Characteristics by groups, $n = 1089$

	Antipsychotic non-user	Typical antipsychotic user	Atypical antipsychotic user	
	$n = 363$	$n = 654$	$n = 72$	
Age (mean ± SD, years)	80.47 ± 7.053	81.48 ± 6.714	79.93 ± 6.052	$F_{2,1086} = 1.167$, $p = 0.229$
Sex, *n* (%)				
Male	131 (36.1)	221 (33.8)	22 (30.6)	$\chi^2 = 1.1036$, $p = 0.596$
Female	232 (63.9)	433 (66.2)	50 (69.4)	
Marital Status, *n* (%)				
Single	21 (5.8)	27 (4.2)	2 (2.9)	$\chi^2 = 3.004$, $p = 0.808$
Married	176 (49.0)	313 (49.1)	35 (50.0)	
Widow(er)	157 (43.7)	288 (45.2)	33 (47.1)	
Divorce	5 (1.4)	9 (1.4)	0 (0.0)	
Education level, *n* (%)				
Less than primary	139 (56.3)	273 (68.3)	26(60.5)	$\chi^2 = 19.860$, $p = 0.003$*
Primary	42 (17.0)	71 (17.8)	9 (20.9)	
Secondary	48 (19.4)	41 (10.3)	8 (18.6)	
Tertiary or above	18 (7.3)	15 (3.8)	0 (0.0)	
Residency, *n* (%)				
Public housing	82 (22.8)	151 (24.1)	17 (23.9)	$\chi^2 = 23.411$, $p < 0.001$*
Private housing	199 (55.4)	260 (41.5)	37 (52.1)	
Institution	78 (21.7)	216 (34.4)	17 (23.9)	
Social Support, n (%)				
Living Alone	51 (14.0)	74 (11.3)	9 (12.5)	$\chi^2 = 18.241$, $p = 0.006$*
Living with spouse	30 (8.3)	40 (6.1)	8 (11.1)	
Living with family	204 (56.2)	323 (49.5)	38 (52.8)	
Institution	78 (21.5)	216 (33.1)	17 (23.6)	
MMSE (mean ± SD)	13.59 ± 6.256	11.92 ± 6.101	12.75 ± 5.928	$F_{2,1086} = 6.178$, $p = 0.002$*
Benzodiazepine use, *n* (%)	74 (20.4)	331 (50.6)	39 (54.2)	$\chi^2 = 94.044$, $p < 0.001$*
Antidepressant use, *n* (%)				
TCA	8 (2.2)	26 (4.0)	1 (1.4)	$\chi^2 = 17.327$, $p = 0.027$*
SSRI	71 (19.6)	97 (14.8)	18 (25.0)	
SNRI	6 (1.7)	7 (1.1)	3 (4.2)	
Other	21 (5.8)	28 (4.3)	1 (1.4)	
Not taking	257 (70.8)	496 (75.8)	49 (68.1)	
Hypnotic use, *n* (%)	61 (16.8)	192 (29.4)	36 (50.0)	$\chi^2 = 40.638$, $p < 0.001$*
Prior Stroke, *n* (%)	108 (29.8)	185 (28.3)	15 (20.8)	$\chi^2 = 2.356$, $p = 0.308$
Atrial Fibrillation, *n* (%)	44 (12.1)	103 (15.7)	9 (12.5)	$\chi^2 = 2.713$, $p = 0.258$
Hypertension, *n* (%)	223 (61.4)	416 (63.6)	44 (61.1)	$\chi^2 = 0.558$, $p = 0.757$
Diabetes Mellitus, *n* (%)	99 (27.3)	183 (28.0)	25 (34.7)	$\chi^2 = 1.683$, $p = 0.431$
Hypercholesterolaemia (%)	44 (12.1)	65 (9.9)	10 (13.9)	$\chi^2 = 1.837$, $p = 0.399$
Ischaemic heart disease, *n* (%)	72 (19.8)	119 (18.2)	15 (20.8)	$\chi^2 = 0.594$, $p = 0.743$
Congestive heart disease, *n* (%)	44 (12.1)	93 (14.2)	7 (9.7)	$\chi^2 = 1.7201$, $p = 0.423$
Rheumatic heart disease, *n* (%)	1 (0.3)	4 (0.6)	1 (1.4)	$\chi^2 = 1.469$, $p = 0.480$
Smoking, *n* (%)	78 (23.5)	166 (28.1)	13 (19.4)	$\chi^2 = 3.999$, $p = 0.135$
Malignant neoplasm, *n* (%)	52 (14.3)	79 (12.1)	4 (5.6)	$\chi^2 = 4.406$, $p = 0.110$
No. of medications prescribed (mean ± SD; median)	1.91 ± 1.941; 1.0	1.69 ± 1.734; 1.0	1.79 ± 1.964; 1.0	$F_{2,1086} = 1.720$, $p = 0.180$
CVAEs, *n* (%)	49 (13.5)	51 (7.8)	7 (9.7)	$\chi^2 = 8.562$, $p = 0.014$*
Ischaemic	36 (73.5)	36 (70.6)	7 (100.0)	$\chi^2 = 2.762$, $p = 0.251$
Hemorrhagic	13 (26.5)	15 (29.4)	0 (0.0)	

(χ^2 = Chi-square value, F = F-statistics in ANOVA, p = p-value, * - significant ($p < 0.05$))

years, respectively. The rate of CVAE in different groups and subgroups were reported in Table 2.

Kaplan Meier curves were plotted to examine the effect of antipsychotic use on the risk of developing CVAEs (Fig. 1). Log rank test was done (log rank statistics = 3.536, $p = 0.171$) and showed no significant difference in the risk of developing CVAEs between groups. Table 3 showed the crude and adjusted hazard ratios of antipsychotic groups when compared with non-user group. In both the unadjusted and the multivariate Cox's regression model, the risk of having CVAEs did not differ in typical or atypical groups compared with non-user group. The adjusted hazard ratio of typical group was 0.964 (95% CI = 0.584–

Table 2 Rate of CVAEs by Antipsychotic Subgroups. *n* (%)

	Total	CVAEs		Observation Time (median)	Observation Time (Total patient years)
		Yes	No		
Antipsychotic non-user	363	49 (13.5)	314 (86.5)	1019 days	1098.7
Antipsychotic users	726	58 (8.0)	668 (92.0)		
Typical Antipsychotic users	654	51 (7.8)	603 (92.2)	697 days	1558.9
Haloperidol	486	36 (7.4)	450 (92.6)		
Chlorpromazine	5	0 (0.0)	5 (100.0)		
Trifluoperazine	29	3 (10.3)	26 (89.7)		
Flupenthixol	7	0 (0.0)	7 (100.0)		
Thioridazine	7	0 (0.0)	7 (100.0)		
Sulpiride	120	12 (10.0)	108 (90.0)		
Atypical Antipsychotic users	72	7 (9.7)	65 (90.3)	628 days	140.7
Quetiapine	28	1 (3.6)	27 (69.4)		
Amisulpride	5	3 (60.0)	2 (40.0)		
Risperidone	35	2 (5.7)	33 (94.3)		
Olanzapine	4	1 (25.0)	3 (75.0)		

1.591), and of atypical group was 1.036 (95% CI = 0.350–3.066). Subgroup analyses were done. Hazard ratios of individual antipsychotic did not show a significant increase in risk of CVAE compared with non-user.

Discussion

Concerns over the excessive risk of CVAEs related to antipsychotics use in patient with dementia had a significant impact on a clinician's decision on whether

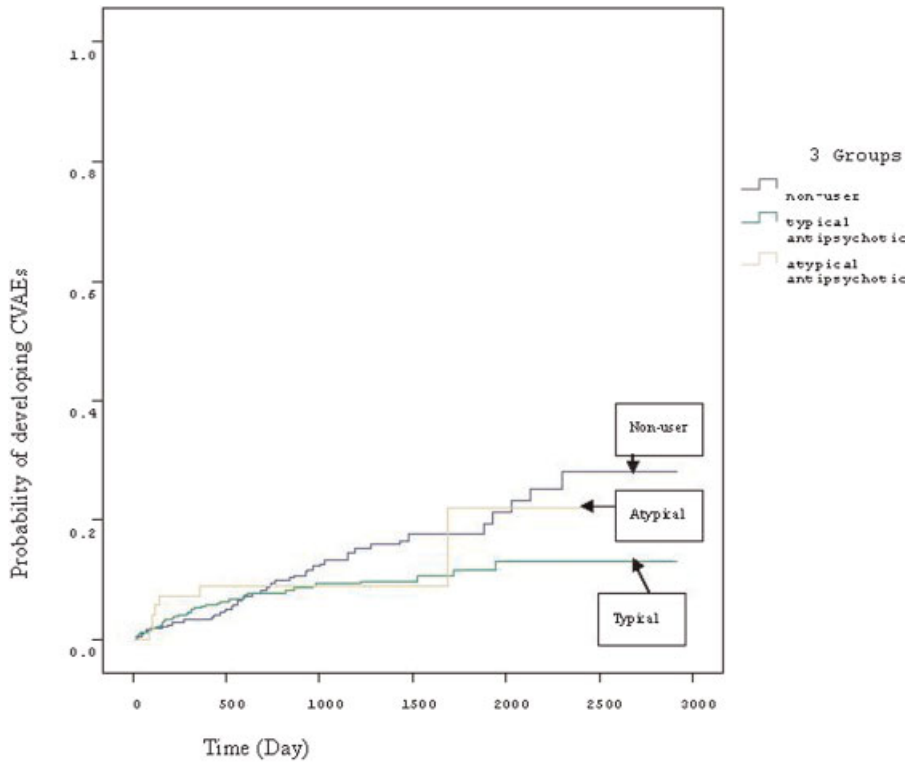

Figure 1 Probability of developing CVAEs over time stratified by antipsychotic exposure (One minus survival functions curve) log rank statistics = 3.536, $p = 0.171$.

Table 3 Risk of CVAEs by antipsychotics (Cox's proportional hazards regression analysis) (versus non-user group)

	Crude Hazard ratio	Adjusted Hazard ratio[1]	95% C.I.
Typical Antipsychotics	0.696	0.964	0.584–1.591
Haloperidol	0.695	0.919	0.528–1.598
Trifluoperazine	0.852	0.794	0.182–3.466
Sulpiride	0.795	1.482	0.691–3.178
Atypical Antipsychotics	1.000	1.036	0.350–3.066
Quetiapine	0.364	0.907	0.119–6.932
Amisulpride	7.594	7.597	0.626–92.263
Risperidone	0.587	0.426	0.055–3.289
Olanzapine	2.189	5.223	0.572–47.730

[1]Adjusted for age, sex, marital status, education level, residency, diagnosis, prior stroke, atrial fibrillation, hypertension, diabetes mellitus, ischaemic heart disease, congestive heart disease, rheumatic heart disease, hypercholesterolaemia, smoking, malignant neoplasm, and number of drugs prescribed, C.I. = confidence interval.

to prescribe antipsychotics for management of BPSD. Although, in our study, the proportion of patients having CVAEs during the observation period appeared higher in non-user group than the other two groups (13.5% *versus* 7.8% {$p = 0.004$} and 9.7% {n.s.}), when observation time and other potential confounding factors were taken into consideration in the Cox's proportional hazards regression model, there was no significant difference between the rates of CVAE in the three studied groups. These findings were consistent with several previous western studies (Herrmann *et al*., 2004; Finkel *et al*., 2005; Gill *et al*., 2005; Liperoti *et al*., 2005; Moretti *et al*., 2005; Barnett *et al*., 2007). Two of the studies had compared typical/atypical antipsychotic groups with non-user group; four other studies compared atypical antipsychotics with typical antipsychotics. Barnett *et al*. had reported that in unadjusted Kaplan-Meier analysis, there was significant difference between the time to admission for a cerebrovascular event according to antipsychotic exposure (log-rank test $p = 0.01$). However, in the multivariate Cox regression model with confounding factors controlled, the risk of a cerebrovascular event admission did not differ in those receiving typical or atypical antipsychotic compared with those not receiving antipsychotic therapy (hazard ratio 1.29, 95% CI = 0.48–3.47; and hazard ratio 1.20, 95% CI = 0.83–1.73, respectively). Gill et al. conducted a cohort study following 32,710 dementia patients who were receiving either typical or atypical antipsychotics for up to five years. In adjusted analyses, there was no increased risk of CVAEs in atypical user compared with typical user. In the population-based cohort study by Herrmann et al., 11 400 patients who were receiving typical antipsychotic, risperidone or olanzapine were followed. The result suggested no statistical significant increase in the risk of CVAEs associated with the use of risperidone or olanzapine compared with typical antipsychotic use in the elderly. In the case control study by Liperoti et al., they reported no increase in risk of CVAEs with patients receiving risperidone, olanzapine, other atypical antipsychotics including clozapine and quetiapine, and conventional antipsychotic when compared with patients taking no drug. In another controlled, open-label study by Moretti et al., 346 outpatients were followed up for 12 months. The study also suggested no statistically significant increase in the risk of CVAEs associated with the use of olanzapine compared with typical antipsychotic use. Another observational study by Finkel et al., 18 987 dementia patients receiving typical, atypical antipsychotic or benzodiazepine were followed for three months. The result showed no significant risk for an inpatient admission related to CVAEs associated with risperidone compared with other atypical antipsychotics, nor between typical, atypical antipsychotics and benzodiazepine. Despite the consistent findings in above studies, attention should still be paid on the limitations of the retrospective observational study design during interpretation of the conclusion.

Also, consistent with various previous studies, our study found no significant difference in risk of developing CVAEs between typical and atypical users. The presence of the non-user group as a control group in our study could further strengthen the conclusion that antipsychotic use did not appear to increase the risk of developing CVAEs in dementia patients in our sample.

The findings of no overall increase in risk in this study were in contrast to a meta-analysis of efficacy and adverse effects of atypical antipsychotics for dementia (Schneider et al., 2006). Although the meta-analysis merited consideration, the data used for the analysis of CVAE was obtained through several sources other than the clinical trials quoted. The quality of the data and the conclusion made needed to be interpreted with

caution. In another review article, the authors pooled the adverse event data from four clinical trials about risperidone and concluded that there was a significantly higher occurrence of cerebrovascular events found in subjects receiving risperidone (4%) than in those receiving placebo (2%). The authors also commented that those studies were not designed to examine a relationship between risperidone therapy and CVAEs and it was only a pooled subgroup analysis of a meta-analysis. The association determined thus might or might not be real and might or might not be cause and effect (Smith and Beier, 2004). In a randomised placebo-controlled trial of risperidone, although CVAEs were reported more in patients treated with risperidone, those patients had significant predisposing medical risk factors. The relationship between risperidone and the adverse event was recorded either as none or doubtful (Brodaty et al., 2003). The findings of another study carried out in Italy comparing the risk of cerebrovascular events in the elderly receiving atypical and typical antipsychotic showed that there was a significantly increased risk for risperidone users (adjusted odds ratio 1.43, 95% CI = 1.12–1.93) when compared with haloperidol users. However, the studied subjects were not exclusively dementia patients, and confounding factors considered in the logistic regression analysis were insufficient (Percudani *et al*., 2005).

On the other hand, in a self-controlled case series study, authors reported a higher rate ratio for stroke with the use of any antipsychotic medication. It reported a rate ratio of 3.50 (2.97 to 4.12) for patients with dementia receiving any antipsychotic drug. The result also showed that patients with dementia were at a higher risk of having an associated stroke than those without dementia (Douglas and Smeeth, 2008). This was the first study using this statistical method on the topic. The self-controlled case series method was developed to investigate associations between acute outcomes and transient exposures using data on cases only, with no separate controls required. This can eliminate the potential confounding effect of factors that vary between subjects (Whitaker *et al*., 2006).

Interestingly, we found that the crude incidence rates reported in our study were higher than those in other western studies. Gill et al. reported a crude incidence rate of stroke in typical antipsychotic users of 22.3 per 1000 person years, and in atypical antipsychotic users of 25.5 per 1000 person years (Gill *et al*., 2005); our study reported 32.7 per 1000 person years and 49.6 per 1000 person years respectively. This might be related to difference in methodology and ethnicity in the study subjects.

Regardless of the results of different observational studies or clinical trials, to date there was no concrete mechanism to explain why antipsychotic use in dementia patients would cause an increase in risk of CVAE, despite several postulations. Orthostatic hypotension as a result of antagonism at α-adrenergic receptors could cause cerebrovascular insufficiency; tachycardia induced by α-adrenergic antagonism might cause dislodge of a thrombus in patients with atrial fibrillation. Another proposed mechanism was due to hyperprolactinaemia which could, in theory, accelerate atherosclerosis. Oversedation followed by dehydration and thus increased risk of a thrombotic cerebrovascular event had been postulated (Smith and Beier, 2004; Herrmann and Lanctot, 2005; Barnett et al., 2007). Idiopathic venous thromboembolism and ventricular arrhythmia might also be related to antipsychotic use (Zomberg and Jick, 2000; Wang et al., 2007), but none of the above-discussed mechanisms could give a consistent biological explanation on why antipsychotic agents might increase the risk of CVAE. Therefore, there is still a gap between clinical observation of CVAE in patients given antipsychotics and the underlying pathophysiological mechanisms, and this warrants further exploration.

Our study's major strength was the high retrieval rate of eligible subjects. The medical records of 97% potential subjects were retrieved for review and screening. Observation time of up to eight years was sufficient when compared with previous studies. Bias in data collection was not likely as the information was largely factual. However, our study also suffered from several methodological weaknesses. Sample size of 1089 was relatively small when compared with previous population-based cohort studies, although this was the largest study in Chinese population on the topic at the time of writing. The generalisability of our study was also limited by the sample being Chinese patients with dementia who resided in our region and were referred to tertiary centre. There might also be under-reporting of CVAE as only such events occurring in public hospitals in Hong Kong were retrievable. It was also likely that mild transient ischaemic attack not requiring hospitalisation would not be identified in this study. Patients receiving antipsychotic treatment in private sector may lead to incorrect exposure status and lead to a bias. As in all retrospective cohort studies, the quality of the medical records' documentation will affect the validity of the results.

Further studies should be undertaken to explore this controversial yet significant topic. A population-based cohort or multi-centre study with larger population

Key points

- Behavioural and Psychological Symptoms of Dementia are commonly treated by antipsychotics.
- It was controversial whether the use of antipsychotics in patients with dementia would result in increased risk of cerebrovascular events.
- Our study did not show an increased risk of cerebrovascular events in patients with dementia who were given antipsychotics (typical or atypical).

size could be carried out to gather clinical data and information from different hospitals for further analysis. A prospective, controlled cohort study should be considered. Future studies should investigate whether there is a dose-related change in risk of developing CVAEs for dementia patients treated with antipsychotics and any difference in risk for different antipsychotic medications.

This study did not show a significant difference in risk of CVAE in patients received typical antipsychotics or atypical antipsychotics *versus* non-user. However, besides CVAE, both typical and atypical antipsychotics were found to be associated with other serious events requiring hospitalisation, including mortality (Rochon *et al*., 2008). Therefore, when caring for a patient with dementia presenting with psychotic symptoms or aggression, clinicians should first look for other aetiologies, including delirium, untreated medical illnesses, overmedication, environmental triggers, and lack of engaging activities, as all of these had specific treatment. Non-pharmacological approaches should be used first. Other possible alternatives, such as cholinesterase inhibitors for apathy and psychosis (National Collaborating Centre for Mental Health, 2006), and memantine for agitation (Wilcock et al., 2008), should be considered.

Conclusion

This retrospective hospital-based cohort study showed that there was no significant difference in risk of CVAEs in treatment of BPSD with typical and atypical antipsychotics compared with non-user control group. Antipsychotic medication was still a relatively safe treatment option for patients with dementia associated with psychotic symptoms or aggression. However, clinicians still need to consider other possible serious adverse effects of antipsychotic treatment including mortality in the assessment of risk/benefit ratio for individual patient. Prescription of antipsychotics should be reserved for severe and distressing symptoms, and time limited. Careful assessment for long-term treatment with antipsychotics is necessary.

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References

Ballard C, Oyebode F. 1995. Psychotic symptoms in patients with dementia. *Int J Geriatr Psychiatry* **10**: 743–752.

Ballard C. 2007. Agitation and psychosis in dementia. *Am J Geriatr Psychiatry* **15**: 913–917.

Barnett MJ, Wehring H, Perry PJ. 2007. Comparison of risk of cerebrovascular events in an elderly VA population with dementia between antipsychotic and non-antipsychotic users. *J Clin Psychopharmacol* **27**: 595–601.

Bewick V, Cheek L, Ball J. 2004. Statistics review 12: Survival analysis. *Critical Care* **8**: 389–394.

Brodaty H, Ames D, Snowdon J, *et al*. 2003. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* **64**: 134–143.

Douglas IJ, Smeeth L. 2008. Exposure to antipsychotics and risk of stroke: self controlled case series study. *BMJ* **337**: a1227.

Finkel S, Kozma C, Long S, *et al*. 2005. Risperidone treatment in elderly patients with dementia: relative risk of cerebrovascular events versus other antipsychotics. *Int Psychogeriatr* **17**: 1–13.

Gill SS, Rochon PA, Herrmann N, *et al*. 2005. Atypical antipsychotic drugs and risk of ischemic stroke: population based retrospective cohort study. *BMJ* **330**: 445. doi:10.1136/bmj.38330.470486.8F.

Herrmann N, Mamdani M, Lanctot KL. 2004. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* **161**: 1113–1115.

Herrmann N, Lanctot KL. 2005. Do atypical antipsychotics cause stroke? *CNS Drugs* **19**: 91–103.

Herrmann N, Lanctot KL. 2006. Atypical antipsychotics for neuropsychiatric symptoms of dementia: Malignant or Maligned? *Drug Saf* **29**: 833–843.

International Psychogeriatric Association. 1999. *Behavioral and psychological symptoms of dementia educational pack*. http://www.ipa-online.org/ipaonlineev3/ipaprograms/bpsdarchives/bpsdrev/toc.asp.

Katz IR, Jeste DV, Mintzer JE, *et al*. 1999. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: A randomized, double-blind trial. *J Clin Psychiatry* **60**: 107–115.

Katz I, De Deyn PP, Mintzer J, *et al*. 2007. The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. *Int J Geriatr Psychiatry* **22**: 475–484.

Liperoti R, Gambassi G, Lapane KL, *et al*. 2005. Cerebrovascular events among elderly nursing home patients treated with conventional or atypical antipsychotics. *J Clin Psychiatry* **66**: 1090–1096.

Mackin P, Bishop D, Watkinson H, *et al*. 2007. Metabolic disease and cardiovascular risk in people treated with antipsychotics in the community. *Br J Psychiatry* **191**: 23–29.

Moretti R, Torre P, Antonello RM, *et al*. 2005. Olanzapine as a possible treatment of behavioral symptoms in vascular dementia: risks of cerebrovascular events: A controlled, open-label study. *J Neurol* **252**: 1186–1193.

National Collaborating Centre for Mental Health. 2006. Dementia: Supporting people with dementia and their carers in health and social care. *In National Institute for Health and Clinical Excellence clinical guideline* 33–39.

Newcomer JW. 2007. Metabolic considerations in the use of antipsychotic medications: A review of recent evidence. *J Clin Psychiatry* **68**: 20–27.

Percudani M, Barbui C, Fortino I, *et al*. 2005. Second-generation antipsychotics and risk of cerebrovascular accidents in the elderly. *J Clin Psychopharmacol* **25**: 468–470.

Rochon PA, Normand SL, Gomes T, *et al*. 2008. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med* **168**: 1090–1096.

Schneider LS. 1999. Pharmacologic management of psychosis in dementia. *J Clin Psychiatry* **60**: 54–60.

Schneider LS, Dagerman K, Philip SI. 2006. Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* **14**: 191–210.

Sink KM, Holden KF, Yaffe K. 2005. Pharmacological treatment of neuropsychiatric symptoms of dementia – A review of the evidence. *JAMA* **293**: 596–608.

Smith DA, Beier MT. 2004. Association between risperidone treatment and cerebrovascular adverse events: Examining the evidence and postulating hypotheses for an underlying mechanism. *J Am Med Dir Assoc* **2**: 129–132.

Valiyeva E, Herrmann N, Rochon PA, *et al*. 2008. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. *CMAJ* **179**: 438–446.

Wang PS, Schneeweiss S, Setoguchi S, *et al*. 2007. Ventricular arrhythmias and cerebrovascular events in the elderly using conventional and atypical antipsychotic medications. *J Clin Psychopharmacol* **27**: 707–710.

Whitaker HJ, Farrington CP, Spiessens B, *et al*. 2006. Tutorial in biostatistics: The self-controlled case series method. *Statist Med* **25**: 1768–1797.

Wilcock GK, Ballard CG, Cooper JA, *et al*. 2008. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: A pooled analysis of 3 studies. *J Clin Psychiatry* **69**: 341–348.

Zomberg GL, Jick H. 2000. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* **356**: 1219–1223.

