Antipsychotic Drugs and Cerebrovascular Events in Elderly Patients with Dementia: A Systematic Review

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Abstract: Recently, Canadian, US and European health regulatory agencies issued warnings about an increased risk of stroke and death in elderly patients with dementia receiving atypical antipsychotics. Assessing both randomised and non-randomised evidence, this systematic review found conflicting findings, particularly for risperidone. More research is needed to better inform clinical practice.

Key Words: Neuroleptics, typical antipsychotics, atypical antipsychotics, dopamine, dementia, cerebrovascular events.

INTRODUCTION

First and Second Generation Antipsychotics

Antipsychotic drugs were serendipitously discovered when an antihistamine drug (chlorpromazine) appeared to be effective on psychotic symptoms of schizophrenic patients, back in the 1950 [1]. Such action on psychotic "positive symptoms", i.e. hallucinations and delusion, of antipsychotic agents, is due to the blockade of D2 dopamine receptor in cerebral mesolimbic dopamine pathway. Unfortunately, the same mechanism underlies the adverse effects of such drugs. Indeed, antipsychotics are paradoxically also known as "neuroleptics", a term that recalls one of the undesirable effect of these drugs. "Neurolepsy" refers to akinesia and apathy in experimental animals treated with antipsychotics, and is due to the blockade of D2 dopamine receptor in the dopamine mesocortical pathway. The same mechanism acts upon the nigrostriatal pathway, causing extrapyramidal effects (parkinsonism with bradikinesia, tremor and rigidity), while its interference within the tuberoinfundibular pathway generates hyperprolactinemia (Fig. **1**). Along with D2-receptor blockage, these drugs have other pharmacologic properties, such as anti-muscarinic effects (responsible of dry mouth, constipation, blurred vision and cognitive impairment), antihistaminic effects (weight gain and drowsiness) and anti-α_1 adrenergic effects (postural hypotension).

Second generation antipsychotics, (SGA) previously called "atypical antipsychotics", share with first generation antipsychotics (FGA) ("conventional" or "typical") their action on positive psychotic symptoms, but they have different side effects profile , possibly because of their combined serotonin (5HT)-2A and D2 antagonism (SDA) (Figs. **2** and **3**). Indeed, concomitant serotonin blockade makes the effect of D2 blockade less dramatic in all the dopamine pathways but in the mesolimbic one. For such a reason, SGA are said to be as effective on positive psychotic symptoms as FGA, without the limitation of extrapyramidal effects (EPS) [2], hyperprolactinemia and worsening of negative symptoms.

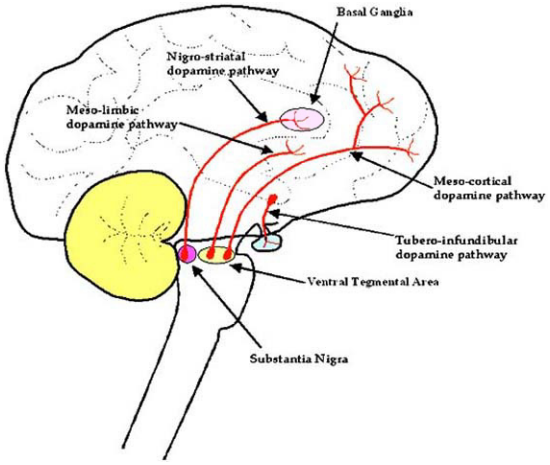

Fig. (1). Anatomy of dopamine pathways in the brain. Meso-limbic and meso-cortical pathways project from the midbrain ventral tegmental area to the nucleus accumbens and to the limbic cortex of the limbic system, respectively; nigro-striatal pathway projects from the substantia nigra to the basal ganglia; the tuberoinfundibular pathway projects from the hypothalamus to the anterior pituitary gland.

Antipsychotics and Dementia

Behavioural and psychological symptoms such as hallucinations, delusion, agitation and aggressive behaviour are common in dementia patients [3]. These symptoms are associated to pathological involvement of specific brain regions, including medial frontal and orbitofrontal cortices, and to altered receptor and neurotransmitter expression, such as increased muscarinic density and decreased cholinergic function. In addition, specific polymorphisms of the serotonin receptors and transporters have been linked to psychosis and agitation. Given the complexity of changes responsible for neuropsychiatric symptoms in dementia, SGA are often con-

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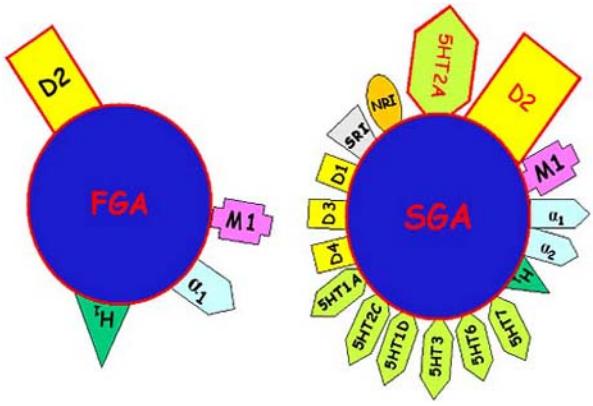

Fig. (2). Representation of pharmacological properties of first generation antipsychotics (FGA) and second generation antipsychotics (SGA).

D1, D2, D3, D4: Dopamine 1, 2, 3, 4 receptors; 5HT2A, 5HT2C: serotonin 2A and 2C receptors; 5HT1A and 1D: serotonin 1A and 1D receptors; 5HT3, 5HT6, 5HT7: serotonin 3, 6, 7 receptors; M1: muscarinic type 1 receptor; α1 and α2: α1 and α2 adrenergic receptors; H1: histamine H1 receptor; SRI: serotonine-reuptake inhibition property; NRI: norepinephrine-reuptake inhibition property.

sidered a first-line treatment of such symptoms, due to their multiple sites of action [4].

Nevertheless, in 2002, the Canadian health regulatory agency was the first to raise concerns about the association of the antipsychotic drug risperidone with cerebrovascular adverse events (CVAEs) in clinical trials of elderly demented patients. In 2003, the Food and Drug Administration (FDA) and other authorities published warnings and required changes to the prescribing information for risperidone [5]. At the beginning of 2004, the European Agency for the evaluation of Medicinal Products (EMEA) issued public advice about an increased risk of CVAEs and mortality in elderly patients with dementia receiving olanzapine. In March 2004, the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) informed clinicians that risperidone and olanzapine should not be used to treat behavioural and psychological symptoms of dementia (BPSD) because of increased risk of strokes with both drugs [6].

Similarly, in 2005 the FDA issued warnings for aripiprazole about the risk of CVAEs, including stroke, in elderly patients with dementia [7]. Therefore, it is possible that findings similar to those for atypical antipsychotics may apply to other neuroleptics, both older and other newer ones. The contribution of old and new neuroleptics to CVAEs and mortality has been previously examined in a systematic review [8]. However, month by month new evidence has been emerging and both clinicians and researchers need to keep abreast with the most recent and robust scientific knowledge. The aim of this paper is to update and systematically review the available evidence about the link between antipsychotic use in dementia and CVAEs.

METHODS

Search Strategy

Medline (1966-2006) and Embase (1974-2006) were searched to identify reports evaluating the relationship between antipsychotic drug consumption and CVAEs. The following terms (and keywords) were used: "antipsychotic$" and “dementia” or “cerebrovascular” or “death$”. Non-English language papers were included. Reference lists of relevant papers and previous systematic reviews were hand searched for published reports up to December 2006. Abstracts were reviewed and full-text articles that met inclusion criteria were retrieved. The official websites of the 4 most important international regulatory agencies (FDA, MHRA, Health Canada, EMEA) were also checked. All reports were reviewed by two authors (SM and AC) and any disagreement was discussed with a third member of the team (CB).

Study Characteristics

Studies were included if they reported data about the outcomes of interest, namely the relationship between antipsychotic drug use and risk of cerebrovascular disease in people with dementia. We included 4 major types of studies for which the research question was clearly defined as assessment of the relationship between antipsychotic consumption and cerebrovascular disease; (1) systematic reviews and meta-analyses of randomized controlled trials (RCTs); (2) individual RCTs not included in systematic reviews; (3) observational studies with a prospective, retrospective or cross-sectional design, carried out with the specific aim of investigating the relationship between antipsychotics and CVAEs in individuals with dementia; and (4) database analysis (retrospective health care or economic studies carried out using administrative medical claims databases) or ecological studies investigating the relationship between antipsychotic consumption, dementia and CVAEs. Included studies were rated following the scheme proposed by the Oxford Centre for Evidence Based Medicine [9] (see Table **1**). According to

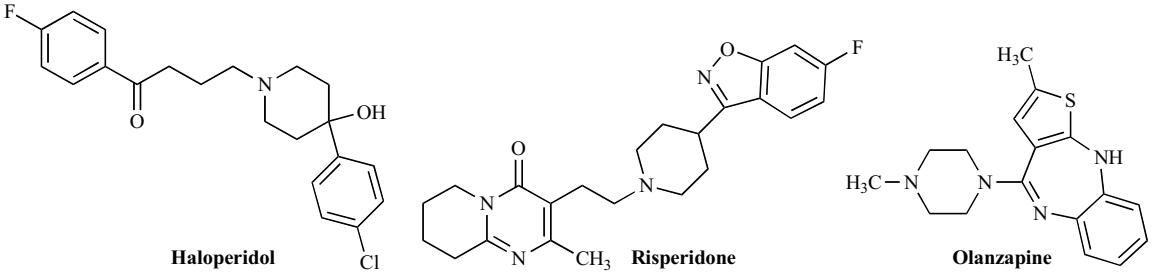

Fig. (3). Chemical structure of haloperidol, the prototype of first-generation antipsychotics, and risperidone and olanzapine, the two most studied atypical antipsychotics.

Table 1. Characteristics of Studies Included in the Systematic Review

Study	Comparator	Study Type	Level*	Population	Results
RANDOMISED EVIDENCE					
Herrmann 2006	Risperidone olanzapine	Systematic review and meta-analysis (including data from Janssen and Eli Lilly) Search update: December 2005	1A	11 placebo-controlled RCTs (a,b,c,d,e,f,g,h,i,l,m) lasting 8 to 12 weeks. 1721 patients with AD, vascular dementia or mixed dementia.	*Risperidone:* Incidence of CVAEs: risperidone, 33/1009 (3.4%) *versus* placebo, 8/685 (1.2%); *Olanzapine:* Incidence of CVAEs: olanzapine. 15/1178 (1.3%) *versus* placebo, 2/478 (0.4%). RR of CVAEs: 1.8 (95% CI 0.5 to 6.3). *Risperidone + Olanzapine:* Incidence of CVAEs: drug-treated patients, 48/2187 (2.2%) *versus* placebo, 10/1190 (0.8%). RR of CVAEs: 2.7 (95% CI 1.4 to 5.3).
Schneider 2006	Risperidone olanzapine aripiprazole quetiapine	Systematic review and meta-analysis. Search update: April 2005	1A	15 placebo-controlled RCTs (a,b,c,h,m,n,o,p,q,r,s,t,u,v,w) lasting 6 to 26 weeks. Overall 3353 patients with AD, vascular dementia, mixed dementia or primary dementia were randomised to drug and 1757 to placebo.	*Overall:* 63 out of 3327 versus 16 out of 1728 events in drug and placebo patients, respectively. Increased OR (2.13, 95% CI, 1.2 to 3.75; p=0.009) by meta-analysis. *Risperidone:* Significantly increased risk with risperidone (OR 3.43, 95% CI 1.6 to 7.32; p=0.001), 3.1% versus 1% pooled.
EMEA 2005	Aripiprazole	Pooled analysis (source not specified)	1A	In 3 placebo-controlled trials (u,v,w) of aripiprazole in elderly AD patients (mean age: 84 y; range: 78-88 y), CVAEs (stroke, TIA), including fatalities, were reported.	Overall, 1.3% of aripiprazole-treated patients reported CVAEs compared with 0.6% of placebo-treated patients in these trials.
Schneider 2006	Risperidone olanzapine quetiapine	42-site, double-blind, placebo controlled RCT	2A	Ambulatory AD or probable AD patients (MMSE score 5-26), with psychosis developed after the onset of dementia and "moderate" severity score on the Brief Psychiatric Rating Scale (BPRS) were enrolled.	421 patients (out of 521 screened) underwent randomization. 82% discontinued medication during the 36-week FU. Discontinuation due to drug intolerance, adverse effects, or death) rated 24% for olanzapine, 16% for quetiapine, and 18% for risperidone, as compared to 5% for placebo.
Allain 2005	Tiapride, haloperidol	116-site, double-blind, placebo controlled RCT	2A	Hospitalized patients aged 55–90 years, with mild or moderate dementia (AD, vascular dementia and mixed dementia) and a 16-30 score at the Multidimensional Observation Scale for Elderly Subjects (MOSES), were randomly allocated to tiapride 100 mg/day, haloperidol 2 mg/day or placebo.	306 patients were included into this 21-day study, 197 (64%) female), mean age 79.6±7.6 years. Twenty-eight adverse events led to study treatment discontinuation: six in the placebo group, five in the tiapride group and 17 in the haloperidol group.

RCTs: Randomised controlled trials, CVAEs: cerebrovascular adverse events, FGAs: first generation antipsychotics, FU Follow-up, SGAs: second generation antipsychotics, AD: Alzheimer's disease, TIA: transient ischaemic attack, AP: antipsychotics, EPS : Extrapyramidal effects, CI: Confidence interval, OR: Odds ratio, RR: Relative risk, HR: Hazard ratio, BDZ: benzodiazepines, m: months, y: years

* Oxford Centre for Evidence Based Medicine: 1A, systematic review of RCTs; 1B, individual RCT; 2A, systematic review of cohort studies; 2B, individual cohort study, low-quality RCT; 2C, ecological studies; 3A, systematic review of case-control studies; 3B, individual case-control study; 4, case series, poor-quality cohort and case-control studies.

(a) Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003; 64: 134-43. (b) De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999; 53: 946-55. (c) Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999; 60: 107-15. (d) Data on file, Janssen, 2004. (e) Data on file, Janssen, 2004. (f) Data on file, Janssen, 2004. (g) Data on file, Eli Lilly, 2004 (h) Street JS, Clarke S, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities. Arch Gen Psychiatry 2000; 57: 968-76. (i) Data on file, Eli Lilly, 2004. (l) Data on file, Eli Lilly, 2004. (m) De Deyn PP, Carrasco MM, Deberdt W, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19: 115-26. (n) Mintzer J, Weiner M, Greenspan A, et al. Efficacy and safety of a flexible dose of risperidone versus placebo in the treatment of psychosis of Alzheimer's isease. Poster presented at the International College of Geriatric Psychopharmacology; Oct 14-17, 2004; Basel, Switzerland. (o) Satterlee WG, Reams SG, Burns PR, et al. A clinical update on olanzapine treatment in schizophrenia and in elderly Alzheimer's disease patients. Psychopharmacol Bull 1995;31:534. (p) Deberdt WG, Dysken MW, Rappaport SA, et al. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry 2005;13:722-730. (q) Kennedy JS, Deberdt W, Micca J, et al. The effect

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of olanzapine on cognition in patients with Alzheimer's disease without psychosis or agitation. Poster presented at the International College of Geriatric Psychopharmacology; Oct 14-17, 2004; Basel, Switzerland. (r) Ballard C, Margallo-Lana M, Juszczak E,et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ 2005;330:874-877. (s) Tariot PN, Schneider LS, Katz IR, et al. Quetiapine treatment of psychoasis associated with dementia: a double-blind, ramdomised, placebo-controlled clinical trial. Am J Geriatr Psychiatry 2006;14:767-776. (t) Zhong K, Tariot P, Minkwitz M, et al. Quetiapine for the treatment of agitation in elderly institutionalised patients with dementia: a randomised, double-blind trial. Poster presented at the 9th International Conference on Alzheimer Disease and Related Disorders; July 17-22, 2004; Philadelphia. (u) Breder C, Swanink R, Marcus R, et al. Dose-ranging study of aripiprazole in patients with Alzheimer's dementia. Poster presented at the 9th International Conference on Alzheimer Disease and Related Disorders; July 17-22, 2004; Philadelphia. (v) Streim J, Breder C, Swanink R, et al. Flexible dose aripiprazole in psychosis of Alzheimer's dementia. Poster presented at the 157th American Psychiatric Association Annual Meeting; May 1-6, 2004; New York. (w) Kujawa M, Marcus R, Breder C, et al. Safety profile of aripiprazole in psychosis of Alzheimer's dementia.Poster presented at the 9th International Conference on Alzheimer Disease and Related Disorders; July 17-22, 2004, Philadelphia.

Study	Comparator	Study Type	Level*	Population	Results
NON-RANDOMISED EVIDENCE					
Liperoti 2005	Risperidone olanzapine quetiapine clozapine haloperidol fluphenazine thiothixene trifluoperazine chlorpromazine thioridazine mesoridazine molindone loxapine perphenazine promazine chlorprothixane	Case-control study	3B	Population: Nursing home residents (90% of sample >75 years old) with diagnosis of dementia. Schizophrenic patients were excluded. Cases (89% of sample >75 years old) included hospitalized residents with primary discharge diagnosis of either ischemic stroke (ICD-9 codes: 433.0–434.9) or TIA (ICD-9 codes: 435–435.9). First event for persons with multiple hospitalizations was used. Controls were residents for whom the primary diagnosis at discharge was either septicemia (ICD-9 codes: 038–038.9) or urinary tract infection (ICD-9 code: 599.0). The final matched sample consisted of 1130 cases and 3658 controls. No significant difference in the overall prevalence of APs (25% among cases and 23% among controls), as well as in the pattern of AP prescribed. Data source: The Systematic Assessment of Geriatric drug use via Epidemiology database, with data from the Minimum Data Set, a standardized, clinically based instrument collecting information on each resident's medical, demographic, functional, psychological, cognitive status.	No significant increase in the risk of being hospitalized for ischemic stroke or TIA was found among AP users. After controlling for potential confounders, the OR was 0.87 (95% CI, 0.67 to 1.12) for risperidone users, 1.32 (0.83 to 2.11) for olanzapine users, 1.57 (0.65 to 3.82) for users of other SGAs, and 1.24 (0.95 to 1.63) for FGAs. These results unchanged when the outcome was restricted to only ischemic strokes or the analysis was stratified by type of dementia and sex. Olanzapine users and users of other SGAs presenting a history of CVAEs were 3.71 (95% CI, 1.55 to 8.84) times and 4.63 (1.35 to 32.63) times, respectively, more likely to be hospitalized for CVAEs compared to nonusers without such history. Similar population of risperidone or FGAs users had no increased risk of being hospitalized for CVAEs (RR 1.49, 95% CI 0.93 to 2.38 and RR 1.23, 95% CI 0.68 to 2.23, respectively).
Layton 2005	Risperidone olanzapine quetiapine	Retrospective cohort study	2B	Population: Patients prescribed risperidone, olanzapine or quetiapine in general practice in England, including patients with dementia	There were no differences in the relative risk of CVAEs or transient ischaemic attacks in the first 180 days of treatment among any of the investigated agents.
Formiga 2005	Risperidone haloperidol olanzapine quetiapine thioridazine levopromazine	Cross-sectional study	3B	Population: 320 consecutive patients (214 women) with dementia aged 65 or older. (mean age: 81.1). 191 patients (60%) had received treatment with AP: 168 risperidone (53%), 10 haloperidol, 6 levomepromazine, 4 olanzapine, 2 quetiapine, 1 thioridazine. Data source: 6 centres in Spain.	6 patients had a stroke during FU: 3 with risperidone and 2 not taking AP; 1 on thioridazine. 4 patients experienced a TIA: 1 on risperidone, 2 not taking AP, 1 on levomepromazine. When data were analyzed depending on whether patients had taken AP treatment, no significant differences were found in stroke (4 vs 2) or TIA (2 vs 2;), nor were they found when both events were analyzed together (6 vs 4).

(Table 1. Contd….)

Study	Comparator	Study Type	Level*	Population	Results
NON-RANDOMISED EVIDENCE					
Finkel 2005	Risperidone olanzapine quetiapine ziprasidone haloperidol benzodiazepines	Database analysis	2C	Population: Inpatients with dementia: 8184 treated with SGAs (olanzapine 2898, risperidone 4093, quetiapine 688), 1249 with haloperidol and 9334 with benzodiazepine. Objective: to assess the incidence of acute inpatient admission for a CVAE within 3 months following initiation of treatment with AP. Data source: Analysis of Medicaid data from 1999 to 2002 representing approximately 8 million enrollees from multiple states in the US.	Descriptive analyses: similar rates of incident CVAEs across evaluated agents. Multivariate analyses: no differences in comparisons of risperidone with olanzapine or quetiapine. Risperidone and other SGAs as a group were not associated with a higher OR of incident CVAE than either haloperidol or BDZ.
Gill 2005	Risperidone olanzapine quetiapine haloperidol fluphenazine thiothixene pimozide trifluoperazine flupenthixol zuclopenthixol thioproperazine chlorpromazine-thioridazine mesoridazine loxapine perphenazine promazine pericyazine chlorprothixane.	Database analysis	2C	Population: Patients aged 65 or older with a diagnosis of dementia and with no history of AP drug use. Primary outcome was admission to hospital for ischaemic stroke (ICD-9 codes 431,434, and 436). Data source: Administrative healthcare databases in Ontario, Canada, between 1 April 1997 and 31 March 2002. (1) Computerised pharmacy records of the Ontario Drug Benefit Database, which records prescription drugs dispensed to all Ontario residents aged 65 years or older. (2) 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 to provide detailed diagnostic records for all hospital admissions. (3) Information on doctors' billing for inpatient and outpatient services from the records of the Ontario Health Insurance Plan. (4) Basic personal information and vital statistics for each patient from the Registered Persons Database.	32710 elderly with dementia (17845 dispensed SGAs and 14865 dispensed FGAs) were identified. The SGA cohort included 13503 (75.7%) patients receiving risperidone, 3459 (19.4%) receiving olanzapine, and 883 (4.9%) receiving quetiapine. In the adjusted and multivariate analyses, the risk of ischemic stroke in older adults with dementia receiving SGAs was not significantly different from those receiving FGAs (HR 1.01, 95% CI 0.81 to 1.26). The subgroup analyses were all consistent with the main analysis: no significant differences in the development of stroke between the cohorts receiving SGAs and those receiving FGAs. The risk of stroke for patients receiving risperidone (HR 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 FGAs.
Kolanowski 2006	Cases were grouped by type of the prescribed AP: no AP, conventional AP only, atypical AP only, and both atypical and conventional AP.	Database analysis	2C	Population and data source: 959 dementia patients with at least one prescription claim were enrolled for three consecutive years and common adverse events associated with AP drug use, but that might also affect persons with dementia who are not prescribed these drugs, were collected, including constipation, delirium, depression, diabetes, falls, hip fracture, stroke, and syncope. Data source: This study used claims data from a large health care insurer located in the southeast region of the United States, with an average membership of 362,975 individuals.	Authors did not find differences for the rates of stroke or diabetes among any of the study groups. However, the observation period was only 45 days from prescription.

RCTs: Randomised controlled trials, CVAEs: cerebrovascular adverse events, FGAs: first generation antipsychotics, FU Follow-up, SGAs: second generation antipsychotics, AD: Alzheimer's disease, TIA: transient ischaemic attack, AP: antipsychotics, EPS : Extrapyramidal effects, CI: Confidence interval, OR: Odds ratio , RR: Relative risk, HR: Hazard ratio, BDZ: benzodiazepines. m: months, y: years

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this classification, systematic reviews of RCTs provide the best and most relevant evidence. Randomised evidence provides the most compelling results of efficacy, while findings of naturalistic studies are largely correlational, indicating that their outcomes need further testing.

RESULTS

The search yielded a total of 426 references (excluding duplicates). From this pool of references, two reviewers independently identified 89 possibly relevant papers. After reading abstracts, 23 papers were retrieved for more detailed evaluation and 11 published articles meeting the inclusion criteria were included. Among the international regulatory agencies, one out of four reported data suitable for analysis which were not included in published papers. Considering the heterogeneity in study methodology and the variety of the sample populations, we decided to present results in a narrative way, dividing findings into *randomised* and *non-randomised* evidence (see method section).

Overall, we found two meta-analysis based on a systematic review of RCTs [10, 11], 1 pooled analysis of RCTs [12], two randomised controlled trials (RCT) [13, 14], 1 retrospective cohort study [15], 1 case-control study [16], 1 cross-sectional study [17] and 3 database analyses [18-20]. In Table **1** full details about study type, study population, and main results are reported.

Randomised Evidence

Combining all RCTs, we found at least 15 studies comparing atypical antipsychotics (risperidone, olanzapine and aripiprazole) with placebo. In the meta-analysis by Herrmann and Lanctot [10], collectively the 11 studies suggested that 48 out of 2187 (2.2%) drug-treated subjects experienced CVAEs compared with 10 out of 1190 (0.8%) placebo-treated subjects. The combined relative risk was 2.7 (95% CI, 1.4 to 5.3). Considering individual comparisons, numerically more risperidone-treated patients (33 of 1009 [3.3%]) experienced CVAEs compared with olanzapine-treated patients (15 of 1178 [1.3%]). The weighted relative risk was statistically significant for risperidone (3.2, 95% CI 1.4 to 7.2), but not for olanzapine (1.8, 95% CI, 0.5 to 6.3).

In the meta-analysis by Schneider and colleagues, 15 placebo-controlled RCTs fulfilled the inclusion criteria and were included in the review. Overall, eleven trials were performed in nursing homes and four in outpatients. Eight trials allowed dosage adjustment, two were fixed-dose and five were dose-ranging RCTs with two to four fixed doses of study drugs. There were five olanzapine trials (1184 patients randomised to olanzapine), lasting 6 to 26 weeks. Of the five risperidone trials (1175 patients randomised to risperidone), four were conducted in nursing homes (8 to 12 weeks duration). Of them, one had an olanzapine comparison and another one an haloperidol comparison. All three quetiapine RCTs were nursing homes trials, one with haloperidol comparison and one compared with rivastigmine (10 to 26 weeks duration and overall 391 patients randomised to quetiapine). The remaining three studies were aripiprazole trials of 10-week follow-up, with 603 patients randomised to aripiprazole. In this systematic review 293 patients randomised to haloperidol were also included. Nine trials (53% of the subjects) allowed only patients with AD to be included. Six studies allowed participants to have various dementia diagnoses, however 87% of all subjects included in the Schneider *et al*. review were clinically classified as AD. The mean age was 81 years (SD 7.8) and up to 70% were female. Only seven trials specifically required psychosis of AD. In this review, authors reported that individual CVAEs were obtained through several sources [11]. There were 63 versus 16 events in drug and placebo patients, respectively, among 3327 patients on drug and 1728 on placebo. There was an increased OR by meta-analysis for CVAEs of 2.13 (95% CI, 1.2 to 3.75; p=0.009). Similarly to the findings of other systematic review, a significantly increased risk was found only for risperidone (OR 3.43, 95% CI 1.6 to 7.32; p=0.001). It's difficult to understand whether the two analyses refer to the same dataset, because one review used unpublished on-file data.

Looking at the data published in the EMEA website, 1.3% of aripiprazole-treated patients reported CVAEs compared with 0.6% of placebo-treated patients in these trials [12]. This difference was reported not to be statistically significant; however, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for CVAEs in patients treated with aripiprazole.

Recently, the effectiveness of atypical antipsychotic drugs in outpatients with Alzheimer's disease was further assessed in a large trial, the CATIE-AD [13]. In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change scale at 12 weeks. There were no statistically significant differences between the four treatment intervention groups neither in terms of incidence of cerebrovascular accident or transient ischemic attack nor in terms of discontinuation of treatment due to CVAEs.

We found another RCT not included in the systematic review [14]. This was an international, multicentre, double blind, short-term trial (21-day duration) comparing the efficacy and safety of tiapride (100–300 mg/day) versus haloperidol (2–6 mg/day) and placebo in the treatment of agitation and aggressiveness in elderly patients with mild or moderate mental impairment. Tiapride is a substituted benzamide derivative with dopamine antagonistic effects, specifically on D2 and D3 dopamine receptors. However, tiapride is sometimes considered as an atypical antipsychotic drug with anxiolytic properties and a lower propensity for sedation, dependence and at low dosages, parkinsonism. In this study, stroke was reported as cause of death for one patient each in the haloperidol and placebo groups.

Non-Randomised Evidence

In general, emerging data from large observational administrative database studies suggested no increased risk of

CVAEs with the atypical antipsychotics compared with typical antipsychotics [15-20]. Consistent with randomised evidence, most of the data come from elderly patients (>65).

DISCUSSION

In this systematic review of the up to date available evidence about the relationship between antipsychotics and CVAEs we found contrasting findings both within randomised evidence and between randomised and non-randomised evidence. Two recent meta-analyses [10, 11] reported a significantly increased risk for CVAE for antipsychotics - and particularly - for risperidone-treated patients, while a subsequent, large, pragmatic RCT [13] was not able to detect differences in terms of increased risk in either risperidone, olanzapine or quetiapine-treated patients when compared with placebo.

Concerns have been raised only for elderly patients treated with APs because of the mean age of the population enrolled in earlier studies suggesting the association between the use of SGAs and CVAEs [21]. Dementia clearly is an age-related disease; among 60-year old people, the prevalence of AD is about 1/10.000, but it increases dramatically to 1 in 3 in the over-eighties [22]. There is no clear evidence of increased risk of CVAEs or mortality coming from extensive use of these drugs in younger-aged patients in functional disorders like schizophrenia and mania. Furthermore, to our knowledge, there is no randomized evidence that the risk of CVAEs or mortality is increased in psychiatric disorders other than dementia.

RCTs are the best tool to assess efficacy and tolerability of treatments and to investigate cause-and-effect relationship. Nevertheless, interpretation of the herein reported data is made hard by the absence of study designs aiming at testing *a priori* hypotheses about causation, preventing from drawing etiopathological conclusions.

The prevalence and incidence of cerebrovascular disease increases dramatically with age and there is a relationship between dementia and stroke in general. Cognitive impairment, regardless of underlying aetiology, has been demonstrated to be a strong independent predictor of ischaemic stroke [23] and there is evidence that individuals with Alzheimer's disease are more likely to die from cerebrovascular disease than normal elderly individuals [24]. Therefore it would not be clinically unreasonable to see CVAEs and even deaths from stroke in an elderly sample of dementia patients treated for 8–12 weeks. However, randomising thousands of individuals would be required to detect an important effect on risk [25]. It is worth noting that the rates of CVAEs in placebo-treated patients also differed in different trials within a 1.1% to a 0.4%. Many factors (dementia type, severity of cognitive impairment, previous history of CVAEs and presence of cerebrovascular risk factors) could have influenced the outcome. Since there are no strong hypotheses about the association between antipsychotics and CVAEs, the subjects in these trials were not randomised or stratified on the basis of stroke risk factors, and it is possible that drug- and placebo-treated groups differed at baseline with respect to their risk for CVAEs. Nevertheless, randomisation of consistent number of subjects from separate trials should have balanced the groups.

Potential mechanistic explanations for the association between CVAEs and atypical antipsychotics have been investigated [26] and they include thromboembolic effects [27-29], cardiovascular effects (orthostatic hypotension, arrhythmias) [30, 31], excessive sedation resulting in dehydration and haemoconcentration [32], and hyperprolactinaemia leading to atherosclerosis [33]. However, it is difficult to reach clear and clinically meaningful conclusions.

As far as epidemiological evidence is concerned, strengths and limitations of observational and administrative database studies are well known [34]. These studies can potentially provide important information from large samples of 'real-world patients' that frequently differ significantly from subjects enrolled in randomised controlled trials. They can also examine multiple risk factors and usually provide longer periods of observation. However, in this case their results have been limited by the inability to control for all confounding variables (i.e. some stroke risk factors such as obesity and smoking) and by considering only hospitalised strokes. This could have led to underestimation of minor CVAEs.

Evidence of CVAEs with atypical antipsychotic came directly from the drug manufacturers. Among the six risperidone trials, three were published and three unpublished RCTs. Data for olanzapine was derived from five randomised placebo-controlled trials, only two of which have been published to date. Data about aripiprazole are yet unpublished. Providing information on this topic by pharmaceutical industry allowed to shorten the time lag between generating evidence and publishing information. At the same time, this highlights how relevant the publication bias can be, when evaluating effectiveness and safety of treatment [35].

A meta-analysis assessing the evidence for mortality from atypical antipsychotic drug treatment in patients with Alzheimer disease or dementia reported a similarly increased risk in treated patients [36]. Fifteen RCTs (9 unpublished) were included and death occurred more often among patients randomized to atypical antipsychotics (118 [3.5%] *vs* 40 [2.3%]), with a risk of 1.54 (95% CI, 1.06 to 2.23). Even for deaths, there is insufficient information available on individual cases, causes or circumstances, base-line clinical characteristics, medical conditions, and concurrent medications. An individual patient meta-analysis might be able to identify characteristics associated with mortality potentially due to drugs, encouraging the pharmaceutical manufacturers to allow their data to be combined and analyzed by an independent organization without a material interest in the outcomes.

Lack of diagnostic specificity in RCTs is something that could clearly affect our understanding of the relationship between antipsychotics and CVAEs. Not only cerebrovascular pathology itself is a remarkably heterogeneous entity. The wide range of CVAE definitions (stroke, transient ischaemic attacks, CVAEs, cerebral ischaemia, cerebral infarct, cerebrovascular disturbance, cerebrovascular disorder) further undermines the possibility of a unequivocal diagnosis. Future research should supply specific data concerning CVAEs' subtypes in treated patients [37]. As dementia patients provide particular diagnostic difficulties, surrogate endpoints (neuroimaging) should be taken into consideration in next RCTs designs [38].

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