American Journal of Alzheimer's Disease & Other Dementias®
26(1) 10-28

DOI: 10.1177/1533317510390351
http://aja.sagepub.com

Risk of Cerebrovascular Adverse Events and Death in Elderly Patients With Dementia When Treated With Antipsychotic Medications: A Literature Review of Evidence

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Abstract

Behavioral and Psychological Symptoms of Dementia (BPSD) are increasingly recognized as a major risk factor for caregiver burden, institutionalization, greater impairment in activities of daily living (ADLs), more rapid cognitive decline, and a poorer quality of life. BPSD contribute significantly to the direct and indirect costs of caring for patients with dementia even after adjusting for the severity of cognitive impairment and other co-morbidities. Research on these symptoms has indicated a complex interplay between the biological, psychological and social factors involved in the disease process. Although some psychotropic medications have shown modest efficacy in the treatment of these behaviors, their use has generated controversy due to increasing recognition of the side effects of these medications especially the antipsychotic medications. In this review, we examine the risk of cerebrovascular adverse events (CVAEs) and death with antipsychotic medications when used to treat elderly patients with dementia.

Keywords

dementia, cerebrovascular adverse events, death, antipsychotics

Introduction

Per the 2000 Medicare report, dementia affects an estimated 5 to 8 million Americans, of which more than half have psychotic symptoms along with aggression or agitation.[1-3] These symptoms are grouped as behavioral and psychological symptoms of dementia (BPSD). They have been defined as a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors, which may be disruptive, unsafe, and impair the care of the patient in a given environment.[4] These symptoms are common in the patients with dementia and have profound impact on both the patients and their caregivers. The prevalence of BPSD tends to increase in the later stages of the illness.[5]

Increasingly, antipsychotic medications are being used to treat these behaviors.[6,7] Recent studies have evaluated the efficacy of these medications, metabolic changes associated with these medications, the benefit of using these medications, their adverse effects, and alternative treatments of BPSD.[8-13] A recent literature review on the pharmacologic treatments of BPSD found that antipsychotics are not conclusively effective in the treatment of these behaviors.[14] Other studies of antipsychotics point to their modest efficacy in the treatment of BPSD.[15,16] The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Dementia (CATIE-AD) study indicated that the adverse effects of this class of medication offsets their potential advantages.[9]

In 2002, the Canadian Health Regulatory Agency first raised concerns about the association of risperidone with cerebrovascular adverse events (CVAEs) in clinical trials of elderly patients with dementia.[17] In 2003, the Food and Drug Administration (FDA) published warnings and required changes in prescribing information for risperidone.[17] In 2004, the European Agency for the Evaluation of Medicinal Products

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(EMEA) issued a public advisory about the increased risk of CVAEs and mortality in elderly patients with dementia receiving antipsychotics. The same year, the UK's Committee on Safety of Medicines (CSM) advised prescribers that risperidone and olanzapine should not be used to treat BPSD because of "clear evidence of an increased risk of strokes."[18]

In 2005, the FDA determined that the treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality. Of a total of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, or quetiapine in elderly patients with dementia having behavioral disorders, 15 showed numerical increases in mortality in the drug-treated group compared to the placebo-treated patients. These studies enrolled a total of 5106 patients, and several analyses have demonstrated an approximately 1.6- to 1.7-fold increase in mortality in these studies. Examination of the specific causes of these deaths revealed that most were due to either heart-related events (eg, heart failure and sudden death) or infections (mostly pneumonia). Because of these findings, the Agency asked the manufacturers of these drugs to include a Boxed Warning in their labeling, describing the risks and indicating that these drugs are not approved for the treatment BPSD. Symbyax, a combination product containing olanzapine and fluoxetine, approved for the treatment of depressive episodes associated with bipolar disorder, was also included in the request. The Agency was also considering adding a similar warning to the labeling for older antipsychotic medications because the limited data available suggest a similar increase in mortality for these drugs.[19] This advisory also mentions that antipsychotic medications are not approved for use in the treatment of behavioral disturbances in dementia.[19]

These warnings from regulatory authorities in various countries highlight the need for clinicians to have an understanding of these 2 most serious adverse events—CVAE and death in the patients with dementia treated with antipsychotics. In this review, we examine the risk of CVAEs and death with antipsychotic medications when used to treat elderly patients with dementia. Using the current data, we provide evidence-based treatment recommendations for these behaviors.

Search Strategies

The following search terms were used "stroke," "cerebrovascular events," "cerebrovascular accidents," "death," "dementia," "behavioral symptoms," "behavioral disturbance," "BPSD," "antipsychotics," and "psychotropics." The terms were searched within the following databases—Cochrane Library, Medline, EMBASE, and PsycINFO—for articles in English and on human beings, from January 1, 1990 to August 31, 2010.

Of all the articles identified from the search, articles were selected that commented on CVAE and death with the use of antipsychotic treatment in patients with dementia. These articles consisted of randomized controlled trials, pooled analysis, meta-analyses, systematic reviews, population-based studies, prospective studies, retrospective studies, reviews, and case reports. In addition, a manual search of bibliographies and the FDA Web site was done. The results are described for CVAEs followed by death. We organized the studies in the results section into subsections from the highest to the lowest level of evidence. Placebo-controlled trials were given first priority followed by pooled analysis, meta-analyses, and systematic reviews. Population-based studies, retrospective analyses, and other studies were considered lower on the level of evidence. We further arranged the studies in each of the subsections based on the date of publication to maintain a chronological order.

Results

Risk of CVAEs

Placebo-controlled trials. Brodaty et al conducted a randomized, double-blind, placebo-controlled trial of elderly patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis of dementia of the Alzheimer's type, vascular dementia, or a combination of the 2 (ie, mixed dementia) and significant aggressive behaviors. Patients were randomized to receive, for a period of 12 weeks, a flexible dose of either placebo or risperidone solution up to a maximum of 2 mg/d.[20] Outcome measures were the Cohen-Mansfield Agitation Inventory (CMAI), the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Rating scale, and the Clinical Global Impression of Severity (CGI-S) and of Change (CGI-C) scales. A total of 345 patients were randomized to treatment with risperidone or placebo, and 337 patients received at least 1 dose of study drug. The trial was completed by 67% of patients in the placebo group and 73% of patients in the risperidone group. Five patients in the risperidone group suffered a stroke and 1 had a transient ischemic attack (TIA). These patients were aged between 79 and 89 years. Five of these patients had vascular/mixed vascular and Alzheimer's type dementia. One patient had Alzheimer's type dementia. Of these 6 patients, 5 had a history of hypertension, 4 had atrial fibrillation, and 1 had diabetes mellitus.

Schneider et al conducted a 42-site, double-blind, placebo-controlled trial of 421 outpatients with Alzheimer's disease (AD) and psychosis, aggression, or agitation.[8] They were randomly assigned to receive olanzapine (mean dose, 5.5 mg/d), quetiapine (mean dose, 56.5 mg/d), risperidone (mean dose, 1.0 mg/d), or placebo for upto 36 weeks. In this trial, there were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks; $P = .52$). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks), $P = .002$. The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received placebo discontinued their assigned treatment

owing to intolerability, $P = .009$. The investigators concluded that adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with AD. However, there were only 2 cerebrovascular events (CVEs) or TIAs in the olanzapine group compared to 1 each in the quetiapine, risperidone, and placebo groups, $P = .92$.

Pooled analysis, meta-analyses, and systematic reviews. De Deyn et al in their review found a total of 29 (3.9%) CVAEs with risperidone-treated patients as compared to 7 (1.6%) in placebo-treated patients.[21] The majority (61.8%) of these were reports of nonspecific symptoms such as obtundation, dizziness, or weakness rather than strokes. When considering the Code of Federal Regulations 312.32 defined "serious" events (a category including all events with lasting disability, hospitalization, or death as might be expected with stroke), 12 (1.6%) patients who received risperidone and 3 (0.7%) who received placebo (all aged >85 years) experienced such an event. Cerebrovascular adverse events were reported at an average of 30.7 days (range: 3-75 days) after beginning treatment with risperidone and 56.7 days (range: 24-82 days) for placebo. The incidence of CVAEs did not appear to be dose dependent (ie, in 3.7%, 3.1%, and 5.0% of patients receiving risperidone <0.75, 0.75 to <1.5 and ≥1.5 mg/d, respectively). In total, 5 patients died of a CVAE 4 (0.5%) risperidone-treated and 1 (0.2%) placebo-treated patient. No correlation between adverse events (eg, purpura or peripheral edema) and CVAEs was observed.

Herrmann and Lanctot in their post hoc analysis of pooled results from 11 randomized controlled trials of risperidone and olanzapine in elderly dementia patients found an increased incidence of CVAEs when compared to placebo-treated patients.[17] Collectively, 48 (2.2%) of 2187 drug-treated patients experienced CVAEs compared to 10 (0.8%) of 1190 placebo-treated patients. The combined relative risk (RR) was 2.7, 95% confidence interval (CI) 1.4 to 5.3. Numerically more risperidone-treated patients (33 of 1009, 3.3%) experienced CVAEs compared to olanzapine-treated patients (15 of 1178, 1.3%). The weighted RR was statistically significant for risperidone, 3.2; 95% CI 1.4 to 7.2; $P = .0004$, but not for olanzapine, 1.8; 95% CI 0.5 to 6.3; $P = .36$. Reanalysis of the risperidone trials suggested that some of the increased incidence may be accounted for by nonspecific events that were not strokes. A larger number of patients with vascular and mixed dementias were included in the risperidone studies compared with the olanzapine studies, which likely accounts for the increased incidence of CVAEs in the risperidone trials compared with the olanzapine studies.

Schneider et al in their excellent meta-analysis reviewed data from MEDLINE, the Cochrane Register of Controlled Trials, meetings, and presentations, and information was also obtained from sponsors.[22] Published and unpublished randomized, placebo-controlled, double-blind, parallel-group trials in patients with AD or dementia of atypical antipsychotics marketed in the United States were studied. A total of 15 trials including 16 contrasts of atypical antipsychotics with placebo met selection criteria: aripiprazole (3), olanzapine (5), quetiapine (3), and risperidone (5). In all 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 odds ratio (OR) by meta-analysis for CVAEs of 2.13; 95% CI 1.20 to 3.75; $P = .009$, 1.9% versus 0.9% pooled. There was a significantly increased risk with risperidone OR = 3.43; 95% CI 1.60 to 7.32; $P = .001$, 3.1% versus 1.0% pooled.

A meta-analysis by Ballard et al concluded that risperidone- and olanzapine-treated patients with dementiahad a significantly higher incidence of CVEs (including stroke) than placebo-treated patients.[15] Five trials evaluated serious adverse CVEs. Data on these events were also taken from the data published by the Committee for the Safety of Medicines. Risperidone- (all doses pooled) treated patients were significantly more likely to have serious adverse CVEs 37 of 1175 versus 8 of 779; OR 3.64; 95% CI 1.72 to 7.69; $P = .0007$.[15] The relevant data for olanzapine were not made available by CSM, but they had concluded that the risk of stroke was similar for olanzapine and recommended that it should not be used for the treatment of people with dementia for this reason.

The European Medicines Agency reviewed 3 placebo-controlled trials where a total of 938 elderly patients with a mean age of 82.4 years (range: 56-99 years), with psychosis associated with AD were treated with aripiprazole.[23] Cerebrovascular adverse reactions (eg, stroke, transient ischemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years).[23] Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials (a fixed-dose trial), there was a significant dose−response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole.

In a systematic review, Sacchetti et al searched the MEDLINE database covering the period from 1966 to June 2009 using selected keywords. Inclusion criteria were (*i*) quantitative reviews on stroke and antipsychotics; (*ii*) double-blind, placebo-controlled clinical trials involving patients with dementia treated with antipsychotics; and (*iii*) observational database cohort studies and observational case−control studies investigating the association between stroke and antipsychotics.[24] Clinical trials were excluded if they were single-blind or if patients were affected by dementia and/or other neurological illnesses. Four reviews with aggregate data, 2 meta-analyses, 13 randomized, double-blind, controlled trials, 7 observational cohort studies, and 4 observational case−control studies were selected and were analyzed. The incidence of cerebrovascular accidents (CVAs) was found to be very low in aggregate reviews and meta-analyses (2%-4%). When the number collected was sufficiently high, or different drug treatments were grouped together, the higher rate in patients exposed to antipsychotics was statistically significant. Inspection of other randomized controlled clinical trials, not included in aggregate reviews and meta-analyses, reported similar rates

of CVAs. The majority of observational cohort studies compared typical and atypical antipsychotics and no significant class differences were found. A comparison with nonusers was carried out in some cohort studies. In case−control studies, the probability of CVAs in users compared with nonusers was in the range of 1.3- to 2-fold greater. The investigators concluded that the preliminary data indicate that the highest risk of stroke is related to the first weeks of treatment, and a risk profile for stroke is emerging, such as older age, cognitive impairment, and vascular illness.

Population-based studies, retrospective analyses, and other studies. Herrmann et al conducted a retrospective population-based cohort study that linked administrative health care databases in Ontario, Canada, and included approximately 1.4 million patients over age 65 from April 1, 1997, through March 31, 2002.[25] Users of risperidone and olanzapine were compared with those dispensed any typical antipsychotic. Clozapine and quetiapine were not examined because of the relatively small numbers of prescriptions written during the observation period. Users were defined as individuals of age 66 and older, who were given at least 2 successive prescriptions, and received enough drug for at least 30 days of observation. Duration of exposure was the period of continuous, exclusive use of any of the study drugs starting from the index date. If patients failed to refill their prescription for the study drug, they were deemed to have discontinued the study drug. Follow-up ended with hospital admission for stroke, exposure to a medication from another study group, discontinuation of the drug, death, or end of the observation period. Hospital admissions for stroke were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes to define stroke-related outcomes. During 13 318 person years of follow-up, there were 92 admissions for stroke; typical antipsychotic users: N = 10; risperidone users: N = 58; olanzapine users: N = 24. The crude stroke rate per 1000 person years did not significantly differ among the patients treated with typical antipsychotics (5.7), risperidone (7.8), and olanzapine (5.7). Relative to typical antipsychotic users, model-based estimates adjusted for covariates revealed a risk ratio for stroke of 1.1; 95% CI 0.5 to 2.3 with olanzapine use and 1.4; 95% CI 0.7 to 2.8 with risperidone use. Relative to olanzapine, users of risperidone were not at significantly increased risk of stroke-related hospital admission, adjusted risk ratio 1.3; 95% CI 0.8 to 2.2. The investigators concluded that olanzapine and risperidone use were not associated with a statistically significant increased risk of stroke compared with typical antipsychotic use.

Finkel et al completed an analysis of Medicaid data from 1999 to 2002, representing approximately 8 million enrollees from multiple states. The incidence of acute inpatient admission for CVAEs within 3 months following initiation of treatment with atypical antipsychotics (risperidone, olanzapine, quetiapine, or ziprasidone), haloperidol, or benzodiazepines was evaluated.[26] A total of 18,987 patients were included in the analysis. Risperidone and other antipsychotics as a group were also not associated with a higher OR of incident CVAEs than either haloperidol or benzodiazepines. The percentage of patients who had CVAEs in each group were risperidone (0.86%), olanzapine (0.87%), quetiapine (0.56%), haloperidol (1.19%), and benzodiazepine (1.04%). With risperidone as the reference group, the OR were olanzapine, 1.05, 95% CI 0.63 to 1.73; quetiapine, 0.66, 95% CI 0.23 to 1.87; haloperidol, 1.91, 95% CI 1.02 to 3.60; and benzodiazepines, 1.97, 95% CI 1.30 to 2.98. With benzodiazepines as the reference group, the OR of incident CVAEs for all antipsychotics as a class was 0.49, 95% CI 0.35 to 0.69. The study controlled for common risk factors for CVAEs (eg, hypertension, diabetes, and atrial fibrillation), but the data did not allow for control of other risk factors such as smoking status, weight, or potentially relevant over-the-counter medication (eg, aspirin) use. Significant predictors of CVAEs included prior CVE and atrial fibrillation, percentage of days in the follow-up period that medication was available. The presence of hypertension was significant in the risperidone versus olanzapine comparison, while the number of preperiod hospital days was significant in some models (risperidone vs haloperidol or benzodiazepines). Age, gender, and indicators for atherosclerosis, diabetes, anticlotting medication, and vascular dementia were not significant predictors in the models.

In a case control study on residents of nursing homes in 6 US states, Liperoti et al used the Systematic Assessment of Geriatric drug use via Epidemiology database, which included data from the Minimum Data Set linked to Medicare inpatient claims.[27] Participants were diagnosed with AD or other forms of dementia on the basis of clinical criteria and medical history (including medical records and neuroradiologic documentation). The sample consisted of 1130 cases and 3658 controls. After controlling for potential confounders, the OR of being hospitalized for CVEs was 0.87, 95% CI 0.67 to 1.12 for risperidone users; 1.32, 95% CI 0.83 to 2.11 for olanzapine users; 1.57, 95% CI 0.65 to 3.82 for users of other atypical agents; and 1.24, 95% CI 0.95 to 1.63 for conventional antipsychotic users compared to nonusers of antipsychotics. Users of risperidone and conventional antipsychotics had no increased risk of being hospitalized for CVAEs, regardless of the presence of a previous history of stroke/TIA; adjusted OR, 1.49, 95% CI 0.93 to 2.38 and adjusted OR 1.23, 95% CI 0.68 to 2.23, respectively. In contrast, olanzapine users and users of other atypical agents presenting with a history of CVEs were 3.71 times and 4.63 times more likely to be hospitalized for CVEs compared to nonusers without such history, adjusted OR, 3.71, 95% CI 1.55 to 8.84 and adjusted OR 4.63, 95% CI 1.35 to 32.63, respectively. This observation might be explained by the worsening of the cardiovascular risk profile documented to occur with these agents relative to risperidone. For example, olanzapine causes more increase in weight, serum lipid levels, glucose levels, and leptin levels relative to risperidone.

Formiga et al in their cross-sectional study, evaluated 320 consecutive patients with dementia aged 65 and older from 6 centers to assess the possibility of an association between use of risperidone and an increased risk of CVAEs.[28] Patients were included in the group on neuroleptic treatment when they had

taken a neuroleptic drug for at least 15 consecutive days. The occurrence of any type of CVAE during follow-up treatment since dementia was recorded. In all, 214 (67%) women and 106 men were included. Mean age was 81.1 ± 6.8 years. Mean time since diagnosis of dementia was 31.1 ± 24.0 months. The mean duration for follow-up was 20 months. A total of 191 (60%) patients had received treatment with neuroleptic drugs: 168 (53%) risperidone, 10 haloperidol, 6 levomepromazine, 4 olanzapine, 2 quetiapine, and 1 thioridazine. The daily dose of risperidone ranged from 0.5 to 3 mg, and the mean time since the start of risperidone was 10.1 ± 12.0 months. Six patients experienced a new stroke during follow-up (mean 20 months): 3 of them in the risperidone group and 3 in the other group (2 patients not taking neuroleptics and 1 on thioridazine); there were no significant differences ($P = 1.0$). Four patients experienced a TIA during follow-up (mean 18.4 months): 1 in the risperidone group and 3 in the other group (2 not taking neuroleptics and 1 taking levomepromazine; $P = .34$). Overall, 10 patients experienced some CVAE during follow-up (mean 19 months): 4 in the risperidone group and 6 in the other group (4 not taking neuroleptics and 1 each on thioridazine and levomepromazine; $P = .52$). When data were analyzed depending on whether patients had taken neuroleptic treatment, no significant differences were found in strokes (4 vs 2; $P = .90$) or TIA (2 vs 2; $P = .90$), nor were they found when both events were analyzed together (6 vs 4; $P = .90$). The investigators concluded that despite the cross-sectional nature of their study using flexible doses and a small sample size, it could be concluded that there is no association between the use of risperidone and an increased incidence of CVAEs.

In a population-based retrospective cohort study by Gill et al from Ontario, Canada, followed 32 710 older adults (≤ 65 years) with dementia who were treated with antipsychotics (17 845 dispensed an atypical antipsychotic and 14 865 dispensed a typical antipsychotic).[29] Patients were observed until they were either admitted to hospital with ischemic stroke, stopped taking antipsychotics, died, or the study ended. The investigators enrolled patients into the cohorts between April 1, 1997 and March 31, 2002. After adjustment for confounding factors, participants receiving atypical antipsychotics showed no significant increase in risk of ischemic stroke compared with those receiving typical antipsychotics, adjusted hazard ratio (HR) 1.01, 95% CI 0.81 to 1.2. The risk of stroke for patients receiving the individual drugs were as follows: risperidone, adjusted HR 1.04, 95% CI 0.82 to 1.31; olanzapine 0.91, 95% CI 0.62 to 1.32; and quetiapine 0.78, 95% CI 0.38 to 1.57, which were not significantly different from that of patients receiving typical antipsychotics. But they found higher incidence rates of stroke in patients with atrial fibrillation who were prescribed atypical antipsychotics, adjusted HR 1.23, 95% CI 0.70 to 2.02. Patients who were dispensed 2 or more consecutive prescriptions (chronic users) of atypical antipsychotics were not at increased risk of stroke compared with chronic users of typical antipsychotics, adjusted HR 0.89, 95% CI 0.69 to 1.17. The investigators concluded that older adults with dementia who take atypical antipsychotics have a similar risk of ischemic stroke to those taking typical antipsychotics.

Moretti et al conducted a controlled, open-label study of nursing care facility residents aged between 71 and 92 years, who were not bedridden. They were manually divided into 2 groups.[30] The duration of study was for 12 months. These patients were matched for age, education levels, and preliminary neuropsychiatric inventory (NPI) scores. Group A received olanzapine 2.5-7.5 mg/d, while group B received typical neuroleptics (60 patients receiving promazine chloridrate 4%, up to 10 drops/thrice daily (tid), and 113 patients received haloperidol 0.2%, up to 10 drops/tid). A total of 356 patients, 198 men and 158 women, were included in the study. Their mean age was 76.78 ± 4.01 years, and they had a mean education level of 8.3 ± 4.23 years. In the 2 groups, the change from baseline on the Hachinski Ischemic Score were +1.7 ± 0.6 and +1.6 ± 0.3, respectively. The change in Matthew's Stroke Scale were –5.4 ± 0.7 and –6.1 ± 0.7, respectively. These changes were not statistically significant. The investigators concluded that in this study, there was no statistically significant increase in the risk of stroke associated with the use of olanzapine as compared to typical antipsychotics.

In a retrospective analysis, Layton et al compared the incidence rates for events reported as CVA and TIA during the first 180 days of treatment in patients prescribed atypical antipsychotics for dementia or other indications.[31] Analysis of data from the 3 observational studies was conducted using Poisson regression modeling and survival analysis. The analysis included 7684 risperidone-treated patients, 1726 quetiapine-treated patients, and 8826 olanzapine-treated patients. Within the risperidone, quetiapine, and olanzapine cohorts, 23 (0.30%), 6 (0.35%), and 10 (0.11%) patients, respectively, were reported to have had a CVA/TIA event. Age, gender, and indication (dementia or other) were identified as important confounding variables, with age being the most important. The crude rate ratios (RRs) for CVA/TIA for risperidone-treated or quetiapine-treated versus olanzapine-treated patients indicated an approximate 3-fold relative difference in rate during the first 6 months but after adjustment for age, sex and indication, the RRs were non-significant 1.2, 95% CI, 0.5 to 3.0 and 2.1, 95% CI, 0.6 to 7.7, respectively. For risperidone-treated versus quetiapine-treated patients, crude and adjusted RRs were not significantly different, 0.84, 95% CI, 0.34 to 2.07, 0.73, 95% CI, 0.27 to 2.00, respectively. Of the 3 drugs, the time to event was shortest for risperidone, 58 days, range 0.5 to 168 days and also shortest for risperidone or quetiapine users where the indication was dementia. The age- and gender-adjusted RR of CVA/TIA in patients prescribed risperidone for dementia versus other indications was 6.7, 95% CI 2.4 to 18.9. The adjusted RRs for quetiapine, according to indication, could not be calculated due to missing information on age and gender. There were no cases of CVA/TIA with dementia for olanzapine, thus the RRs and time to event curves according to indication could not be examined. The investigators concluded that there was no significant difference in the adjusted RR of CVA/TIA events in the first 180 days of treatment in patients

prescribed risperidone or quetiapine when compared with olanzapine. However, dementia appeared to be an important risk factor, RR, 54.52, 95% CI 19.41 to 153.16 and RR 16.91, 95% CI 2.32 to 120.5 for risperidone and quetiapine, respectively.

In a database review, Percudani et al investigated the relationship between exposure to second-generation antipsychotics (SGAs) and the occurrence of CVAs in the elderly patients.[32] From the regional database of hospital admissions of Lombardy, Italy, they extracted data on all patients aged 65 or older with cerebrovascular-related outcomes for the year 2002. The cerebrovascular-related outcomes included subarachnoid hemorrhage, intracerebral hemorrhage, other and unspecified intracranial hemorrhage, occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries, transient cerebral ischemia, acute, but ill-defined, cerebrovascular disease, and other and ill-defined cerebrovascular disease. From the regional database of prescriptions reimbursed by the National Health Service, they extracted data for all patients aged 65 or older who received antipsychotic prescriptions during 2001. The 2 databases were linked anonymously using the individual patient code. The proportions of CVAs were 3.31%, 95% CI 2.95-3.69 in elderly patients exclusively exposed to SGAs and 2.37%, 95% CI 2.19 to 2.57 in elderly patients exclusively exposed to first-generation antipsychotics (FGAs). After background group differences were controlled for, exposure to SGAs increased the risk of accidents. The analysis of CVEs in elderly patients exposed to each individual SGA, in comparison with exposure to haloperidol, showed an increased risk of risperidone only, adjusted OR, 1.43, 95% CI 1.12 to 1.93. The investigators concluded that the data provide preliminary epidemiological evidence that exposure to SGAs, in comparison with exposure to FGAs, significantly increased the risk of CVAs in the elderly patients.

Kolanowski et al conducted an analysis of the claims data from a large health care insurer located in the southeast region of the United States.[33] Claims data were collected on all individuals who were 45 years or older on January 1, 1998. From this database, all individuals with any *ICD-9* code for dementia and only those cases that had at least 1 prescription claim and were enrolled for 3 consecutive years were selected. Using these parameters, the investigators obtained 959 unique individuals with dementia. Overall, 27% of this sample of community-dwelling persons with dementia was dispensed antipsychotic drug therapy. The observation period was for 45 days. The investigators included only those cases that had at least 1 prescription claim for the 3-year period. In this study, the investigators found that the OR for stroke was 0.98, 95% CI 0.64 to 1.52 when the prescription was for typical antipsychotics. The OR was 1.18, 95% CI 0.63 to 2.24 when the prescription was for atypical antipsychotics. The OR was 1.22, 95% CI 0.55 to 2.68 when both groups were considered together. The overall *P* value was .91, indicating that the risk of stroke was not statistically significant.

Barnett et al conducted a prospective study of 14,029 patients aged 65 years and older using patient information from Veterans Administration and Medicare databases.[34] Patients who received care for dementia were categorized according to dementia subtype (vascular or Alzheimer) and antipsychotic use during an 18-month period. Patients were observed until they were admitted to a hospital for CVEs, stopped taking or switched antipsychotics, died, or until the 18-month observation period ended. In the multivariate Cox regression model controlling for age, gender, race, marital status, Veterans Affairs (VA) means status, comorbid conditions, previous CVE, and prescription drug therapy, the risk of a CVE admission did not differ in those receiving FGA or SGA compared with those not receiving antipsychotic therapy, RR 1.29, 95% CI 0.48 to 3.47; and RR 1.20, 95% CI 0.83 to 1.73, respectively. The coefficient associated with the indicator variable identifying patients with vascular dementia relative to patients with Alzheimer's dementia was, however, found to be significant, RR 1.14, 95% CI 1.07 to 1.34, suggesting an increased CVE risk associated with vascular-type dementia. Among subgroup analyses of patients receiving antipsychotics (FGA or SGA), no differences in risk of CVE admission was found in patients receiving quetiapine, olanzapine, or risperidone, relative to haloperidol, RR 0.70, 95% CI 0.30 to 1.65; RR 0.62, 95% CI 0.25 to 1.53; and RR 0.49, 95% CI 0.21 to 1.12. The subgroup analysis of patients receiving quetiapine, olanzapine, or risperidone, relative to haloperidol showed the RR to be 1.04, 95% CI 0.33 to 3.91; RR 1.00, 95% CI 0.30 to 3.35; and RR 0.80, 95% CI 0.26 to 2.43 for Alzheimer's dementia and RR 0.32, 95% CI 0.07 to 1.46; RR 0.23, 95% CI 0.04 to 1.38; and RR 0.14, 95% CI 0.02 to 1.68 for vascular dementia. The risk associated with patients having vascular dementia relative to patients with Alzheimer's dementia was significant, RR 1.39, 95% CI 1.04 to 2.11. There was, however, a decreased risk of CVE seen in patients with vascular dementia receiving risperidone relative to those receiving haloperidol, RR = 0.13, 95% CI 0.03 to 0.63. In the SGA subgroup analyses, no differences were seen in patients receiving either olanzapine or risperidone, relative to quetiapine, RR 0.84, 95% CI 0.36 to 2.11 and RR 0.73, 95% CI 0.41 to 1.76, respectively. When stratified by the type of dementia, the RR was 0.96, 95% CI 0.39 to 2.32 and RR 0.79, 95% CI 0.36 to 1.71 for patients with Alzheimer's and vascular dementia, respectively. No increase in the risk associated with vascular dementia relative to Alzheimer's dementia was seen, RR 1.08, 95% CI 0.55 to 2.18. The investigators concluded that in the overall model, no risk of FGA or SGA exposure was found in analysis stratified by type of dementia. Overall, CVE risk did not differ whether patients were receiving a FGA, SGA, or no antipsychotic therapy. However, patients with vascular dementia had an increased risk of hospitalization for a CVE.

Wang et al conducted a retrospective study based on the information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program and Medicare data. This study[35] included both parts A and B on all Pennsylvania Pharmaceutical Assistance Contract for the Elderly enrollees, during January 1, 1994 to December 31, 2003 All individuals were 65 years or older and filled a first recorded (index)

prescription for an oral antipsychotic medication from January 1, 1994 to December 31, 2003. Atypical antipsychotic drugs included aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Other antipsychotics were considered conventional drugs. By 30 days, the adjusted hazard ratios were not higher for conventional than atypical antipsychotics in developing CVEs, HR 1.08, 95% CI 0.99 to 1.18. By 60 days, conventional compared to atypical antipsychotics was associated with a significantly increased hazard ratio of developing CVEs, HR 1.10, 95% CI 1.02 to 1.19. The hazard ratios of developing CVEs were also significantly greater for conventional than atypical antipsychotic use at 120 days, HR 1.09, 95% CI 1.02 to 1.16. The investigators concluded that if confirmed, these results add to growing evidence that conventional antipsychotic agents not be safer than atypical antipsychotic medications for the elderly and should not simply replace the latter drugs stopped in response to recent FDA warnings.

Sacchetti et al conducted a retrospective review from the Health Search Database, which stores information on about 1.5% of the total Italian population served by general practitioners.[36] All elderly patients (65+ years) prescribed an antipsychotic in monotherapy from January 2000 to June 2003 were selected for the study. A cohort of patients not exposed to antipsychotics was taken from the same database. Patients who previously had a stroke were excluded. The main outcome measure was the incidence of first-ever stroke during exposure to an antipsychotic. The sample included nonusers (69 939), users of atypicals (599), butyrophenones (749), phenotiazines (907), and substituted benzamides (1968). The crude incidence of stroke in patients not exposed to antipsychotics was 12.0/1000 person years, 95% CI 11.5 to 12.5. When compared to this estimate, risk was significantly higher in those on butyrophenones, 47.1/1000, 95% CI 22.1 to 88.8, phenotiazines 72.7/1000, 95% CI 43.3 to 107.7 and in the atypical antipsychotic group 47.4/1000, CI 23.4-86.5. Substituted benzamides higher risk, 25.0/1000, 95% CI 12.0 to 34.1. The mean interval from first prescription to new-onset stroke was 103.3 days, standard deviation (SD) 112.7 in atypicals; 57.5 days, SD 22.2 in butyrophenones; 21.3 days, SD 18.8 in phenotiazines; and 120.5 days, SD 119.6 in substituted benzamides. Two multivariate models were applied. In the first model, the reference group was made up of patients not exposed to antipsychotics (default risk 1). The risk of stroke was again higher for the group of phenotiazines, 5.79 times, 95% CI 3.07 to 10.9, butyrophenones, 3.55 times, 95% CI 1.56 to 8.07, and atypical 2.46 times, 95% CI 1.07 to 5.65 when compared with unexposed patients. The group of substituted benzamides had an almost significantly higher risk, 2.2, 95% CI 0.98 to 4.90. The second model took atypical users as the reference group (default risk 1) and compared typical versus atypical antipsychotic drugs, while weighing for the same covariates entered in the previous model. Phenotiazines had a significantly higher risk, 2.34, 95% CI 1.01 to 5.41, for stroke when compared with atypical antipsychotics. Older age, male gender, a Chronic Disease Score higher than 5, a diagnosis of Parkinson disease, and the use of anticoagulants increased the risk of strokes. Dementia, per se, had only a weak effect on stroke risk, and affective disorders were not associated to the risk. The investigators opined that clinicians should be cautious in prescribing phenotiazines and butyrophenones in elderly patients as the risk of stroke appeared comparable or even greater than with atypicals.

Douglas and Smeeth conducted an electronic primary care records review in the United Kingdom. In this review, the general practice research database (GPRD) was evaluated.[37] The investigators identified 6790 eligible patients in the database with at least 1 prescription for an antipsychotic drug and a recorded incident stroke between January 1988 and the end of 2002. Of these, 905 patients were prescribed at least 1 atypical antipsychotic drug and 6334 were prescribed at least 1 typical antipsychotic drug during the study period. The most commonly used typical antipsychotics were phenothiazines (5153 patients), and the most common atypical antipsychotic drug was risperidone (729 patients). Of these 64% were women. The median age at first exposure to any antipsychotic drug was 80, while median age at the time of first recorded stroke was 81. In all, 1423 patients had a recorded diagnosis of dementia before the incident stroke, and these patients were slightly older than those without dementia at the time the first antipsychotic drug was prescribed. In total, 5885 patients received a prescription for a typical but not an atypical antipsychotic drug during the study period, and 456 patients received prescriptions only for atypical antipsychotics. The age at first recorded antipsychotic drug exposure was similar for patients exposed only to typical or atypical antipsychotics. The 449 remaining patients received prescriptions for both typical and atypical antipsychotics. Among patients with dementia, 1212 received only typical antipsychotics and 85 received only atypical antipsychotics. The median duration of total observation period included in the analysis was at least 4 years for each subgroup. Rate ratio for stroke in periods of time exposed to antipsychotics was compared with unexposed periods. The use of any antipsychotic drug was associated with a rate ratio for stroke of 1.73, 95% CI 1.60 to 1.87; 1.69, 95% CI 1.55 to 1.84 for typical antipsychotics and 2.32, 95% CI 1.73 to 3.10 for atypical antipsychotics. In patients receiving any antipsychotic drug, the rate ratios were 3.50, 95% CI 2.97 to 4.12 for those with dementia and 1.41, 95% CI 1.29 to 1.55 for those without dementia. In patients with dementia and only typical antipsychotic drug prescriptions, the rate ratio for stroke was 3.26, 95% CI 2.73 to 3.89. In patients with dementia and only treated with atypical antipsychotics, the rate ratio was 5.86, 95% CI 3.01 to 11.38. Patients without dementia before stroke and receiving only typical antipsychotics had a rate ratio of 1.40, 95% CI 1.26 to 1.54 compared with a figure of 1.90, 95% CI 1.36 to 2.65 in patients without dementia and receiving only atypical antipsychotics. The investigators concluded that all antipsychotics are associated with an increased risk of stroke, and the risk might be higher in patients receiving atypical antipsychotics than those receiving typical antipsychotics. They further stated that patients with dementia seem to be at a higher risk of an associated stroke than people without

dementia and the use of antipsychotics should whenever possible be avoided in these patients.

Chan et al conducted a retrospective cohort study in Hong Kong. Patients aged 65 or above, who were diagnosed with AD, vascular, or mixed dementia, and first attended the psychiatric service of an inpatient unit between January 1, 2000 and June 30, 2007 were studied.[38] The patients were divided into 3 groups according to their antipsychotic usage. A total of 1089 patients were included in this study. The median observation time was 1019 days for the antipsychotic nonuser group, 697 days for the typical antipsychotic user group, and 625 days for the atypical antipsychotic user group. The risk of CVAEs was studied by means of Cox regression analysis. Incidence rate of CVAE for the 3 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 nonuser group. The adjusted HR for the typical and atypical antipsychotic user groups were 0.964, 95% CI 0.584 to 1.591 and 1.036, 95% CI 0.350 to 3.066, respectively. Subgroup analyses of individual antipsychotic did not show a significant increase in risk of CVAEs. The investigators concluded that there was no statistical difference in risk of CVEs in the treatment of BPSD with typical and atypical antipsychotics compared with nonuser group (Table 1).

Risk of Death

Placebo-controlled trials. In the study by Brodaty et al, 10 patients—6 (3.6%) in the risperidone group and 4 (2.4%) in the placebo group—died during the course of the trial.[20] The most common cause of death was pneumonia; 3 in the risperidone group and 1 in the placebo group. The second most common cause of death was stroke, 2 in the risperidone group. The investigators opined that the adverse events leading to the patient's deaths to have no drug relationship.

In the 42-site, double-blind, placebo-controlled trial of 421 outpatients with AD and psychosis, aggression, or agitation, conducted by the Schneider et al, there was 1 death in the olanzapine and risperidone groups.[8] There were 3 deaths each in the quetiapine and the placebo groups. The results were not statistically significant, $P = .58$.

In a prospective study conducted by Ballard et al in the United Kingdom, between October 2001 and December 2004, patients with AD who resided in care facilities in the United Kingdom were enrolled into a randomized, placebo-controlled, parallel, 2-group treatment discontinuation trial.[39] Participants were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or to switch their medication to an oral placebo. The primary outcome was mortality at 12 months. An additional follow-up telephone assessment was done to establish whether each participant was still alive 24 months after the enrollment of the last participant (range 24-54 months). Causes of death were obtained from death certificates. Analysis was by intention to treat (ITT) and modified intention to treat (mITT). In all, 165 patients were randomized (83 to continue antipsychotic treatment and 82 to placebo), of whom 128 (78%) started treatment (64 continued with their treatment and 64 received placebo). Comparisons between the patients who continued antipsychotic treatment and the placebo group during the 12-month randomized, double-blind phase of the trial showed that the respective cumulative probabilities of survival were 89.7%, 95% CI 71.3% to 96.5% versus 97.1%, 95% CI 80.9% to 99.6% in the patients who continued to take their allocated treatment for 12 months, 70.3%, 95% CI 57.5% to 79.9% versus 76.6%, 95% CI 64.2% to 85.2% in the patients who started their allocated treatment (mITT population), and 74.7%, 95% CI 63.9% to 82.7% versus 79.3%, 95% CI 68.8% to 86.6% in the ITT population. The Kaplan-Meier estimates show that during the extended follow-up, the patients who continued antipsychotic treatment had significantly higher mortality compared with those who took placebo, mITT population log rank $P = .03$, HR 0.58, 95% CI 0.35 to 0.95; ITT population log-rank $P = .02$, HR 0.58, 95% CI 0.36 to 0.92. The difference in mortality was more pronounced after the first year. The differences in survival were similar whether the analysis was done on the mITT population, the ITT population, or on the patients who continued to take their allocated treatment for the first 12 months of the study (or until death, whichever occurred first). The only difference between the analyses was a clearer separation of the groups over the 12-month randomized period of the trial. On the basis of the results for the mITT population, the cumulative survival was 46% versus 71%, respectively, between the continued treatment and placebo groups at 24 months, 30% versus 59% at 36 months, and 26% versus 53% at 42 months. The numerical differences at months 24, 36, and 42 were similar in the analyses for the ITT population and the patients who took their medication for the first 12 months. The investigators opinionated that there is still an important but limited place for atypical antipsychotics in the treatment of severe BPSD, particularly aggression. However, the accumulating safety concerns, including the substantial increase in long-term mortality, emphasis the urgent need to put an end to unnecessary and prolonged prescribing.

Meta-analysis and systematic review. Schneider et al in their meta-analysis extracted data from MEDLINE (1966 to April 2005), the Cochrane Controlled Trials Register (2005, Issue 1), and meeting presentations (1997-2004), and information was also obtained from the sponsors.[40] They evaluated 15 trials (9 unpublished), generally 10 to 12 weeks in duration, including 16 contrasts of atypical antipsychotic drugs with placebo met criteria (aripiprazole [n = 3], olanzapine [n = 5], quetiapine [n = 3], and risperidone [n = 5]). A total of 3353 patients were randomized to study drug and 1757 were randomized to placebo. Death occurred more often among patients randomized to drugs 118 (3.5%) versus 40 (2.3%). The OR by meta-analysis was 1.54, 95% CI 1.06 to 2.23, $P = .02$; and risk difference was 0.01, 95% CI 0.004 to 0.02, $P = .01$. Sensitivity analyses did not show evidence for differential risks of individual drugs, severity, sample selection, or diagnosis. The investigators concluded that

Table 1. Risk of CVAEs

Author (Year of Publication)	Type of Study	Study Information	Conclusions
Brodaty et al[20] (2003)	Randomized double-blind, placebo-controlled trial.	Compared risperidone to placebo.	More patients in the risperidone group had CVAEs when compared to placebo group during the course of the trial.
Schneider et al[8] (2006)	Double-blind, placebo-controlled trial.	Compared olanzapine, quetiapine, and risperidone to placebo.	The risk of CVAEs was no greater in the drug-treated group compared to the placebo group.
De Deyn et al[21] (2005)	Pooled analysis including 3 randomized, placebo-controlled double-blind trials.	Compared risperidone to placebo.	Increased risk of CVAEs with risperidone compared to placebo.
Herrmann and Lanctot[17] (2005)	Post hoc analysis of pooled data.	Compared risperidone and olanzapine to placebo.	Increased risk of CVAEs with risperidone and olanzapine compared to placebo.
Schneider et al[22] (2006)	Meta-analysis of published and unpublished randomized, placebo-controlled, double-blind, parallel-group trials of atypical antipsychotics marketed in the United States.	Compared aripiprazole, olanzapine, quetiapine, and risperidone to placebo.	The risk of CVAEs in patients treated with the atypical antipsychotics was higher than placebo-treated patients. The risk of CVAEs was 3 times higher in risperidone-treated patients compared to placebo-treated patients.
Ballard and White[15] (2006)	Meta-analysis of data published by the Committee for the Safety of Medicines.	Compared atypical antipsychotics, butyrophenones, phenotiazines, and substituted benzamides to placebo	The risk of CVAEs in the risperidone-treated patients is significantly higher than in the placebo-treated patients. Although the data for olanzapine were not made available, the risk of CVAEs appears similar to that of risperidone.
European Agency[23]	Meta-analysis of 3 placebo-controlled trials.	Compared aripiprazole to placebo.	The risk of CVAEs with aripiprazole was not statistically significant. In 1 trial (a fixed-dose trial), there was a significant dose−response relationship for CVAEs in patients treated with aripiprazole.
Sacchetti et al[24] (2010)	Systematic review of MEDLINE database.	Compared antipsychotics (typical and atypicals) to nonexposure to drugs.	The incidence of CVAEs was found to be very low (2%-4%). The risk of CVAEs in the exposed group is about 1.3 to 2 times the nonexposed groups. The risk of CVAEs in the typical and the atypical antipsychotic group is similar. Highest risk of CVAEs is related to the first weeks of treatment. Risk is higher in those who are older, with cognitive impairment and vascular illness.
Herrmann et al[25] (2004)	Retrospective population-based cohort study.	Compared risperidone and olanzapine to any typical antipsychotic.	Olanzapine and risperidone use was not associated with a statistically significant increased risk of stroke compared with typical antipsychotic use.
Finkel et al[26] (2005)	Retrospective analysis of Medicaid data.	Compared risperidone, olanzapine, quetiapine, and ziprasidone to haloperidol or benzodiazepines.	Risperidone has similar risk of CVAEs compared to olanzapine, quetiapine, and haloperidol. The risk of CVAEs with antipsychotics is no greater than with benzodiazepines

(continued)

Table 1 (continued)

Author (Year of Publication)	Type of Study	Study Information	Conclusions
Liperoti et al[27] (2005)	Case-control study on residents of nursing homes in 6 US states.	Compared risperidone, olanzapine, other atypical antipsychotics, and conventional antipsychotics to nonusers of antipsychotics.	Users of risperidone and conventional antipsychotics had no increased risk of being hospitalized for CVAEs, regardless of the presence of a previous history of stroke/TIA. Olanzapine users and users of other atypical agents presenting with a history of CVEs were more likely to be hospitalized for CVEs compared to nonusers without such history.
Formiga et al[28] (2005)	Cross-sectional study.	Compared risperidone to haloperidol, levopromazine, olanzapine, quetiapine, and thioridazine.	No significant differences in CVAEs when comparing risperidone to haloperidol, levopromazine, olanzapine, quetiapine, and thioridazine.
Gill et al[29] (2005)	Population-based retrospective cohort study.	Compared older adults ($\leq$ 65 years) with dementia who were treated with antipsychotics, an atypical antipsychotic and dispensed a typical antipsychotic. Patients were observed until they were admitted to hospital with ischemic stroke, stopped taking antipsychotics, died, or the study ended.	No difference in the risk of ischemic CVAEs comparing atypical to typical antipsychotics. The risk of ischemic CVAEs is similar for risperidone, olanzapine, and quetiapine. Atrial fibrillation may be a risk factor for ischemic CVAEs in patients treated with atypical antipsychotics.
Moretti et al[30] (2005)	Controlled, open-label study.	Nursing care facility residents, who were aged between 71 and 92 years, were manually divided into group A, who received olanzapine, while group B received typical neuroleptics (promazine, chloridrate, and haloperidol).	There is no statistically significant increase in risk of CVAEs with olanzapine compared to typical antipsychotics; promazine and haloperidol.
Layton et al[31] (2005)	Retrospective analysis of 3 observational studies.	Compared risperidone, quetiapine, and olanzapine.	The risk of CVAEs is similar for risperidone and quetiapine when compared to olanzapine. Dementia appeared to be an important risk factor for CVAEs when treated with risperidone and quetiapine.
Percudani et al[32] (2005)	Retrospective analysis of regional database of hospital admissions.	Investigated the relationship between exposure to SGAs and the occurrence of cerebrovascular accident.	The risk of CVAEs is similar in SGAs compared to FGAs except for risperidone where the risk may be higher.
Kolanowski et al[33] (2006)	Retrospective analysis of the claims data from a large health care insurer.	Compared typical and atypical antipsychotics to placebo.	The risk of CVAEs was no greater in the typical or atypical antipsychotic group compared to placebo group.

(continued)

Table 1 (continued)

Author (Year of Publication)	Type of Study	Study Information	Conclusions
Barnett et al[34] (2007)	Prospective study of using patient information from Veterans Administration and Medicare databases.	Compared FGAs and SGAs to placebo.	There was no increase in the risk of CVAEs with FGA or SGA in the analysis stratified by type of dementia. Overall, CVAE risk did not differ whether patients were receiving a FGA, SGA, or no antipsychotic therapy. Patients with vascular dementia had an increased risk in hospitalization for CVAEs.
Wang et al[35] (2007)	Retrospective study based on the information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program and Medicare data.	Compared conventional antipsychotics to atypical antipsychotic drugs	The risk of CVAEs is higher with conventional antispychotics compared to atypical antipsychotics by 60 days and continues to 120 days.
Sachetti et al[36] (2008)	Retrospective review from the Health Search Database.	Compared antipsychotics (typical and atypicals) to nonexposure to drugs.	Phenotiazines had a significantly higher risk of CVAEs when compared with atypical antipsychotics. Older age, male gender, a Chronic Disease Score higher than 5, a diagnosis of Parkinson disease, and the use of anticoagulants increased the risk of CVAEs. Dementia, per se, had only a weak effect on CVAEs and affective disorders were not associated to the risk.
Douglas and Smeeth[37] (2008)	Records review of the GPRD.	Compared antipsychotics (typical and atypicals) to nonexposure to drugs.	All antipsychotics are associated with an increased risk of CVAEs. The risk of CVAEs might be higher in patients receiving atypical antipsychotics than those receiving typical antipsychotics. Patients with dementia appear to be at higher risk of CVAEs when treated with these medications.
Chan et al[38] (2010)	Retrospective cohort study.	Compared antipsychotics (typical and atypicals) to nonexposure to drugs.	The risk of developing CVAEs did not differ in typical or atypical antipsychotic user groups compared with nonuser group. Subgroup analyses of individual antipsychotic did not show a significant increase in the risk of CVAEs.

Abbreviations: CVAEs, cerebrovascular adverse events; FGA, first-generation antipsychotic; GPRD, general practice research database; SGA, second-generation antipsychotic; TIA, transient ischemic attack.

atypical antipsychotic drugs may be associated with a small increased risk of death compared with placebo. This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives.

In the European Medicines Agency review discussed earlier, the rate of death in aripiprazole-treated patients was 3.5% compared to 1.7% in the placebo group.[23] Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. The agency cautioned that aripiprazole is not indicated for the treatment of dementia-related psychosis.

Population-based studies, retrospective analyses, and other studies. Nasrallah et al, in an observational study, tracked the mortality over a 2-year period in patients aged 65 years or older receiving haloperidol (N = 299) or the atypical antipsychotics risperidone or olanzapine (N = 1254).[41] In all, 64 (21.4%) patients in the haloperidol group and 61 (4.75%) patients in the atypical group died during the 2-year study period. This 4-fold difference in mortality was highly significant ($P < .00001$). The findings suggested that the mortality in elderly patients receiving haloperidol is significantly higher than in those receiving the atypical antipsychotics risperidone or olanzapine. The investigators cautioned that this was a pilot study with its limitations and should be considered a "signal" worthy of future investigation rather than a definite finding.

In a Finnish study, Raivio et al, in a prospective study of elderly institutionalized patients with dementia, followed patients for up for 2 years.[42] The investigators examined 254 very frail patients with dementia, mean age 86 years, from 7 Finnish nursing homes and 2 hospitals in 1999-2000. Medical records provided information on the use of daily antipsychotic medication; central registers confirmed mortality for up to 2 years. Nearly one half (48.4%) of the patients used antipsychotic medication: 37.4% received conventional neuroleptics (N = 95) and 11.0% received atypical antipsychotics (N = 28). Of the users of atypical antipsychotics (risperidone, olanzapine), 32.1% died within 2 years. The respective figures for users of conventional neuroleptics were 45.3%, and for the nonusers 49.6%. When comparing the users of any antipsychotic to the nonusers, the combined end point of hospital admissions and mortality was again higher among the nonusers (72%) than among the users (58%), $P = .019$. Mortality was at first year among users 17% and among nonusers 27%, $P = .064$ and at 2 years 42% and 50%, respectively, $P = .24$. In the Cox proportional hazard model, a high number of medications and the use of physical restraint predicted higher mortality at 2 years; HR 1.12, 95% CI 1.05 to 1.20, $P < .001$ and HR 1.72, 95% CI 1.04 to 2.83, $P = .03$, respectively. The use of atypical antipsychotic agents seemed to decrease the mortality risk, and the effect of conventional antipsychotics was nonsignificant; HR 0.49, 95% CI 0.24 to 0.99, $P = .047$ and HR 0.68, 95% CI 0.46 to 1.03, $P = .069$.

In a retrospective study by Barnett et al, 14,057 VA patients admitted for pneumonia in fiscal year (FY) 2003 were evaluated for exposure to typical and atypical antipsychotics and other neuropsychiatric drugs based on a prescription within 120 days preceding admission.[43] The referent group for each analysis was patients with pneumonia not receiving neuropsychiatric drugs. In adjusted analyses, the odds of in-hospital mortality for VA patients admitted with pneumonia was higher for recent exposure to typical antipsychotics OR = 1.51, 95% CI 1.04 to 2.19, $P = .03$ when compared to patients not receiving neuropsychiatric medications. Patients exposed to atypical antipsychotics OR = 1.20, 95% CI 0.96 to 1.50, $P = .10$; tricyclic antidepressants OR = 1.20, 95% CI 0.44 to 1.55, $P = .15$; other antidepressants OR = 1.07, 95% CI 0.93 to 1.23, $P = .37$; or mood stabilizers OR = 0.91, 95% CI 0.73 to 1.14, $P = .41$ had no significant difference in in-hospital mortality. The investigators conclude that in spite of recent safety concerns for atypical antipsychotics, they found no increased risk of mortality in acutely ill pneumonia patients. They opined that the contrasting mortality risks for patients taking typical and atypical antipsychotics may represent unmeasured severity of illness or comorbidity. They, however, warned that regardless, any antipsychotics should be used with caution and the efficacy and safety of alternative agents should be considered.

Suh and Shah in their prospective study evaluated the risks and benefits of antipsychotics. They measured the rate of mortality in patients with dementia, AD, and vascular/mixed dementia and compared the mortality rates between those who had received antipsychotics and those who had not received antipsychotics.[44] The overall 1-year mortality rate in dementia was 23.8%. The mortality rate in those who had not received antipsychotics (26.8%) was higher than that in those who had received antipsychotics (20.6%). In the unadjusted Cox proportional hazards models, those who had not received antipsychotics were more likely to have died than those who had received antipsychotics, unadjusted RR 1.168, 95% CI 1.100 to 1.239. After adjusting for age and severity of dementia, 1-year mortality remained higher in those who had not received antipsychotics adjusted model I: RR 1.202, 95% CI 1.107 to 1.324. When medical comorbidities (ie, cerebrovascular disease, cardiovascular disease, hypertension, diabetes mellitus) were added to the adjusted model I along with age and severity of dementia, the result was almost identical, adjusted model II, RR 1.211, 95% CI 1.107 to 1.324. When the total Mini-Mental State Examination (MMSE) score was added to the adjusted model II, the RR in those who had not received antipsychotics slightly increased to 1.244, 95% CI 1.122 to 1.379 (adjusted model III). When both total scores of the MMSE and the BEHAVE-AD rating scale were added, the RR of mortality increased to 1.277, 95% CI 1.134 to 1.437 (adjusted model IV). Comparing those who had received both risperidone and haloperidol (n = 119) with those who had not received antipsychotics (n = 142), identical patterns were observed. The RRs for all dementia, AD, and vascular/mixed dementia in adjusted model IV (adjusting for age, severity of dementia, medical comorbidities, cognitive impairment measured by

MMSE, and BPSD measured by BEHAVE-AD) were 1.225, 95% CI 1.101 to 1.364; 1.226, 95% CI 1.063 to 1.414; and 1.154, 95% CI 0.959 to 1.389, respectively. The results suggest that antipsychotics, especially risperidone and/or haloperidol, may be safe for the treatment of AD in terms of mortality. The use of antipsychotics reduced mortality in AD and did not increase mortality in vascular/mixed dementia. The investigators concluded that this study does not support reports that antipsychotics increase mortality in dementia

Nonino et al carried out an observational cohort study in the province of Modena, Italy (644 000 inhabitants), on a cohort of 294 patients with BPSD diagnosed by a dementia specialist who were treated with atypical antipsychotics and a cohort of 2020 demented adults who were not dispensed any atypical antipsychotics.[45] Patients were 65 years of age or older. Measured outcomes were death by any cause and death by CVA at the end of the study. After a median follow-up of 1-year, lower mortality rate was noted in the cohort of patients not exposed to treatment with antipsychotics, overall mortality rate 0.52 versus 0.55/1000 years/person, rate ratio 0.95, 95% CI 0.71 to 1.25; and RR reduction 0.047, 95% CI 0.251 to0.286. Mortality was higher among males, 0.74 versus 0.46/1000 years/person, rate ratio 1.61, 95% CI 1.33 to 1.94 and among patients with older age at entry, 0.33, 0.37, 0.61, and 0.87 for ages 65 to 77, 78 to 82, 83 to 87, and 88 to 105 years, respectively. Multivariate survival analysis showed that older age at entry, male gender, severe dementia, and functional impairment were associated with a higher risk of death, HR 1.06, 95% CI 1.04 to 1.08, $P < .001$; HR 2.20, 95% CI 1.76 to 2.75, $P < .001$; HR 1.67, 95% CI 1.32 to 2.11, $P < .001$; and HR 1.81, 95% CI 1.41 to 2.33, $P < .001$, respectively. The investigators opined that although the sample size did not allow the exclusion of small differences in the short term, age, gender, and dementia severity but no treatment with atypical antipsychotics seemed to influence survival among elderly patients with dementia.

In a population-based, retrospective cohort study conducted by Gill et al in Ontario, Canada, older adults with dementia were followed between April 1, 1997 and March 31, 2003.[13] The risk of death was determined at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication. Two pairwise comparisons were made, atypical versus no antipsychotic use and conventional versus atypical antipsychotic use. Groups were stratified by place of residence (community or long-term care). A total of 27 259 matched pairs were identified. New use of atypical antipsychotics was associated with a statistically significant increase in the risk of death at 30 days compared with nonuse in both the community-dwelling cohort adjusted HR, 1.31, 95% CI 1.02 to 1.70; absolute risk difference, 0.2 percentage point and the long-term care cohort adjusted HR 1.55, 95% CI 1.15 to 2.07; absolute risk difference, 1.2 percentage points. Excess risk seemed to persist to 180 days, but unequal rates of censoring over time may have affected these results. The use of conventional antipsychotics was associated with an even greater risk of death than that observed with atypical antipsychotic use. This risk was evident at 30 days: the adjusted HR was 1.55, 95% CI 1.19 to 2.02 for the community-dwelling cohort and 1.26, 95% CI 1.04 to 1.53 for the long-term care cohort; adjusted risk difference for both groups, 1.1 percentage points. The risk again persisted to 180 days, adjusted HR 1.23, 95% CI 1.00 to 1.50; absolute risk difference, 2.6 percentage points and 1.27, 95% CI 1.09 to1.48; absolute risk difference, 2.2 percentage points, respectively. The investigators concluded that atypical antipsychotic use is associated with an increased risk of death compared with nonuse among older adults with dementia. The risk of death may be greater with conventional antipsychotics than with atypical antipsychotics.

Schneeweiss et al conducted a population-based cohort study of elderly people in British Columbia (BC) who were prescribed conventional and atypical antipsychotic medications in whom the short-term mortality was assessed.[46] Residents aged 65 years or more who filled a first-recorded (index) prescription for an oral antipsychotic medication between January 1, 1996 and December 31, 2004 were included. To ensure a uniform 1-year eligibility period before filling the index prescription, all study patients were required to have used at least 1 medical service and have filled at least 1 prescription in the two 6-month intervals before the index date. They could not have used an antipsychotic medication in the year before the index date. The analysis included only new users of antipsychotic medications to guard against selection bias among prevalent users from early symptom emergence, drug intolerance, or treatment failure. The investigators then compared the 180-day all-cause mortality between residents taking conventional antipsychotic medications and those taking atypical antipsychotic medications. Of the 37 241 elderly people in the study cohort, 12 882 were prescribed a conventional antipsychotic medication and 24 359 an atypical formulation. Within the first 180 days of use, 1822 (14.1%) patients in the conventional drug group died, compared with 2337 (9.6%) in the atypical drug group, mortality ratio 1.47, 95% CI 1.39 to 1.56. Multivariable adjustment resulted in a 180-day mortality ratio of 1.32, 95% CI 1.23 to 1.42. In comparison with risperidone, haloperidol was associated with the greatest increase in mortality; mortality ratio 2.14, 95% CI 1.86 to 2.45 and loxapine the lowest, mortality ratio, 1.29, 95% CI 1.19 to 1.40. The greatest increase in mortality occurred among people taking higher (above median) doses of conventional antipsychotic medications, mortality ratio 1.67, 95% CI 1.50 to 1.86 and during the first 40 days after the start of drug therapy, mortality ratio, 1.60, 95% CI 1.42 to 1.80. The investigators concluded that among elderly patients, the risk of death associated with conventional antipsychotic medications is comparable to and possibly greater than the risk of death associated with atypical antipsychotic medications. They opined that until further evidence is available, physicians should consider all antipsychotic medications to be equally risky in elderly patients.

In a retrospective cohort study conducted by Liperoti et al, the investigators compared the risk of death associated with atypical and conventional antipsychotics in a large population

of nursing home residents with dementia.[47] They identified 6524 new users of atypical antipsychotics and 3205 new users of conventional antipsychotics living in 1581 Medicare- or Medicaid-certified nursing homes in 5 US states during the years 1998-2000. The outcome measure was all-cause mortality, which was determined during 6 months of follow-up. There were 1907 deaths during the 6-month follow-up time; the rate of death was 44.6 per 100 person years. The median follow-up time was 180 days for users of both atypical and conventional antipsychotics. Survival curves for users of atypical antipsychotics and users of conventional agents differed at the Mantel-Haenszel test ($P < .001$). The occurrence of death started early (8-10 days) and was distributed throughout the entire follow-up time. The number of residents at risk decreased over time in an equal manner, and models of mortality in the first 30 days, 31-90 days, and 91-180 days of drug use gave similar results. After adjusting for potential confounders relative to users of atypical antipsychotics, the rate of death was increased for users of conventional antipsychotics HR, 1.26, 95% CI 1.13 to 1.42. Relative to risperidone, a higher rate of death was documented for haloperidol HR, 1.31, 95% CI 1.13 to 1.53; phenothiazines HR, 1.17, 95% CI 1.00 to 1.38; and other conventional medications HR, 1.32, 95% CI 0.99 to 1.80. No atypical antipsychotic was associated with a differential risk relative to risperidone HR, clozapine 0.94, 95% CI 0.40 to 1.79; olanzapine 0.95, 95% CI 0.80 to 1.12; and quetiapine 1.05, 95% CI 0.80 to 1.39. The excess mortality associated with conventional antipsychotics was found only among those patients with dementia other than AD, HR 1.31, 95% CI 1.14 to 1.50. The excess mortality associated with the use of conventional antipsychotics is apparent within the initial 8 to 10 days of treatment and persists over 6 months. The investigators concluded patients receiving conventional agents, especially haloperidol, are at greater risk of death than those on atypical antipsychotics. The effect of conventional antipsychotics on increasing the risk of death relative to atypical medications seems to be clustered in residents with dementia other than AD.

In a recent retrospective study by Rossom et al, the investigators reviewed 5-year data from the Veterans national health care database.[48] Outpatient prescription records from October 1998 to September 2005 were obtained from the Veterans Health Administration (VHA) Pharmacy Benefits Management Strategic Healthcare Group. The first VHA prescription for an antipsychotic medication dispensed concurrently or after each patient's dementia diagnosis was used to define the index date for each patient. Four cohorts of exposed patients (haloperidol [n = 2217], olanzapine [n = 3384], quetiapine [n = 4277], and risperidone [n = 8249]) were identified for further analysis. The cohort consisted mainly of males, aged 65 and older, with a diagnosis of dementia and no other indication for an antipsychotic. Patients who received an antipsychotic were compared with randomly selected controls who did not receive antipsychotics. Exposed and control cohorts were matched according to their date of dementia diagnosis and time elapsed from diagnosis to the start of antipsychotic therapy. Cohorts who were exposed to haloperidol, olanzapine, quetiapine, or risperidone had more comorbidities than their control cohorts. During the first 30 days, there was a significant increase in mortality in subgroups prescribed a daily dose of haloperidol greater than 1 mg, HR 3.2, 95% CI 2.2 to 4.5, $P < .001$, olanzapine greater than 2.5 mg, HR 1.5, 95% CI 1.1 to 2.0, $P = .01$, or risperidone greater than 1 mg, HR 1.6, 95% CI 1.1 to 2.2, $P = .01$, adjusted for demographic characteristics, comorbidities, and medication history using Cox regression analyses. Greater mortality was not seen when a daily dose of quetiapine greater than 50 mg, HR 1.2, 95% CI 0.7 to 1.8, $P = .50$, was prescribed and there was no greater mortality associated with a dose less than 50 mg, HR 0.7, 95% CI 0.5 to 1.0, $P = .03$. After excluding inpatients and patients discharged within 30 days and adjusting for any differences in baseline covariates, including time since previous discharge, prescriptions for haloperidol or olanzapine were still associated with greater risk of mortality during the initial 30 days of exposure, adjusted HR 2.3, 95% CI 1.6 to 2.9, $P < .001$ and 1.4, 95% CI 1.9, $P = .03$ respectively. The secondary estimate of the greater risk associated with risperidone changed little and was not statistically significant but had an upper limit on the CI that did not exclude a substantially increased risk, adjusted HR 1.2, 95% CI 0.95 to 1.4, $P = .13$. In this secondary analysis, prescriptions for quetiapine were associated with significantly lower risk of mortality, and the upper limit of the CI excluded any greater risk, adjusted HR 0.7, 95% CI 0.5 to 0.97, $P = .03$. No antipsychotic was associated with greater mortality after the first 30 days. The investigators concluded that commonly prescribed doses of haloperidol, olanzapine, and risperidone, but not quetiapine, were associated with a short-term increase in mortality (Table 2).

Summary of Findings (Please refer to Tables 1 and 2 for details)

In our review of the literature, we found 22 studies that evaluated the risk of CVAEs. Of these 22 studies, only 2 were placebo-controlled trials. The majority of the studies were population-based studies or retrospective analysis. The available data indicate that the risk of CVAEs is higher in the drug-treated group by about 1.3 to 2 times. Although preliminary, existing data for atypical versus typical antipsychotics indicate that the risk of CVAEs is similar in both groups. No one drug has been found to be safer than the other in terms of the CVAEs. A higher than median doses of a drug, older age, a diagnosis of dementia especially vascular dementia, and comorbid atrial fibrillation have been noted as risk factors for CVAEs. It appears that the time frame for which the risk of CVAEs remains elevated is about 20 months.

For the risk of death, we found a total of 14 studies which addressed this risk. Of these 14 studies, only 3 were placebo-controlled trials. Preliminary data indicate that risk of death with atypical and typical antipsychotics is greater than when compared to the placebo group or the group that did not use these medications. The risk is about 1.2 to 1.6 times higher in the drug-treated group. Existing data for atypical versus typical antipsychotics indicate that the risk of death is similar in

Table 2. Risk of Death

Author (Year of Publication)	Type of Study	Study Information	Conclusions
Brodaty et al[20] (2003)	Randomized double-blind, placebo-controlled trial.	Compared risperidone to placebo.	More patients in the risperidone group died when compared to the placebo group during the course of this trial
Schneider et al[8] (2006)	Double-blind, placebo-controlled trial.	Compared olanzapine, quetiapine, and risperidone to placebo.	The risk of death was no greater in the drug-treated group compared to the placebo group.
Ballard et al[39] (2009)	Randomized, placebo-controlled, parallel, 2-group treatment discontinuation trial.	Patients with AD were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or to switch their medication to an oral placebo.	The probability of survival in the antipsychotic group was less than the placebo group during the first 12 months. The probability of survival decreases with continued treatment with drugs.
Schneider et al[22] (2005)	Meta-analysis of published and unpublished studies.	Compared aripiprazole, olanzapine, quetiapine, risperidone with placebo.	Death occurred more often among patients randomized to drugs compared to placebo.
European Agency[23]	Meta-analysis of 3 placebo-controlled trials.	Compared aripiprazole to placebo.	The rate of death is higher in the aripiprazole group compared to the placebo group.
Nasrallah et al[41] (2004)	Observational study	Compared haloperidol to risperidone and olanzapine.	The risk of death with haloperidol was greater than the risk of death with risperidone or olanzapine in this study.
Raivio et al[42] (2005)	Prospective study.	Medical records provided information on the use of daily antipsychotic medication and central registers confirmed mortality for up to 2 years.	When comparing the users of any antipsychotic to the nonusers, the combined end point of hospital admissions and mortality was higher among the nonusers than among the users.
Barnett et al[43] (2006)	Retrospective analysis of the VA database.	Patients admitted for pneumonia in FY 2003 were evaluated for exposure to typical and atypical antipsychotics and other neuropsychiatric drugs based on a prescription within 120 days preceding admission.	The odds of in-hospital mortality for patients admitted with pneumonia were higher for recent exposure to typical antipsychotics when compared to patients not receiving neuropsychiatric medications. Patients exposed to atypical antipsychotics, tricyclic antidepressants, other antidepressants, or mood stabilizers had no significant difference in in-hospital mortality.
Suh and Shah[44] (2006)	Prospective longitudinal study	The rates of mortality in patients with dementia, AD, and vascular/mixed dementia were compared when they did and did not receive antispychotics.	The rate of mortality was higher in the group not receiving any antipsychotic medication.
Nonino et al[45] (2006)	Observational cohort study	Patients who were treated with atypical antipsychotics were compared to adults with dementia not treated with atypical antipsychotics	There was no increase in mortality in patients treated with atypical antipsychotics.

(continued)

Table 2 (continued)

Author (Year of Publication)	Type of Study	Study Information	Conclusions
Gill et al[30] (2007)	Population-based retrospective cohort study	Compared older adults with dementia who were dispensed antipsychotic medication. Two pairwise comparisons were made, atypical versus no antipsychotic use and conventional versus atypical antipsychotic use.	Atypical antipsychotic use is associated with an increased risk of death compared with nonuse among older adults with dementia. The risk of death may be greater with conventional antipsychotics than with atypical antipsychotics. The risk of death is evident from 30 days to 180 days.
Schneeweiss et al[46] (2007)	Population-based cohort study.	Short-term mortality was assessed in elderly people in who were prescribed conventional and atypical antipsychotic medications.	The risk of death associated with conventional antipsychotic medications is comparable to and possibly greater than the risk of death associated with atypical antipsychotic medications. The risk with typical antipsychotics is greater in doses above the median doses. All antipsychotic medications to be equally risky in elderly patients.
Liperoti et al[47] (2009)	Retrospective cohort study	All-cause mortality during 6-months follow-up of new users of atypical antipsychotics and new users of conventional antipsychotics living in nursing homes in 5 US states during the years 1998-2000 was measured.	Those receiving conventional agents, especially haloperidol, are at greater risk of death than those on atypical antipsychotics. The excess mortality associated with the use of conventional antipsychotics is apparent within the initial 8 to 10 days of treatment and persists over 6 months. The effect of conventional antipsychotics on increasing the risk of death relative to atypical medications seems to be clustered in residents with dementia other than AD.
Rossom et al[48] (2010)	Retrospective database study.	Patients who received haloperidol, olanzapine, quetiapine, and risperidone were compared with randomly selected controls who did not receive antipsychotics.	The investigators concluded that commonly prescribed doses of haloperidol, olanzapine, and risperidone, but not quetiapine, were associated with a short-term increase in mortality.

Abbreviations: AD, Alzheimer's disease; FY, fiscal year.

both groups. No one drug has been found to be safer than the other in terms of the death. Older age, male gender, severe dementia, and functional impairment are associated with a higher risk of death. The risk remains elevated in the first 30 days and possibly to 2 years.

Potential mechanisms by which antipsychotics can cause CVAEs include the development of orthostatic hypotension, most likely as a result of antagonism at α-adrenergic receptors.[17,49] In an individual with cerebrovascular insufficiency or atherosclerosis, they might experience a CVAE as a consequence of hypotension, aggravating the deficit in cerebral perfusion. Also, tachycardia induced by α-adrenergic antagonism might cause a decrease in cerebral perfusion as a result of a rate-induced decrease in diastolic filling, and cardiac output or tachycardia might dislodge a thrombus in the patient with atrial fibrillation. Antipsychotics have a variable degree of effect on prolactin levels by their actions on dopamine transmission involved in the tuberoinfundibular tract. Theoretically, hyperprolactinemia can accelerate atherosclerosis and increase the risk of TIAs and strokes. It is possible that sedation or obtundation might cause antipsychotic-treated patient to develop dehydration and hemoconcentration, leading on to the development of a thrombus. Antipsychotic medications have also been associated with an increased risk of venous thromboembolism. These thrombi could be potentially dislodged into the arterial circulation, causing TIAs and strokes especially in patients with atrial fibrillation.[17,49] The mechanisms by which antipsychotic medications may contribute to death remain to be established. Most deaths are thought to be due to cardiovascular events (mostly arrhythmias) and infections (pneumonia for the great majority).[47] Antipsychotic use has been associated with a lengthening of QTc interval on electrocardiograms. Recently, atypical medications, such as ziprasidone, quetiapine, risperidone, and olanzapine, have been linked to QTc prolongation, although the highest estimate of risk has been documented for thioridazine.[46] An increased risk of ischemic CVEs has been also linked to the use of atypical antipsychotics in patients with dementia.[17,30] The comorbidities in these demented patients along with the use of these medications only adds to this risk.[17,49]

Conclusion

Available evidence indicates that antipsychotic medications increase the risk of CVAEs and death when used to treat elderly patients with BPSD. The data indicate that the risk is very similar when comparing typical and atypical antipsychotic agents. The risk is higher when used in patients with vascular dementia and above the recommended doses for these medications. The risk of CVAEs appears to remains high for about 20 months and the risk of death is elevated in the first 30 days and possibly to 2 years. These risks should be considered in the context of the patient's age, diagnosis of vascular dementia, severity of dementia, male gender, functional impairment, and comorbid conditions like atrial fibrillation before prescribing these medications. Judicious use of these medications with careful assessment of the risk–benefit ratio and close monitoring of the risk factors will reduce side-effects like CVAEs and death thereby prevent undue suffering to patients and their families.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

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