Chapter 1
Do Atypical Antipsychotics Cause Stroke?

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Objectives The objective of the article was to review the data from randomized controlled trials that prompted warnings from multiple health regulatory agencies regarding the association of atypical antipsychotics and risks of cerebrovascular accidents in the geriatric population. Furthermore, the authors wanted to determine the level of evidence and how strong of a risk is associated between these factors to develop guidance on the risk-benefit analysis for the possible severity of these outcomes [1].

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Methods The authors completed a MEDLINE search using the above indicated keywords as well as reference lists of identified papers. The authors had direct contact with Janssen and Eli Lilly for the data and materials of unpublished trials. Eleven articles were identified and an overall relative risk for cerebrovascular events in individuals was calculated based on the above results.

Results When reviewing the role of dementia and CVAEs, cognitive impairment is a strong predictor of ischemic stroke independent of vascular risk factors. Patients with Alzheimer's disease were more likely to die from cerebrovascular disease than elderly individuals without Alzheimer's disease. The rate of death from CVAEs was higher than all other causes of death in patients with vascular dementia compared to other groups of dementia. In a sample elderly of dementia patients who had a stroke and were treated with an antipsychotic for 8–12 weeks, CVAEs and death were possible outcomes. The authors postulated that if patients with Alzheimer's disease and vascular dementia are at an increased risk of CVAEs, then treatment with an antipsychotic would also be associated with CVAEs and death. Throughout the reviewed articles, CVAEs included stroke, transient ischemic attacks (TIAs), cerebrovascular accidents (CVA), cerebral ischemia, cerebral infarct, cerebrovascular disturbance, and cerebrovascular disorder.

The review of risperidone included six studies; three of which were published. The published data documented information that was included on patients with Alzheimer's disease, vascular dementia, and mixed dementia, whereas the unpublished data includes information on patients with vascular and mixed dementia. 33% of included patients had vascular and mixed dementia. Individuals with vascular dementia and mixed dementia are independently more at risk of CVAEs; in the published data, more of that at-risk population was included.

The rate of serious CVAEs in those with risperidone exposure (15 of 1009, 1.5%) was not shown to be statistically significantly different from placebo (4 of 712, 0.6%) [$p = 0.27$]. The rate of all-cause mortality was similar for risperidone and placebo exposed individuals, though the stroke rate was slightly higher with risperidone exposure. Most of these participants who experienced serious CVAEs had significant risk factors including hypertension, atrial fibrillation, and history of stroke. It was found that the stroke risk factors were poorly controlled hypertension, poorly controlled diabetes mellitus, and atrial fibrillation without anticoagulant treatment. Plus, there was a concern for miscoding of events by investigators. For example, a TIA was labeled as an accidental overdose on risperidone when documented as 5 mg instead of a 0.5 mg dose. Overall, it was found that the rates of CVAEs were low in those exposed to risperidone, though subjects were not randomized or stratified based on stroke risk factors. It was also reported that events of CVAE frequency differ for nonserious events for the risperidone versus placebo treated subjects, possibly due to low power or miscoding events.

The review of olanzapine included five studies. Two of these studies were unpublished, included individuals with Alzheimer's disease, and excluded other DSM-IV

disorders. One study included approximately 500 participants with vascular dementia and mixed dementia. In another study, there was no information on the number of patients with vascular dementia or details of their characteristics. There was a statistically significant difference in mortality for CVAEs in the olanzapine (42 of 1184, 3.5%) compared to the placebo (7 of 478, 1.5%) exposed individuals, ($p = 0.015$). However, there was no statistically significant difference found when accounting for serious versus nonserious CVAEs versus all-cause mortality.

There was no statistically significant difference in CVAEs or all-cause mortality rates for olanzapine (5 of 204, 2.5%) exposed individuals compared to risperidone (4 of 196, 2.0%) exposed individuals. There was no statistically significant difference in CVAEs or all-cause mortality for olanzapine exposed individuals (5 of 149, 3.4%) compared to first-generation antipsychotic exposed individuals (6 of 141, 4.3%). These values are reported without p values. It was noted that the sample sizes of the studies were small. Randomized controlled trials did indicate a significant increased risk of CVAEs with olanzapine compared to placebo. However, there was a small sample size and it is unclear if these were serious versus nonserious events.

Of the published risperidone articles, none reviewed differences in blood pressure and orthostatic blood pressure for individuals receiving risperidone compared to placebo. There were no statistically significant differences in vital signs and "clinically meaningful" orthostatic hypotension for individuals receiving olanzapine compared to individuals receiving placebo. Specifically, one article noted ≥ 30 mm HG decreases in systolic blood pressure were similar for olanzapine (7.2%) and placebo (7.0%) [Fisher's exact test, $p > 0.99$].

Discussion The authors acknowledged that no formal studies have determined casualty in this patient population. Potential mechanisms that contribute to the occurrence of CVAEs were discussed which included interactions between a patient's physiology, past medical history, and risk factors that were not better accounted for by the presence of an atypical antipsychotic:

1. Typical and atypical antipsychotics increased risk for venous thromboembolism. Possible mechanisms discussed included enhanced aggregation of platelets and presence of anticardiolipin antibodies. Yet, risperidone has not been shown to influence fibrinolysis, plasma coagulation, arachidonic acid metabolism, or platelet function reactions.
2. Cardiac effects causing CVAEs may be due to antipsychotics. Risperidone is a potent α1-adrenoreceptor blocker and olanzapine is a potent muscarinic M1 receptor antagonist. Despite these potential mechanisms, data has not shown within group differences in heart rate changes, vital signs, and EKG parameters in risperidone and olanzapine exposed groups compared to placebo groups.
3. Orthostatic hypotension from α1-adrenoreceptor blockade may cause cerebral perfusion impairment and thus CVAEs.
4. Excessive sedation and stiffness due to extrapyramidal symptoms (EPS), especially parkinsonism and dystonia, could lead to venous stasis, dehydration, and

hemoconcentration. This could put individuals at risk for CVAEs, which is another potential for miscoded events. Some individuals with EPS have been reported to experience more frequent CVAEs with atypical antipsychotics in comparison to placebo, which was a dose-dependent trend in the risperidone exposed group.

The authors revealed that the risperidone trials were longer (12 weeks) than olanzapine trials (6 weeks), and this time frame may account for CVAEs in risperidone trials. Lilly Pharmaceuticals suggested that the incidence of CVAEs with olanzapine exposure is no greater than with risperidone or typical antipsychotics.

The authors noted many studies did not have a priori hypotheses which prevented them from stratifying or randomizing patients to treatment or placebo groups. This made it difficult for these studies to delineate a cause and effect relationship. As a result, most CVAEs were detected post hoc.

Lastly, data from observational studies offered more information on the impact of multiple risk factors with longer periods of patient review. From this perspective, the odds ratio was not statistically significant for the following: hospitalization for stroke and TIAs due to risperidone exposure; all class atypical antipsychotics; and all class typical antipsychotics after adjusting for confounders. There was no difference in rates of CVAE occurrence in risperidone groups compared to olanzapine or quetiapine groups. There were an increased risk for CVAE-related admissions in the haloperidol group compared to the risperidone group and an increased risk for CVAE-related admissions in the benzodiazepine group compared to risperidone group. However, this is based on data from unpublished articles. Published data from one article found no increased risk for CVAEs with atypical antipsychotics compared to typical antipsychotics. Another published article suggested no increased risk for CVAEs associated with atypical antipsychotics compared to no antipsychotic treatment at all.

Conclusions Studies of risperidone report an increased risk for CVAEs when it is prescribed. These studies have also indicated that these CVAEs were mostly nonserious events and were more likely to occur in individuals with multiple risk factors for CVAEs. There does not seem to be an increased risk of CVAEs with atypical antipsychotics when compared to typical antipsychotics, benzodiazepines, and no exposure to antipsychotics. The association of these adverse outcomes with atypical antipsychotics is possible due to other factors like sedation, lethargy, and hypotensive episodes.

Strengths of the Study This was a well-designed meta-analysis study that appropriately elucidated concern for power, reviewed how cerebrovascular adverse events were classified, and took into consideration the multiple static and/or preexisting risk factors for cerebrovascular events. This is important in helping to counsel patients on the risks of these classes of medications and for clinicians to better understand the synergistic impact of these medications upon a patient's health.

Limitations of the Study This study used data and articles that were unpublished. Those articles did not go through the strenuous critique, feedback, validation, and fine tuning of peer-reviewed articles. Additionally, some information used in the analysis were obtained directly from pharmaceutical companies which could have provided biased information.

Take-Home Points Clinicians should continue to be mindful of the effects of polypharmacy, continue to take thorough medical and psychiatric histories from patients, and understand that use of atypical antipsychotics in the geriatric population likely has an additive role of contributing to various CVAEs rather than being the sole agent responsible for these episodes.

Practical Applications of the Take-Home Points There is some risk of CVAEs with antipsychotic use. However, this occurs mostly in individuals with preexisting risk factors and is not found to be consistently statistically significant when reviewing the data. Thus, one should weigh the risks and benefits of antipsychotics when treating geriatric patients with a neurocognitive disorder.

Reference

1. Herrmann N, Lanctôt KL. Do atypical antipsychotics cause stroke? CNS Drugs. 2005;19(2):91–103.