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Title: *Cardiovascular Adverse Events Related to Alzheimer's Treatments: Data from the FDA Adverse Events Reporting System*

Abstract

Purpose: There is limited post market safety data comparing cholinesterase inhibitors in its use for a diagnosis of dementia or Alzheimer's disease, specifically cardiovascular safety. The purpose of this study is to analyze and compare the risk of syncope, bradycardia, or QT interval prolongation and subsequent morbidity and mortality associated with individual cholinesterase inhibitors in patients with a diagnosis of dementia or Alzheimer's disease.

Methods: This study utilized data from the FDA Adverse Event Reporting System (FAERS) from January 1, 2015-December 1, 2018. Adults diagnosed with dementia or Alzheimer's disease using a cholinesterase inhibitor or memantine were included in the analysis. Reports of cardiovascular events were identified using search terms from the standardized quarries in the medical dictionary for regulatory activities (MedDRA). Outcomes related to cardiovascular morbidity and mortality were compared among the cholinesterase inhibitors and memantine from the documented reports. A case/non-case methodology was used to evaluate the association between cardiovascular events and the use of cholinesterase inhibitors and memantine. The reporting odds ratio (ROR) was utilized to represent and compare the effects the cholinesterase inhibitors and memantine on cardiovascular events.

Results: A total of 6,220 patient adverse drug event (ADE) reports with a cholinesterase inhibitor or memantine were identified. Of the 6,220 ADE reports, 634 were unique cardiovascular reports, of which, 352 were linked to donepezil, 115 were linked to rivastigmine, 16 were linked to galantamine, and 151 were liked to memantine. The RORs (95% CI) of cardiovascular events for all indications for donepezil, galantamine, rivastigmine, and memantine were 2.06 (1.75-2.44), 0.81 (0.49-1.37), 0.81 (0.66-1.00), and 0.51 (0.43-0.62) respectively. In patients with Alzheimer's disease, the ROR for donepezil was 2.50 (2.02-3.08), the ROR for galantamine was 1.54 (0.86-2.74), the ROR for rivastigmine was 0.68 (0.505-0.91), and the ROR for memantine was 0.46 (0.36-0.58). In patients with dementia, the ROR for donepezil was 1.61 (1.23-2.11), the ROR for galantamine was 0.20 (0.05-0.81), the ROR for rivastigmine was 1.05 (0.77-1.44), and the ROR for memantine was 0.58 (0.41-0.82). For mortality outcomes the percentage of events that lead to death were 10.5% for donepezil, 7.4% for galantamine, 12.8% for rivastigmine, and 29.6% for memantine.

Conclusion: The risk of cardiovascular events was increased overall and when stratified by disease state for the drug donepezil when compared to the other cholinesterase inhibitors and memantine. Donepezil also had the highest percentage of events that lead to life-threatening outcomes, hospitalization, disability outcomes, and other serious outcomes. Memantine had the highest percentage of events that lead to death. Cardiovascular health, comorbidities, and risk should be assessed in all patients and considered when selecting medication therapy.