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

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BACKGROUND

- Cholinesterase inhibitors (AChEI) are first line therapy for dementia and Alzheimer's disease
- There is little evidence demonstrating one treatment is more effective than the others
- Often, therapy decisions are based on safety/adverse effects
- Due to the mechanism of action, cardiovascular (CV) adverse effects are relatively common with AChEI, but no clear evidence that the risk of CV events varies among the agents

OBJECTIVE

- To analyze and compare the risk of syncope, bradycardia, and QT interval prolongation and subsequent morbidity and mortality associated with AChEI and memantine (as a reference) in patients with dementia or Alzheimer's disease
- To assess the relative cardiovascular safety profile for each cholinesterase inhibitor to aid in determining the more safe medication choice for patients with dementia

METHODS

Study Design
- Retrospective, cross-sectional, database review

Data Source
- FDA Adverse Events Reporting System (FAERS)

Inclusion Criteria
- Valid report in FAERS between January 1, 2015-December 1, 2018
- Reported diagnosis of dementia or Alzheimer's disease
- Reported use of cholinesterase inhibitor or memantine

Study Measures: Dependent Variables
- **Primary Outcome:** Reported CV adverse event, including bradycardia, syncope, or QT interval prolongation
- **Secondary Outcome:** Morbidity and mortality severity hierarchy

Study Measures: Independent Variables
- Gender / Source of report / Reporting country

Data Analysis
- Case/non-case methodology
  - Case: Report of CV adverse event
  - Non-case: Report of non-CV adverse event
- Reporting odds ratio used to estimate the odds of bradycardia, syncope, and QT interval prolongation among individuals taking a cholinesterase inhibitor or memantine

RESULTS

Table 1: Demographic Information

	Cardiovascular Reports n=606	All other adverse event reports n=5,038
Age in years, mean (SD)	79.96 (8.63)	79.53 (10.55)
Sex, n (%)		
Male	295 (48.68)	1,857 (36.71)
Female	211 (34.82)	2,755 (54.86)
Not specified	100 (16.50)	426 (8.42)
Reporter Country, n (%)		
United States	58 (9.57)	864 (17.08)
All other countries	548 (90.43)	4,194 (82.92)
Reporter's occupation, n (%)		
Physician	162 (26.73)	1,781 (35.21)
Other health professional	255 (42.08)	1,241 (24.54)
Consumer	103 (17.00)	1,483 (29.32)
Pharmacist	66 (10.89)	415 (8.20)
Not specified	20 (3.30)	138 (2.73)
Report date, n (%)		
2015	186 (30.69)	1,358 (26.56)
2016	161 (26.57)	1,339 (26.58)
2017	113 (18.65)	1,139 (22.61)
2018	146 (24.09)	1,222 (24.26)

Table 2: Cardiovascular ADE Reporting Odds Ratio

Overall	Donepezil (Aricept)	Galantamine (Razadyne)	Rivastigmine (Exelon)	Memantine (Namenda)	Total
Unique Patients	2,457	188	1,312	2,263	6,220
No. of cardiovascular reports (%)	352 (14.3)	16 (8.5)	115 (8.8)	151 (6.7)	634 (10.2)
All Other ADRs (%)	2,105 (85.7)	172 (91.5)	1,197 (91.2)	2,112 (93.3)	5,586 (89.8)
ROR (95% CI)	**2.06 (1.75-2.44)**	**0.81 (0.49-1.37)**	**0.81 (0.66-1.00)**	**0.51 (0.43-0.62)**	
Alzheimer's Disease					
Unique Patients	1,302	90	708	1,605	3,705
No. of cardiovascular reports (%)	220 (16.9)	14 (15.6)	57 (8.1)	110 (6.9)	401 (10.8)
All Other ADRs (%)	1,082 (83.1)	76 (84.4)	651 (91.9)	1,495 (93.1)	3,304 (89.2)
ROR (95% CI)	**2.50 (2.02-3.08)**	**1.54 (0.86-2.74)**	**0.68 (0.505-0.91)**	**0.46 (0.36-0.58)**	
Dementia					
Unique Patients	1,155	98	604	658	2,515
No. of cardiovascular reports (%)	132 (11.4)	2 (2)	58 (9.6)	41 (6.2)	233 (9.3)
All Other ADRs (%)	1,023 (88.6)	96 (98)	546 (90.4)	617 (93.8)	2,282 (90.7)
ROR (95% CI)	**1.61 (1.23-2.11)**	**0.20 (0.05-0.81)**	**1.05 (0.77-1.44)**	**0.58 (0.41-0.82)**	

RESULTS

Table 3: Morbidity and Mortality

Overall	Donepezil (Aricept)	Galantamine (Razadyne)	Rivastigmine (Exelon)	Memantine (Namenda)	Total
Unique patients	2,457	188	1,312	2,263	6,220
Deaths (%)	**255 (10.4)**	**14 (7.4)**	**168 (12.8)**	**669 (29.6)**	**1,106 (17.8)**
Life-Threatening Outcomes (%)	191 (7.8)	9 (4.8)	52 (4)	66 (2.9)	318 (5.1)
Hospitalization (%)	1,139 (46.4)	111 (59)	590 (45)	757 (33.5)	2,597 (41.8)
Disability outcomes (%)	94 (3.8)	11 (5.9)	28 (2.1)	38 (1.6)	171 (2.7)
RITPPID (%)*	1 (0.04)	0 (0)	2 (0.2)	1 (0.04)	4 (0.06)
Other serious outcomes (%)	777 (31.6)	43 (22.9)	472 (36)	732 (32.3)	2,024 (32.5)
Alzheimer's Disease					
Unique patients	1,302	90	708	1,605	3,705
Deaths (%)	**126 (9.7)**	**12 (13.3)**	**79 (11.2)**	**500 (31.2)**	**717 (19.4)**
Life-Threatening Outcomes (%)	100 (7.7)	5 (5.6)	22 (3.1)	45 (2.8)	172 (4.6)
Hospitalization (%)	599 (46)	41 (45.6)	326 (46)	531 (33.1)	1,497 (40.4)
Disability outcomes (%)	37 (2.8)	7 (7.8)	19 (2.7)	23 (1.4)	86 (2.3)
RITPPID (%)*	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.03)
Other serious outcomes (%)	440 (33.8)	25 (27.8)	261 (36.9)	506 (31.5)	1,232 (33.3)
Dementia					
Unique patients	1,155	98	604	658	2,515
Deaths (%)	**129 (11.2)**	**2 (2)**	**89 (14.7)**	**169 (25.7)**	**389 (15.5)**
Life-Threatening Outcomes (%)	91 (7.9)	4 (4.1)	30 (5)	21 (3.2)	146 (5.8)
Hospitalization (%)	540 (46.8)	70 (71.4)	264 (43.7)	226 (34.4)	1,100 (43.7)
Disability outcomes (%)	57 (4.9)	4 (4.1)	9 (1.5)	15 (2.3)	85 (3.4)
RITPPID (%)8	1 (0.1)	0 (0)	1 (0.2)	1 (0.2)	3 (0.1)
Other serious outcomes (%)	337 (29.2)	18 (18.4)	211 (35)	226 (34.4)	792 (31.5)

***RITPPID: Required intervention to prevent permanent impairment/damage**

CONCLUSION

- Donepezil is associated with a higher probability of reporting a cardiovascular event
- Memantine is associated with the highest proportion of events (all cause) that lead to death
- Evaluation of cardiovascular health, comorbidities, and risk should be performed in all patients with dementia/Alzheimer's disease
- AChEI, in particular donepezil, should be used with caution in patients with increased risk of CV adverse events

LIMITATIONS
- Non-randomized; Reporting bias; selection bias

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