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

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## BACKGROUND

- Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) are first line therapy for dementia and Alzheimer's disease
- There is currently no evidence demonstrating one treatment to be more effective than the other
- It is reasonable to select therapy based on safety and adverse effect profiles
- Few studies have been performed investigating the safety of cholinesterase inhibitors, specifically cardiovascular (CV) safety

## OBJECTIVE

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

## 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 medication of cholinesterase inhibitor or memantine

Study Measures: Dependent Variables
- **Primary Outcome:** Reported 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 percentage of events that lead to death
- Evaluation of cardiovascular health, comorbidities, and risk should be performed in all patients
- Patients at a greater risk of cardiovascular events should avoid initiation of donepezil

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