Anticholinergic medications are commonly used to treat a variety of conditions, such as stomach ulcers, depression, and Parkinson's disease. However, there is strong evidence of a link between anticholinergic drugs and impaired physical functioning, cognitive decline, and even death among older adults. Nevertheless, anticholinergic drugs are still widely prescribed in this population.

Anticholinergic drug use is even more problematic among older adults with dementia who take acetylcholinesterase inhibitors (AChEIs) to slow the progression of their symptoms. The concurrent prescribing of anticholinergics and AChEIs is considered to be a "never event"—that is, a medical error that should never occur. This is because the two drugs have opposing mechanisms of action. Anticholinergic drugs block the neurotransmission of acetylcholine in the central and peripheral nervous systems, while AChEIs increase the availability of acetylcholine in the synapses by blocking the enzyme acetylcholinesterase.

Because concurrent anticholinergic and AChEI use is so risky for older adults, researchers at the AARP Public Policy Institute designed a study to determine if taking both drugs increases the likelihood of fall, fracture, and traumatic brain injury (TBI) among older adults with dementia.

Methods
We conducted a retrospective review of data from the OptumLabs® Data Warehouse, a de-identified administrative claims database for commercially insured and Medicare Advantage (MA) enrollees, representing a diverse mixture of ages, ethnicities, and geographic regions across the United States.

The cohort included 71,360 adults ages 65 and older with dementia and enrolled in MA for at least 18 months between January 1, 1998, and December 31, 2017. We defined the concomitant use of anticholinergic and AChEI drugs as an overlap of the two medications for 30 days or more. Participants with 1–29 days of overlapping anticholinergic and AChEI drug use were excluded from the analyses.

Results
Nearly one-third (29 percent) of adults ages 65 years and older who were taking AChEI drugs for dementia were concurrently prescribed anticholinergic drugs for 30 or more days. Half (51 percent) of concurrent users were prescribed an AChEI first, 46 percent were prescribed an anticholinergic first, and 3 percent received prescriptions for both drugs on the same day.

Older adults with dementia who had concomitant anticholinergic and AChEI use were 18 percent more likely to experience a fall, 16 percent more...
likely to have a fracture, and 25 percent more likely to have a TBI than were those taking an AChEI alone (see figure). Women were more likely than were men to experience these adverse outcomes. Additional risk factors included having 20 or more treating clinicians involved in patient care and a high number of comorbid conditions (see table).

FIGURE
Odds of Fall, Fracture, and TBI in Adults Ages 65+ with Dementia Taking Anticholinergic and AChEI Drugs versus Those Taking AChEI Drugs Alone

Discussion
This study provides evidence that anticholinergic use among older adults with dementia taking AChEIs puts them at higher risk for several adverse outcomes, including fall, fracture, and TBI. Because potentially inappropriate medication use is especially concerning among older adults with poor health and chronic conditions, the American Geriatrics Society maintains a list of drugs older adults should use with caution, refrain from using in combination with other drugs, or avoid altogether. This list, the Beers Criteria for Potentially Inappropriate Medication, strongly discourages the use of anticholinergics in adults ages 65 and older. Moreover, researchers have known about the risks of combining anticholinergic and AChEI drugs for years, yet the practice continues.

Beyond the specific findings concerning concurrent anticholinergic and AChEI drug use, the results of this study highlight the importance of medication reconciliation in older adults. Two-thirds of older adults take at least three prescription medications, often prescribed by more than one clinician. As an essential step toward high-quality care, health care providers should regularly assess patients and their prescription drug regimens to ensure they remain appropriate. The Medicare Annual Wellness visit includes a medication and provider inventory for just this purpose and is a free benefit for traditional Medicare and MA enrollees.

Appendix A: Methods
Detailed Inclusion and Exclusion Criteria
Study subjects had to have dementia as evidenced by either a dementia diagnosis (using International Classification of Diseases (ICD) 9/10 codes) or at least one claim for memantine (Namenda®) or an AChEI drug: donepezil (Aricept®), donepezil plus memantine (Namzaric®), rivastigmine (Exelon®), or galantamine (Razadyne®). Subjects had to have at least one AChEI prescription in the 12 months following the diagnosis date. Subjects also had to be enrolled in MA 6 months prior to the dementia index date (defined as date of dementia diagnosis or, if no diagnosis, the date of the first AChEI/memantine prescription) and 12 months following the index date.

Inclusion Criteria
Adults ages 65 and older with one of the following dementia diagnosis codes:
- Alzheimer’s disease (ICD-9: 331.0)
- Vascular dementia (ICD-9: 290.40, 290.41, 290.42, 290.43)
- Lewy body dementia (ICD-9: 331.82)
- Fronto-temporal dementia (ICD-9: 331.1, 331.19)
- Other dementias (290.0x–290.3x, 290.8x, 290.9x, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, 797)

OR
### TABLE
Factors Related to a Fall, Fracture, or TBI among MA enrollees Ages 65+ with Dementia Taking AChEI Drugs

<table>
<thead>
<tr>
<th></th>
<th>Fall $N = 68,719^*$ OR (95% CI)</th>
<th>Fracture $N = 68,668^*$ OR (95% CI)</th>
<th>TBI $N = 69,600^*$ OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinergic (ACH) Drug</strong></td>
<td>1.18 (1.11, 1.24)</td>
<td>1.16 (1.10, 1.23)</td>
<td>1.25 (1.17, 1.33)</td>
</tr>
<tr>
<td>Memantine</td>
<td>0.76 (0.72, 0.80)</td>
<td>0.73 (0.69, 0.77)</td>
<td>0.87 (0.82, 0.92)</td>
</tr>
<tr>
<td><strong>Elixhauser Index (REF ≤ 4)</strong></td>
<td>1.20 (1.13, 1.26)</td>
<td>1.15 (1.09, 1.21)</td>
<td>1.15 (1.08, 1.22)</td>
</tr>
<tr>
<td>5–15</td>
<td>1.43 (1.32, 1.56)</td>
<td>1.33 (1.21, 1.45)</td>
<td>1.50 (1.37, 1.65)</td>
</tr>
<tr>
<td>16+</td>
<td>2.77 (2.58, 2.98)</td>
<td>2.80 (2.60, 3.01)</td>
<td>3.22 (2.94, 3.52)</td>
</tr>
<tr>
<td><strong>Female (REF = Male)</strong></td>
<td>1.39 (1.32, 1.47)</td>
<td>1.78 (1.68, 1.88)</td>
<td>1.17 (1.10, 1.24)</td>
</tr>
<tr>
<td>Age (REF = 65–69)</td>
<td>1.13 (1.00, 1.27)</td>
<td>1.05 (0.93, 1.17)</td>
<td>0.93 (0.82, 1.07)</td>
</tr>
<tr>
<td>70–74</td>
<td>1.42 (1.27, 1.59)</td>
<td>1.29 (1.16, 1.44)</td>
<td>1.29 (1.14, 1.46)</td>
</tr>
<tr>
<td>75–79</td>
<td>2.23 (2.00, 2.48)</td>
<td>1.67 (1.50, 1.85)</td>
<td>1.86 (1.65, 2.10)</td>
</tr>
<tr>
<td><strong>Race (REF = White)</strong></td>
<td>0.76 (0.63, 0.91)</td>
<td>0.91 (0.76, 1.08)</td>
<td>0.81 (0.65, 0.99)</td>
</tr>
<tr>
<td>Asian**</td>
<td>0.70 (0.65, 0.76)</td>
<td>0.61 (0.56, 0.67)</td>
<td>0.78 (0.71, 0.85)</td>
</tr>
<tr>
<td>Black</td>
<td>0.73 (0.66, 0.81)</td>
<td>0.89 (0.81, 0.98)</td>
<td>0.90 (0.81, 1.00)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.03 (0.91, 1.18)</td>
<td>1.26 (1.12, 1.43)</td>
<td>1.02 (0.88, 1.19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.08 (1.02, 1.14)</td>
<td>0.99 (0.94, 1.05)</td>
<td>1.01 (0.95, 1.07)</td>
</tr>
<tr>
<td>Net Worth (REF = $250k+)</td>
<td>1.10 (0.97, 1.25)</td>
<td>1.07 (0.94, 1.22)</td>
<td>0.87 (0.74, 1.02)</td>
</tr>
</tbody>
</table>

Hosmer Lemeshow GOF

<table>
<thead>
<tr>
<th></th>
<th>$p = 0.258$</th>
<th>$p = 0.111$</th>
<th>$p = 0.159$</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-statistic</td>
<td>0.666</td>
<td>0.663</td>
<td>0.661</td>
</tr>
</tbody>
</table>

*N < 71,360 because those with the event occurring before the initiation of ACH and AChEI medications were excluded.

OR=odds ratio; CI=confidence interval; GOF=goodness of fit

**Asian=Asian American and Pacific Islander

Prescription fill at baseline for at least one of the following drugs:
- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Razadyne®)
- Memantine (Namenda®)
- Memantine/donepezil (Namzaric®)

**AND

Prescription fill 12 months post-index date for at least one of the following drugs:
- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Razadyne®)
- Memantine/donepezil (Namzaric®)

**Exclusion Criteria**
- Alcohol or substance abuse (ICD-9: 303.xx, 304.xx, 305.xx)
- Memantine prescription and NO dementia diagnosis AND one of the following diagnoses:
  - Obsessive-compulsive disorder (OCD) (ICD-9: 300.3)
  - Attention deficit hyperactivity disorder (ADHD) (ICD-9: 314.01)
  - Migraine headache (ICD-9: 346.x)
  - Posttraumatic stress disorder (PTSD) (ICD-9: 309.81)
Statistical Analyses

We used Chi-square tests to identify differences in proportions between subjects taking AChEI drugs with and without concurrent ACH use and Student’s t-tests to determine differences in means for continuous variables between the two groups. A two-sided p-value less than 0.05 indicated statistical significance.

We conducted multiple logistic regression analyses to identify factors independently associated with adverse outcomes (fall, fracture, and/or TBI) among those taking anticholinergic and AChEI drugs concurrently compared with those using AChEI drugs alone. Covariates in the logistic regression models included age, gender, race/ethnicity, net worth, the number of treating clinicians (20 or more v. less than 20), memantine use, and the Elixhauser Index (≤4, 5–15, 16+), a composite comorbidity score based on the presence or absence of 30 health conditions including diabetes, hypertension, and liver disease.

Study Limitations

Our sample consisted of members enrolled in a subset of all MA plans in the United States; therefore, our results are not generalizable to the MA population as a whole or to Medicare fee-for-service beneficiaries. Claims data do not contain information on the severity of dementia.

Due to data limitations we were not able to disaggregate Native Hawaiians/Pacific Islanders from Asian Americans. We were also not able to analyze Native Americans as a separate racial category.

AChEI and/or anticholinergic use could be misclassified due to either over-the-counter (OTC) use of anticholinergics (e.g., Benadryl® or Zantac®) or nonadherence to prescription medications. Failure to account for OTC anticholinergic use will result in an underestimate of effects of ACH, while failure to capture medications delivered both in-hospital or in-office will result in an overestimate of effects. Finally, the delivery of either of these medications in office or hospital settings, though rare, could not be captured.

1 OptumLabs. OptumLabs and OptumLabs Data Warehouse (OLDW) Descriptions and Citation. Eden Prairie, MN: n.p., July 2020. PDF. Reproduced with permission from OptumLabs.