Elderly patients are particularly susceptible to adverse effects from anticholinergic medications including memory impairment, confusion, hallucinations, dry mouth, constipation, urinary retention, and tachycardia. However these medications are still used by a significant proportion of older adults. Estimates of the prevalence of use of anticholinergics in older adults ranges from 8% to 37%. In addition, a nationally representative sample of non-institutionalized patients with dementia in the United States (US) determined about 23% of elderly dementia patients used medications considered to be clinically significant anticholinergic agents. The 2004 US National Nursing Home Survey evaluated more than 690,000 elderly patients with dementia and found 74% of elderly residents with dementia were using medications with anticholinergic properties.

The anticholinergic effect from these medications may be the intended effect or an adverse effect. For medication classes such as the antimuscarinics for overactive bladder and the antispasmodics for gastrointestinal symptoms, the anticholinergic properties of the drug are the intended therapeutic effect. However, for other classes of medications such as the first generation antihistamines and some antipsychotics, the anticholinergic properties may result in unwanted side effects. In addition, a recently published population-based case-control study in older adults determined that acute and chronic use of anticholinergic medications was associated with a significantly greater risk for the development of pneumonia. This article will review new evidence regarding anticholinergic use in the elderly and the risk of dementia and Alzheimer’s disease (AD).

**Previous Observational Studies**

The effects of anticholinergics on the risk for dementia in elderly adults has been previously evaluated in observational studies conducted outside of the US. In a longitudinal cohort study of 372 patients older than 60 years without dementia, elderly patients who were taking anticholinergic medications were found to have a five times increased odds of having mild cognitive impairment compared with non-users at 1 year follow-up. However after 8 years of follow-up, no difference was found between users and non-users in the risk of developing dementia.
Another population-based cohort study, with more than 6900 patients 65 year of age or older, found patients with long-term anticholinergic use had an increased risk for dementia and Alzheimer’s disease. However, these increased risks were not statistically significant (p=0.05 for both). This study also found that patients who were taking anticholinergic drugs were at an increased risk for cognitive decline and dementia. However, when continuous users were compared with patients who discontinued use, the risk of dementia and cognitive decline was not observed in patients who discontinued using these medications.7

A longitudinal cohort study was also conducted in Germany that evaluated 2,605 elderly patients older than 75 years of age without dementia. Patients were identified from a primary care medical record registry sample and followed up a year and a half and then three years after enrollment. It was determined that patients chronically taking drugs with anticholinergic properties had a two times greater risk for dementia (hazards ratio [HR] 2.08, p<0.001). However the drugs evaluated in this study were different from some of the typical classes expected to have anticholinergic properties and included cardiovascular agents, anti-inflammatories, and anti-diabetic agents.8

All three of these studies used patient interview to evaluate anticholinergic use and exhibited variations in the assessments used to determine anticholinergic burden.6-8 As two of these studies were conducted in France and one in Germany, the generalizability of the results to the US population is unclear due to differences in medication approval and use in other countries. The applicability of these studies to the long-term care population may be limited, as the majority of patients evaluated in these studies were community-dwelling.

While experimental studies and cohort studies have demonstrated that acute impairment in cognition can occur from use of anticholinergic medications, it is generally thought changes in cognition are reversible with discontinuation of the anticholinergic medication. However, these recent studies suggest anticholinergics may be associated with mild cognitive impairment, dementia, and AD. A prospective cohort study addressing the risk for dementia in elderly US adults using strong anticholinergics was published in the March 2015 issue of *JAMA Internal Medicine*. A summary of this study is provided in the following section.2

**New Evidence**

The prospective population-based study included 3434 participants 65 years or older randomly sampled from the Seattle area Group Health plan. Subjects were required to have 10-years of health care plan enrollment prior to study entry and at least one follow up visit. Patients with dementia at baseline were excluded. Cognitive function of participants was assessed at study entry and every other year using the Cognitive Abilities Screening Instrument
The primary endpoint was 10-year cumulative anticholinergic exposure, which was assessed at study entry and updated periodically as participants were followed over time.²

Assessment of anticholinergic use was determined by computerized pharmacy dispensing data that allowed the retrieval of the medication name, strength, route, date dispensed, and amount dispensed. Patients’ total standardized daily dose (SDD) over the study period was calculated based on the tablet strength, number dispensed, and the minimum effective dose per day for each individual agent. This calculation was made for each individual anticholinergic medication filled during the exposure period, and the total cumulative SDD was calculated by adding the SDD for each individual agent together. This method has been previously described in the literature and allows for different anticholinergics to be combined into a cumulative exposure measure (total SDD or TSDD). Medications determined to be strong anticholinergics were based on the 2012 Beer’s criteria with minimum effective doses of the drugs determined from a geriatric dosing reference.² ⁹ Table 1 provides a summary of commonly used medications considered to have strong anticholinergic properties derived from the list used in this study.

### Table 1. Strong Anticholinergic Medications Commonly Used in Clinical Practice

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medications with Strong Anticholinergic Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, paroxetine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine</td>
</tr>
<tr>
<td>Antiparkison Agents</td>
<td>Benztropine, trihexphenidyl</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine, clozapine, olanzapine</td>
</tr>
<tr>
<td>Antivertigo / Antiemetics</td>
<td>Dimenhydrinate, meclizine, prochlorperazine, promethazine</td>
</tr>
<tr>
<td>Bladder Antimuscarinics</td>
<td>Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium</td>
</tr>
<tr>
<td>GI Antispasmodics</td>
<td>Dicyclomine, glycopyrrolate, hyoscyamine, scopolamine</td>
</tr>
<tr>
<td>Skeletal Muscle Relaxants</td>
<td>Cyclobenzaprine, orphenadrine</td>
</tr>
</tbody>
</table>

Adapted from Supplementary Appendix of Gray et al.
Not an all-inclusive list of medications with anticholinergic properties.
The majority of participants at study entry were white (~91%), female (~60%), and had at least 1 anticholinergic fill in the 10 years before study entry (~78%). Before study entry, participants who had used anticholinergics in the past were more likely to be women, have fair or poor self-rated health, have higher levels of depressive symptoms, and have comorbidities (hypertension, stroke, or coronary heart disease) compared to participants who had not used anticholinergics. However, regression analysis was used to adjust for these and other potential confounding variables identified from a literature search.2

At the end of the study period, patients were categorized based on their total cumulative exposure (TSDD) into the following categories: 1 to 90, 91 to 365, 365 to 1095, or >1095 (i.e., >3 years). A TSDD of 1 to 90 represented less than three months of continuous daily anticholinergic exposure, while a TSDD >1095 equated to continuous daily treatment for more than three years. The study demonstrated a dose-response relationship for 10-year cumulative strong anticholinergic exposure and risk of dementia and AD (p<0.001). In other words, patients who were exposed to anticholinergics for more than three years had a higher risk for the development of dementia. It was determined patients in the highest cumulative anticholinergic exposure group (TSDD >1095) had a significantly increased risk for dementia (adjusted HR 1.54, 95% CI 1.21-1.96) and Alzheimer disease (adjusted HR 1.63, 95% CI 1.24-2.14). Results of a post-hoc analysis of this highest exposure group suggested the risk of dementia may continue even after stopping the anticholinergic medication. In terms of cumulative anticholinergic exposure, antidepressants, antihistamines and bladder antimuscarinics were the classes of medications most commonly used.2

Strengths of this study include the number of participants, study duration, and assessment of cumulative exposure. In addition, this study was able to assess whether a dose-response relationship was present for the patient-oriented endpoint of dementia. To adjust for potential confounding variables, regression analysis was used to account for differences between the exposure groups at study entry; however, the potential for additional unknown confounders exists. Limitations include that the majority of patients were Caucasian, female, and from one specific geographical location. As exposure was based on prescription records, compliance to medications is unknown and over-the-counter (OTC) medications purchased at pharmacies outside of the group health care plan were not assessed.

Overall, this study demonstrated that higher cumulative anticholinergic use was associated with an increased risk for dementia and provides further justification for minimizing the use of these medications in older adults.2
Discussion

While this recent study by Gray et al. does not address a biological plausibility for the association between anticholinergics and dementia, other preliminary studies have provided a potential underlying mechanism.\textsuperscript{10} A neuropathology study done on autopsy of 120 confirmed Parkinson’s disease cases determined those patients who received chronic (>2 years) of antimuscarinic drugs were found to have thicker amyloid plaque densities and increased neurofibrillatory tangle densities when compared to patients who received no antimuscarinic drugs or were only treated short-term (<2 years). This study suggests with long-term anticholinergic use, there may be an increase in the neuropathological features of AD. In addition, preliminary animal studies have demonstrated that decreased cholinergic transmission results in increased amounts of beta-amyloid,\textsuperscript{2} further suggesting a possible biological mechanism for the increased risk of dementia in patients using anticholinergics.

Medications with significant anticholinergic properties are considered to be potentially inappropriate for use in elderly patients.\textsuperscript{8} However, evidence from past observational studies has produced conflicting results in terms of whether use of these medications increases the risk for sustained cognitive deficits.\textsuperscript{6-8} A recently published observational cohort study from a group health care plan within the US has provided further evidence for the association between cumulative anticholinergic exposure and the risk for dementia and Alzheimer’s disease.\textsuperscript{2} This trial adds to the currently expanding body of evidence describing the risks of using these medications in the elderly population, and it provides further justification for the role of pharmacists in educating nurses and providers on the potential harms of using these medications long-term and helping to identify acceptable alternatives for these patients.

References

Creighton University’s Center for Drug Information & Evidence-Based Practice, in collaboration with PharMerica, is offering Drug Information Services to all PharMerica-affiliated healthcare professionals.

**Drug Information Consultation Service**

Monday through Friday  
830 am – 430 pm Central  
Submit your questions online at  
http://creighton.edu/pharmerica  
or call us at 1-800-561-3728  
*Voicemail service is available afterhours*

Contact us through our online submission form or call us for help with answering medication-related questions. Be sure to identify your affiliation with PharMerica, as this affords you priority status with our service. We will provide an evidence-based response within 24-48 hours. Let us help you provide top-quality resident care!