

Cognitive Impact of Medications with Anticholinergic Effects

Adverse drug effects present a considerable challenge for clinicians and caregivers of older patients. Greater risk of cognitive impairment, falls and functional decline have been observed in older persons exposed to a variety of prescription and over-the-counter (OTC) medications. In the US, people over the age of 65 make up only 13% of the overall population but consume 30% of the prescription medications and 40% of OTC agents. These statistics make the identification and prevention of adverse drug events in the older population an important public health issue.



Among the most common adverse effects are those associated with anticholinergic (ACH) medications. "Anticholinergic" means blocking the effects of the neurotransmitter acetylcholine. Since acetylcholine is involved with learning, memory, glands and involuntary muscles, effects from an ACH drug can include constipation, heat intolerance, dry eyes and mouth, tachycardia, urinary retention, forgetfulness, agitation, paranoia and delirium to name a few. ACH medications are more likely to have a more toxic effect on an aging brain because of increased permeability of the blood brain barrier, slower metabolism/drug elimination and polypharmacy. The use of ACH medications are often deemed inappropriate in elderly patients, however a recent study¹ conducted in a Veterans Administration Internal Medicine Clinic, revealed 27.1% of the patients (mean age 74.3 years) were taking at least one prescription and/or OTC ACH medication. Despite efforts to limit exposure, ACH medications continue to be a source of potential problems in patients.

Many articles have been published correlating ACH effects with significant functional and cognitive disability and delirium. This article will review the findings and recommendations from a number of these articles.

ACH Effects and Delirium

Drugs are one of the most common, and most easily avoided, causes of delirium and ACH medication use is a common precipitating risk factor.²

The impact of ACH medications on the frequency and severity of delirium symptoms was investigated in a longitudinal study of medical inpatients (n=278) 65 years and older with and without pre-existing dementia.³ In this cohort of older medical inpatients with delirium, researchers observed that a change in exposure to ACH medications was independently associated with a change in the severity of delirium symptoms. The increase in delirium symptoms persisted after adjusting for the number of medications and was independent of the initial severity of delirium and presence of dementia and other comorbid conditions.

Cognitive Impairment and ACH Medications

Mild cognitive impairment is a general term used to describe subclinical cognitive deficits in older people that are likely to evolve towards dementia.

Clinical studies have consistently shown that dysfunction of the cholinergic system has a detrimental impact on cognitive function. Patients (n=372) enrolled in a longitudinal study of cognitive aging were evaluated annually for cognitive performance that included standardized testing of verbal, memory, language and motor skills.⁴ Compared with non-users, ACH medication users had significantly poorer performance on reaction time, attention, delayed non-verbal memory, recall and language tasks. Of the continuous ACH medication users 80% were classified as having mild cognitive impairment compared to 35% of non-users. ACH drug use was a strong predictor of mild cognitive impairment (odds ratio 5.12, P=0.001). It is important to note that no difference was found between users and non-users of ACH medications in risk of developing dementia during eight years of follow-up in this study.

Studies that have linked ACH medications to cognitive decline are not isolated. A review of existing evidence regarding the effects of ACH medications on cognition in older adults was conducted by a panel of geriatric specialists.⁵ Search of existing literature revealed 27

studies that met rigorous inclusion criteria for this review. All were cross-sectional, case control or retrospective/prospective observational cohort studies that investigated the cognitive burden of ACH drugs. The findings of this review panel scoring found:

- A consistent association between the use of ACH medication and cognitive impairment and delirium in older adults.
- This adverse effect does not arise exclusively from acute exposure of an agent with strong ACH effect but an accumulation of multiple medications with varying degrees of activity.
- All but two studies associated ACH use with worsening cognitive performance either through acute (delirium) or chronic (mild cognitive impairment) impact.
- Minimal changes in global measures of cognitive function with exposure to ACHs, and instead identified deficits in processing speed, psychomotor performance, concentration and attention, problems solving and language skills.

It was the conclusions of this panel that in the clinical setting many practitioners rely on global measures to evaluate cognitive performance and therefore may not identify a decline in specific measures of cognition. Recognizing patients at risk due to exposure to ACHs should warrant cognitive evaluation when subjective complaints of impairment supplement clinical suspicion. Removal of potentially harmful medications in lieu of equally effective alternatives with lower ACH activity is a good practice.

Cumulative ACH Exposure

The cumulative exposure of men over the age of 65 to ACH medications and the resulting impact on memory and executive function was studied in a Veterans Affairs primary care clinic.⁶ Five hundred forty-four community-dwelling men were evaluated using standardized verbal recall tests for short-term memory and an activity of daily living scale for executive function. ACH medications were tracked throughout this one year study and two year follow-up period. Cumulative exposure to ACH medications over the 12 month period was associated with significantly poorer performance on both verbal and functional testing. This association remained statistically significant when adjusted for other potential risk factors for cognitive and functional impairment including age, education, ADL function, comorbidities, severity of hypertension and use of other non-ACH medications.

As observed in other studies, these associations may arise from long-term cumulative anticholinergic insult over time. Most medications taken by older adults in this study had only mild to moderate ACH effects and the dosages taken were not considered to be extremely high.

It was the conclusion of these researchers that clinicians prescribing drugs with ACH effects should pay close attention to potential adverse effects that may arise with long-term use of these drugs in older persons and to minimize exposure to the greatest extent possible.

Conclusion

The potential for acute and long-term negative effects of ACH medication in the older patients are significant. Prescribers should take steps to minimize exposure of patients to medications with these side effects.

Dr. Sally Rigler, a geriatrician with the University of Kansas Medical Center, offers these suggestions for reducing the opportunities for ACH drug exposure:

- Eliminate hospital standing orders that could result in diphenhydramine being used for sleep in older patients.
- Attempt behavioral modalities first for urinary incontinence before launching right into medication therapy.
- For allergic rhinitis, use only “nonsedating” antihistamines or perhaps a nasal steroid instead.
- Meclizine is not effective for non-vestibular forms of dizziness and if used, the results of the treatment can be worse than the disease.
- For viral URIs, advise patients to avoid the “bedtime” and “PM” type products, as they all contain some form of sedating antihistamine.
- For treatment of neuropathy or fibromyalgia try to avoid tri-cyclic antidepressants like amitriptyline. Medications like gabapentin are generally better tolerated.
- Avoid using amitriptyline for sleep, trazadone is a better choice if a inexpensive cyclic antidepressant is going to be exploited for its sedative properties.
- Avoid the use of oral antihistamines for itching, consider topical diphenhydramine or a corticosteroid cream.
- Routinely evaluate patients for ACH toxicity. Remember these effects may come on slowly and can be difficult to distinguish from changes in clinical status.

1. Ness J, et al. Anticholinergic medications in community-dwelling older veterans: prevalence of symptoms, symptom burden, and adverse drug events. *Am J Geriatr Pharmacother* 2006;4(1):42-51.
2. Elie M, et al. Delirium risk factors in elderly hospitalized patients, *J Gen Intern Med* 1998; 13:203-12.
3. Han L, et al. Use of medications with anticholinergic effect predict clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001;161:1099-1105.
4. Ancelin ML, et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 2006;332:455-9.
5. Campbell N, et al. The cognitive impact of anticholinergic: a clinical review. *Clinical Interv Aging* 2009;4:225-33.
6. Han L, et al. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *J Am Geriatr Soc* 2008;56:2203-10.