Anticholinergic Burden on the Elderly Patient

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Disclosures

• Dr. Brodeur has no conflicts of interest to disclose.
• Components of this presentation were developed by the IPRO DADE expert panel of which Dr. Brodeur was a member.

Learning Objectives

1. Review the function of the cholinergic nervous system.
2. Identify potentially inappropriate anticholinergic medications.
3. Describe the various methodologies used to quantify the anticholinergic properties of medications.
4. Describe the latest evidence documenting the adverse effects of anticholinergic medications in the elderly.
Learning Objectives (cont.)

5. Given a patient case recommend safer alternatives to anticholinergic medications.
6. Identify tools to alert prescribers of the dangers of anticholinergic medications.

“Aging America

“Baby Boomer” Impact

“Any symptom in an elderly patient should be considered a drug side effect until proved otherwise.”

J Gurwitz, M Monane, S Monane, J Avorn
Brown University Long-Term Care Quality Letter 1995
Increased Risk for Adverse Drug Reaction

- Polypharmacy
- Inadequate clinical assessment
- Lack of Compliance
- Altered physiology
- Multiple disease states
- Supervision

The Autonomic Nervous System

http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/P/PNS.html

Cholinergic Pathways

- FC = Frontal cortex
- PC = Parietal cortex
- OC = Occipital cortex
- H = Hippocampus
- M = Medial septal nucleus and diagonal band of Broca
- T = Diagonal band of Broca projecting into the olfactory tubercle
- B = Nucleus basalis of Meynert

http://www.seniorcare.alaska.gov/dbh/mh/ppt/Medication.ppt#580,28,Slide 28
Muscarinic Receptor Subtypes

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>CNS Distribution</th>
<th>Non-CNS Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>M₁</td>
<td>Cerebral cortex, hippocampus, neostriatum (40-50% of ACH receptors)</td>
<td>Salivary glands, sympathetic ganglia</td>
</tr>
<tr>
<td>M₂</td>
<td>Throughout brain</td>
<td>Smooth muscle, cardiac muscle</td>
</tr>
<tr>
<td>M₃</td>
<td>Low levels throughout brain</td>
<td>Smooth muscle, salivary glands, eyes</td>
</tr>
<tr>
<td>M₄</td>
<td>Abundant in neostriatum, cortex and hippocampus</td>
<td>Salivary glands</td>
</tr>
<tr>
<td>M₅</td>
<td>Projection neurons of substantia nigra pars, compacta and ventral tegmental area and hippocampus</td>
<td>Eyes (ciliary muscle)</td>
</tr>
</tbody>
</table>

Anticholinergic Side Effects

“Mad as a hatter” Delirium
“Blind as a bat” Mydriasis
“Red as a beet” Flushed
“Dry as a bone” Dry Skin
“Hot as a hare” Hyperthermia

Confusion, drowsiness, hallucinations, dry mouth, constipation, palpitations, tachyarrhythmia, urinary retention, dry eyes, blurred vision, falls
Commonly Used Anticholinergic Drugs*
(Used clinically for their antimuscarinic effects)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs for movement disorders</td>
<td>trihexyphenidyl, benztropine, biperiden, procyclidine</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>oxybutynin, flavoxate, propantheline</td>
</tr>
<tr>
<td>Dizziness, motion sickness, antiemetic</td>
<td>meclizine, scopolamine, trimethobenzamide</td>
</tr>
<tr>
<td>Gastrointestinal antispasmodic</td>
<td>atropine, dicyclomine, hyoscyamine,</td>
</tr>
<tr>
<td>Mydriatic-cycloplegic</td>
<td>homatropine, cyclopentolate</td>
</tr>
</tbody>
</table>

*Table includes examples only- list is not exhaustive

Anticholinergic Drugs*
(Not primarily targeted at cholinergic receptors)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic Antidepressants</td>
<td>amitriptyline, imipramine, nortriptyline, desipramine, doxepin</td>
</tr>
<tr>
<td>Sedating Antihistamines</td>
<td>diphenhydramine, brompheniramine, chlorpheniramine, clemastine, doxylamine, hydroxyzine, promethazine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>chlorpromazine, clozapine, promethazine, thioridazine, olanzapine</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>disopyramide, procainamide</td>
</tr>
<tr>
<td>Muscle Relaxants</td>
<td>methocarbamol, carisoprodol, chlorzosazine, metaxalone, cyclobenzaprine</td>
</tr>
</tbody>
</table>

*Table includes examples only- list is not exhaustive
Examples of Other Drugs With Anticholinergic Effects (based on in vitro ACh binding)

- Cardiovascular: furosemide, captopril, digoxin, hydralazine, isosorbide dinitrate, warfarin
- Infectious disease: Ampicillin, gentamicin, piperacillin, tobramycin, corticosteroids, theophylline
- Miscellaneous: benzodiazepines, opiates, phenobarbital, H2 antagonists,


Potentially Inappropriate Anticholinergics

<table>
<thead>
<tr>
<th>Anticholinergic</th>
<th>Score</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Isosorbide</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dinitrate</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>H2 Antagonist</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Anticholinergic agents identified in either Beers List or NCQA HEDIS Measures®
Anticholinergic Burden

- The cumulative effect of taking multiple medications with anticholinergic properties
- Factors that may influence ACh burden:
  - Anticholinergic potency of drugs involved
  - Co-morbid conditions (such as dementia)
  - Pharmacokinetic changes with aging (longer half life.)
  - Drug interactions
  - Physiologic changes in elderly (Blood-brain barrier integrity.)


Clinical Relevance of Anticholinergic Burden

- A growing body of evidence consistently demonstrates measurable and clinically relevant adverse effects in the elderly
- Impact on CNS is most widely documented
- Other potential adverse outcomes may also result in significant disability for seniors.
- Patients with dementia may be at higher risk for negative clinical outcomes.

Calculating Anticholinergic Burden

- Clinical judgement
- Anticholinergic Rating Scales
  - Anticholinergic Burden Scale
  - Anticholinergic Risk Scale
- Measure total serum ACh activity
- Measure individual drug related ACh activity

Clinical Evidence of Harm

- Delirium
- Mild Cognitive Impairment
- Dementia
- Other clinical effects
- Objective physiological findings

Delirium

The use of medications with anticholinergic effects predicts clinical severity of delirium symptoms in older medical inpatients

- 278 medical inpatients with delirium
- Exposure to ACh drugs measured as clinician-rated score and total number of ACh drugs
- Exposure was independently associated with a subsequent increase in delirium severity (p= 0.02)


Delirium (cont)

The association of serum anticholinergic activity with delirium in elderly medical patients

- 67 acutely ill elderly medical inpatients
- 20 patients developed delirium
- Elevated SAA was independently associated with delirium (p=0.006; OR=2.38; 95% CI=1.29, 4.40)
- In those who developed delirium, a greater number of delirium symptoms was associated with higher serum ACh activity

Mild Cognitive Impairment

Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study

- 372 patients aged > 60 without dementia at recruitment
- ACh burden assessed by literature review and clinical judgment
- 9.2% continuously used ACH medications in year prior
- 80% of the continuous users were classified as mild cognitive impairment (MCI) compared with 35% of nonusers
- ACh drug use was a strong predictor of MCI (p = 0.001, OR = 5.12)

Ancelin ML. BMJ. 2006 February 25; 332(7539): 455–459

Dementia

Serum anticholinergic activity in a community-based sample of older adults

- Measured serum ACh activity in elderly (n= 201)
- 90% had detectable serum ACh activity
- Significant association between ACh activity and Mini Mental State Examination (MMSE) score (Pearson \(\chi^2=10.18, p=0.006\))
- Subjects with serum ACh activity in the 90th percentile were 13 times more likely than subjects with undetectable serum ACh activity to have an MMSE score of 24 or less. (p=.04)

Chronic Exposure to Anticholinergic Medications Adversely Affects the Course of Alzheimer Disease

Ching-ju Lu, B.A., and Larry E. Tune, M.D.

Objective: Authors examined the effect of chronic exposure to anticholinergics in a cohort of Alzheimer disease (AD) patients. Methods: All patients were examined annually with standard neuropsychologic tests and received the cholinesterase inhibitor donepezil hydrochloride at a dose of 10 mg/day. The study population (N=69) was divided into two groups: those receiving one or more concomitant medications with significant anticholinergic properties (N=16) and those receiving no concomitant medications with anticholinergic properties (N=53). Results: At 2 years, MMSE scores were significantly worse for patients receiving anticholinergic medications than for those not on anticholinergics. Conclusion: Although very preliminary, these data suggest that concomitant therapy with anticholinergics may be associated with significant deleterious effects on acetylcholinesterase therapy, or, more speculatively, that chronic exposure to anticholinergics may have adverse effects on the clinical course of AD.

Prescribing Cascade in Dementia

A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs

- 44,884 older adults with dementia
- After adjusting for potential confounders, older adults with dementia who were dispensed cholinesterase inhibitors had an increased risk of receiving an ACh drug to manage urinary incontinence
- This may represent an important example of a prescribing cascade, suggesting that one medication is being prescribed to manage the side effects of another.


Medical Research Council Cognitive Function and Ageing Study

- Dose response relationship between greater total anticholinergic burden score and lower MMSE scores.
- Odds of dying increased by 26% (OR=1.26, 95% CI=1.30-2.16) for each additional point on the ACB scale
- Direct causality?

Paradox Studies

- Laser-AD
  – Weak anticholinergic medications not associated with a deterioration in cognition in Alzheimer's disease patients

- Anticholinergics and Incident of Delirium
  – Anticholinergic medications did not increase the incidence risk of delirium in older adults with cognitive impairment

Fox C. Age and Ageing 2011;0:1-6 doi: 10.1093/ageing/afr102
Campbell N. J Am Geriatr Soc. 2011;59:S277-S281

Physiological Changes

Increased Alzheimer’s disease pathology in Parkinson’s disease related to antimuscarinic drugs

- Studied brains of 54 patients with Parkinson’s Disease for evidence of plaques and tangles
- Categorized drug use as none, short, or chronic (2-18 yrs) and matched for age, sex and disease duration
- Most of the treatment was with trihexyphenidyl for tremor control
- Amyloid plaque densities 2.5 fold higher in the patients receiving chronic antimuscarinic therapy


Physiological Changes

Serum anticholinergic activity, white matter hyperintensities, and cognitive performance

Neurology 2005;65:1487-1489

“Thus, the cognitive decrements associated with increased WMH volume may be exacerbated by the many anticholinergic medications, both prescribed and over the counter, taken by older individuals.”
**Additional ACh effects**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry Mouth</td>
<td>Communication problems, malnutrition, mucosal damage, dental caries, risk of serious respiratory infection 2x to loss of antimicrobial activity of saliva</td>
</tr>
<tr>
<td>Mydriasis and accommodation</td>
<td>Narrow angle glaucoma, increased risk of accidents/falls</td>
</tr>
<tr>
<td>Constipation</td>
<td>Fecal impaction</td>
</tr>
<tr>
<td>Urinary hesitancy</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Worsening angina</td>
</tr>
<tr>
<td>Decreased sweating</td>
<td>Heat stroke or hyperthermia</td>
</tr>
</tbody>
</table>


**Don’t Start! and Stop if Started!**

- A large number of anticholinergic drugs have been identified as potentially inappropriate for seniors due to side effects and inefficacy
- Latest evidence consistently and objectively shows detrimental effect of ACH’s on older adults

**Alternatives to Anticholinergics in Seniors**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alternative to Anticholinergics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergies</td>
<td>Non-sedating antihistamines</td>
</tr>
<tr>
<td>Cholinesterase inhibitor effects</td>
<td>Adjust dose/interval, switch agent, consider DC</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRI or non-cholinergic antidepressant</td>
</tr>
<tr>
<td>Neuropathic Pain</td>
<td>Gabapentin, pregabalbin, duloxetine, others</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>Dopamine agonists, levodopa, others</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Cetirizine, topical therapy</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Assessment of underlying cause</td>
</tr>
</tbody>
</table>
Case 1

- Doris, an 83-year-old woman suffering from moderate Alzheimer's disease, arrives for an office visit with her primary care provider accompanied by her 85-year-old spouse. Her spouse made the appointment to seek guidance in managing Doris's behavior as her Alzheimer's disease progresses. He is having increasing difficulty managing their life together at home. When interviewing Doris's husband he appears frustrated and perhaps depressed. As he is leaving the exam room he confides that Doris has recently begun to experience incontinence of urine. She seems to urinate without warning and he can't keep up with cleaning her clothes and the house.

Case 2

Jane is a 71-year-old woman coming to your pharmacy today for a refill. Her overall health is very good. The only medications she takes on a regular basis are hydrochlorothiazide 25 mg daily for mild isolated systolic hypertension and calcium/vitamin D for osteoporosis prevention.

She complains of new onset postnasal drip and chronic mild cough. She notes that the symptoms are present all year round. She would like your advice on what to take for these symptoms.
Questions?