Anticholinergics and Risk of Dementia

Shelly Gray, PharmD, MS
School of Pharmacy
University of Washington
Objectives

1. Discuss the adverse effects and epidemiology of anticholinergic (AC) use in older adults

2. Discuss the challenges in measuring overall AC medication burden

3. Describe a study evaluating AC use and dementia risk

4. List possible alternatives to anticholinergic medications
Anticholinergic Medications
Block acetylcholine from interacting with cholinergic receptor

- **Intended pharmacological effect**
  - Bladder medications
  - Antispasmodics
  - Antiparkinson agents

- **Nuisance side effect**
  - Antidepressants
  - Antipsychotics
  - Cold and allergy agents
Anticholinergic Adverse Effects

Others: Dry mouth/skin, orthostasis, tachycardia, urinary retention, constipation
Increased Vulnerability to AC Adverse Effects in the Elderly

• Greater sensitivity
  – Age-related pharmacokinetic effects
  – Increased blood-brain barrier permeability
  – Decreased central cholinergic activities

• Pre-existing cognitive impairment

• High probability of exposure

AC Medication Use is Common

- Prevalence in community dwelling older adults is 12-25%
- Use is high even in frail elderly with dementia (20-24%)
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4. List possible alternatives to anticholinergic medications
Challenges in Measuring AC Burden

• No gold standard list of AC medications
• Differences in potency
• Differences in CNS penetration?
• Various methods used:
  – Serum Anticholinergic Activity (SAA)
  – In vitro measurement of muscarinic receptor affinity
  – Expert opinion
How Do We Measure AC Burden?

**Weighted Scales**

- Anticholinergic Cognitive Burden Scale (ACB)
- Anticholinergic Risk Scale (ARS)
- Anticholinergic Drug Scale (ADS)

**Scales Using Standardized Dose**

- AC component of the Drug Burden Index (DBI-ACh)
- Summated Anticholinergic Medication Scale (SAMS)
  - Modified from 2012 Beers Criteria
  - Corresponds with 2015 Beers Highly AC List
## 2015 AGS Drugs with Strong Anticholinergic Properties

<table>
<thead>
<tr>
<th>Class</th>
<th>Example Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Disopyramide</td>
</tr>
<tr>
<td>Antihistamine (1st gen)</td>
<td>Diphenhydramine, meclizine, hydroxyzine</td>
</tr>
<tr>
<td>Antiparkinson</td>
<td>Benztropine, trihexyphenidyl</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine</td>
</tr>
<tr>
<td>GI antispasmodic</td>
<td>Atropine, belladonna, clidinium</td>
</tr>
<tr>
<td>GU antispasmodics</td>
<td>Oxybutynin, solifenacim, tolterodine</td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>Cyclobenzaprine, orphenadrine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, desipramine, doxepin, paroxetine</td>
</tr>
</tbody>
</table>
Concordance Among Anticholinergic Burden Scales

JG Naples, ZA Marcum, S Perera, SL Gray, AB Newman, EM Simonsick, K Yaffe, RI Shorr, JT Hanlon

J Am Geriatr Soc 2015 In press

Universities of Pittsburgh, WA and UCSF; NIA; N.FL/S.GA VA GRECC
# Methods

**Design:** Cross-sectional secondary analysis

**Data Source:** Health Aging Body Composition study

**Participants:** 3055 adults ≥ 70 years old with no mobility limitations and self-reported prescription and OTC medication data at baseline using a brown bag method

**Statistics:** Descriptive statistics, kappa (κ) statistics, Spearman rank correlation

Weighted Anticholinergic Scales

• Ranked from 1 (low) to 3 (high) AC activity
• Anticholinergic Drug Scale (ADS)
  – Original 2002, Updated 2014
• Anticholinergic Cognitive Burden Scale (ACB)
  – Original 2008, updated 2012
• Anticholinergic Risk Scale (ARS)
  – Original 2008

## Example Calculation

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADS</th>
<th>ACB</th>
<th>ARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>---</td>
<td>---</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Anticholinergic Scales Using Standardized Daily Doses (SDD)

- SDD = Total Daily Dose (DD) / Minimum Effective DD [MED])
- DBI-ACh
  - Original 2007
  - Utilizes adult MED
- SAMS
  - Original 2015
  - Utilizes geriatric MED
- Summed across agents to yield Total SDD

## Example Calculation

<table>
<thead>
<tr>
<th>Drug</th>
<th>TDD</th>
<th>MED</th>
<th>SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>50mg</td>
<td>40mg</td>
<td>1.25</td>
</tr>
<tr>
<td>Benadryl®</td>
<td>25mg</td>
<td>75mg</td>
<td>0.33</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>10mg</td>
<td>10mg</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Total SDD</strong></td>
<td></td>
<td></td>
<td><strong>2.58</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>TDD</th>
<th>MED</th>
<th>SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>50mg</td>
<td>10mg</td>
<td>5.00</td>
</tr>
<tr>
<td>Benadryl®</td>
<td>25mg</td>
<td>50mg</td>
<td>0.50</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>10mg</td>
<td>5mg</td>
<td>2.00</td>
</tr>
<tr>
<td><strong>Total SDD</strong></td>
<td></td>
<td></td>
<td><strong>7.50</strong></td>
</tr>
</tbody>
</table>
Prevalence of Any AC Use Among Year 1 HABC Study Participants (n=3,055)

Summary

• Three-fold difference in overall prevalence detected between 5 scales

• Only moderate pairwise concordance among weighted and SDD scales

• For clinically-relevant outcomes, scales may not be interchangeable
Objectives

1. Discuss the adverse effects and epidemiology of anticholinergic (AC) use in older adults

2. Discuss the challenges in measuring overall AC medication burden

3. Describe a study evaluating AC use and dementia risk

4. List possible alternatives to anticholinergic medications
Cumulative Use of Strong Anticholinergics and Incident Dementia
A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanlon, PharmD, MS; Rebecca Hubbard, PhD; Rod Walker, MS; Onchee Yu, MS; Paul K. Crane, MD, MPH; Eric B. Larson, MD, MPH

Background & Objective

• AC medications are associated with cognitive effects that are thought to be reversible at discontinuation

• Cumulative use of AC drugs may lead to pathologic changes in cerebral white matter

• Observational studies suggest AC agents may result in sustained cognitive deficits, but these studies have a number of limitations

• Examine relation of 10-year cumulative use of anticholinergic medications with risk of dementia and Alzheimer’s disease

Study Population

• Adults age 65+, community-dwelling and dementia-free at baseline

• This analysis required:
  – 10+ years Group Health enrollment prior to ACT study entry
  – At least one follow-up visit

• N=3434
Dementia Outcomes

• Participants screened every 2 years
  – Abnormal screen prompted dementia evaluation

• Multidisciplinary committee assigned diagnoses using research criteria

Exposure Ascertainment

- Computerized pharmacy data
- Focused on highly-AC agents (i.e., SAMS)
  - Calculated SDD for each AC medication
  - SDD summed across all fills x 10 years to yield cumulative Total Standardized Dose (TSD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>TDD</th>
<th>MED</th>
<th>SDD</th>
<th>Days</th>
<th>TSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>10mg</td>
<td>10mg</td>
<td>1.00</td>
<td>730</td>
<td>730.0</td>
</tr>
<tr>
<td>Benadryl®</td>
<td>25mg</td>
<td>50mg</td>
<td>0.50</td>
<td>120</td>
<td>60.0</td>
</tr>
<tr>
<td>Cumulative TSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>790.0</td>
</tr>
</tbody>
</table>

- Categorized based on 10-year cumulative risk (5 categories)

10-year Cumulative Exposure

- Excluded most recent 1 year because of possible prodromal symptoms
- Time varying: moves forward in time

Covariates

- Self-rated health
- Comorbidities
  - Hypertension (Med)
  - Diabetes (Med)
  - Stroke (Med & SR)*
  - Heart disease (SR)*
  - Parkinson’s disease (SR)
  - Depressive symptoms (CED)*
- Health status
  - Body mass index
  - Smoking status
- Demographics
  - Age at entry
  - Sex
  - Education
  - Exercise
- Medications
  - Benzodiazepine use* (proxy measure for sleep or anxiety)

*Time varying variable

Statistical Analysis

• Multivariable Cox regression models with age as the time scale

• Censored if died, withdrew from ACT, or disenrolled from GH

• Examined interaction with age at entry, sex and \textit{APOE} ε4
RESULTS
## Select Baseline Participant Characteristics \( (n=3,434) \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>% or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>74 (70 – 80)</td>
</tr>
<tr>
<td>Male</td>
<td>40</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>72</td>
</tr>
<tr>
<td><strong>Health Status</strong></td>
<td></td>
</tr>
<tr>
<td>Fair or poor self-rated health</td>
<td>16</td>
</tr>
<tr>
<td>Heart disease</td>
<td>18</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>6</td>
</tr>
<tr>
<td>High depressive symptoms</td>
<td>10</td>
</tr>
<tr>
<td>Developed dementia*</td>
<td>23</td>
</tr>
</tbody>
</table>

*637 (79.9%) dementia cases were Alzheimer’s disease*
## Summary of Anticholinergic Use

<table>
<thead>
<tr>
<th>AC Medication Class</th>
<th>% of all TSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>63%</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>17%</td>
</tr>
<tr>
<td>GU antispasmodics</td>
<td>11%</td>
</tr>
<tr>
<td>GI antispasmodics</td>
<td>5%</td>
</tr>
<tr>
<td>Antivertigo/antiemetics</td>
<td>2%</td>
</tr>
</tbody>
</table>

91%

<table>
<thead>
<tr>
<th>TSD Category</th>
<th>Dementia HR (95% CI)</th>
<th>AD HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1-90</td>
<td>0.92 (0.74-1.16)</td>
<td>0.95 (0.74-1.23)</td>
</tr>
<tr>
<td>91-365</td>
<td>1.19 (0.94-1.51)</td>
<td>1.15 (0.88-1.51)</td>
</tr>
<tr>
<td>366-1095</td>
<td>1.23 (0.94-1.62)</td>
<td>1.30 (0.96-1.76)</td>
</tr>
<tr>
<td>&gt; 1095</td>
<td>1.54 (1.21-1.96)</td>
<td>1.63 (1.24-2.14)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Cumulative Use (TSD)</td>
<td>Dementia HR (95% CI)</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>1-365</td>
<td>1.12 (0.92-1.36)</td>
</tr>
<tr>
<td></td>
<td>366-1095</td>
<td>1.49 (1.12-1.98)</td>
</tr>
<tr>
<td></td>
<td>&gt; 1095</td>
<td>1.29 (1.01-1.65)</td>
</tr>
<tr>
<td>Other AC classes</td>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>1-365</td>
<td>0.98 (0.92-1.18)</td>
</tr>
<tr>
<td></td>
<td>366-1095</td>
<td>1.19 (0.90-1.58)</td>
</tr>
<tr>
<td></td>
<td>&gt; 1095</td>
<td>1.31 (1.00-1.72)</td>
</tr>
</tbody>
</table>

Strengths & Limitations

**STRENGTHS**
- Able to characterize medication use 10 years prior to study entry
- Lag time to account for possible protopathic bias
- Large community-based sample with prolonged follow-up

**LIMITATIONS**
- No gold standard for defining AC medications
- Potential misclassification related to OTC use
- Possible residual confounding (i.e., by indication)

Conclusions

• High use of AC medications was associated with increased dementia risk

• Provides support for current recommendations to limit AC exposure when possible

• Exploration of association between AC medications and neuropathology may enhance understanding of results
“I have been using 1-2 tablets of benadryl a night for sleep for the past 12 years. I have tried to stop but I am unable to sleep without taking this medicine. Should I go to my doctor and be evaluated for dementia?”
Implications for Patients?

• How to explain risk (e.g. HR of 1.63) in lay terms?

• In terms of the risk, we found that this level of use (e.g. greater than 50 mg of benadryl daily for 3 years) was associated with a 10 percentage point increase in the probability that an exposed person will experience dementia onset before an unexposed person.
Another question.....

• “....my 12 year daughter suffers from very severe irritable bowel syndrome, to the point it is really impacting her ability to enjoy life, and her doctor is recommending amitriptyline to help relieve the symptoms. We have tried multiple diets in hopes to avoid resorting to medication, but with little luck. If my daughter takes this medication, and it works, she may be on it for years. If she stops as a young adult, based on your research, will the increased risk remain?”
Advice for Patients

• Discuss concerns (risk versus benefit) of AC medication use with their health care provider.
• Many medications—including some available OTC, such as sleep aids—have strong anticholinergic effects.
• Ask pharmacist and prescribers about how to avoid OTC medications with strong anticholinergic effects.
• Inform health care providers of all OTC use so that they can account for all anticholinergic medications and advise on how to reduce use if possible.
Implications for Healthcare Providers

• Perform thorough medication history, including OTC use (sleep aids).
• Routinely look for opportunities to reduce AC medication burden.
• Select alternative treatments to AC medications when initiating new therapy.
Studies have yielded conflicting results with AC medications and falls risk

- Women’s Health Initiative
- Prospective cohort study of 61,451 women over 65 y
- AC use was associated with multiple falls (OR 1.51; 95% CI, 1.43-1.60).
- Women using multiple AC drugs had a 100% increase in likelihood of multiple falls (OR 2.00, 95% CI 1.73-2.32).

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Common Reactions to Presentations about Potentially Inappropriate Medication Use
Beatrice is a 68 year old female who is frail due to multiple medical conditions including overactive bladder, depression, heart disease, diabetes and osteoporosis. She has great difficulty with ADLs and medication management.

She takes...

- Aspirin 81 mg daily
- Hydrochlorothiazide 25 mg daily
- Lisinopril 40 mg daily
- Metoprolol 50 mg BID
- Pravastatin 40 mg daily
- Glipizide 10 mg daily
- Metformin 500 mg twice daily
- Tolterodine 2 mg twice daily
- Calcium 1,000 mg daily
- Vitamin D 800 IU daily
- Glucosamine/chondroitin TID
- Advil PM at bedtime as needed
Non-pharmacologic Options are Key

<table>
<thead>
<tr>
<th>Condition</th>
<th>AC Drug</th>
<th>Nonpharm Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior Issues</td>
<td>Antipsychotics</td>
<td>Massage/touch or music therapy</td>
</tr>
<tr>
<td>Depression</td>
<td>TCA, paroxetine</td>
<td>CBT</td>
</tr>
<tr>
<td>Pain</td>
<td>TCA</td>
<td>PENS, TENS, acupuncture, CBT</td>
</tr>
<tr>
<td>Sleep</td>
<td>Antihistamines</td>
<td>Sleep Hygiene, exercise</td>
</tr>
</tbody>
</table>

## Alternatives for High-Risk AC Medications in the Elderly (NCQA HEDIS Criteria)

<table>
<thead>
<tr>
<th>Condition</th>
<th>AC Drug(s)</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Disopyramide</td>
<td>Diltiazem (rate control)</td>
</tr>
<tr>
<td>Allergies</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; gen antihistamines</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; gen antihistamines Nasal steroids Leukotriene inhibitors</td>
</tr>
<tr>
<td>Depression</td>
<td>TCAs, paroxetine</td>
<td>SSRI/SNRI</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>TCAs</td>
<td>SNRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsaicin topical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lidocaine patch</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Benztropine, trihexyphenidyl</td>
<td>Carbidopa/levodopa</td>
</tr>
<tr>
<td>Acute back spasm</td>
<td>Cyclobenzaprine, Orphenadrine</td>
<td>Acetaminophen Non-acetylated salicylate NSAID</td>
</tr>
</tbody>
</table>
Questions?

A special thanks to Jennifer Naples, PharmD and Joe Hanlon, PharmD, MS for their contribution to this slideset.