Unintended consequences of drug therapy in older adults: Cognitive and functional effects of anticholinergics

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Section of Gerontology and Geriatric Medicine
Learners will be able to:

1. Identify 5 medications with anticholinergic properties
2. Describe the impact anticholinergic medications have on cognitive function acutely and chronically
3. Describe the impact of anticholinergic burden on physical function
4. Give 2 examples of therapeutic substitutions for anticholinergics

I have no conflicts of interest to report
Why should you care?

- Growing numbers of old people

Number of people age 65 and over, by age group, selected years 1900–2006 and projected 2010–2050

Note: Data for 2010–2050 are projections of the population.
Reference population: These data refer to the resident population.
Why should you care?

- Old people use disproportionate amount of health care
  - 25% of outpatient visits
  - >30% of admitted patients

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Proportion over age 65 in FY 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology/Oncology</td>
<td>31.5%</td>
</tr>
<tr>
<td>IM/Hospitalist</td>
<td>33.4%</td>
</tr>
<tr>
<td>Nephrology</td>
<td>35.7%</td>
</tr>
<tr>
<td>Pulmonary/Critical Care</td>
<td>37.4%</td>
</tr>
<tr>
<td>Cardiology</td>
<td>44.2%</td>
</tr>
</tbody>
</table>
>50% of admissions will be elderly in the next 20 years
Why should you care?

- Up to 50% of older adults are taking one or more anticholinergic medications
- Anticholinergics are everywhere (lots of drugs with anticholinergic properties)
- Bad things happen to old people who take anticholinergics
  - Acutely
  - Possibly chronically

Mulsant B, et all. Arch Gen Pysch. 2003
79-y.o. woman with PMH of hypertension, irritable bowel syndrome, anxiety, CVA in 2000, chronic back pain, and dementia.

Presents to ED from home after several weeks of worsening generalized weakness, fatigue, poor p.o. intake, and confusion. Over the last several weeks she has had fairly rapid progressive changes in mental status including general confusion, hallucinations, and agitation as well as increased sleepiness, worsening disinterest in daily activities, and recent falls.

amitryptiline recently started for depression.

ROS: + for constipation, dry mouth, headache; negative for fever, SOB, chest pain.
Medications on Admission

- DONEPEZIL 10 MG once a day
- MEMANTINE 10 MG two times a day
- ALPRAZOLAM 0.5 MG three times a day
- AMITRIPTILINE 50 MG QHS
- BUPROPION HCL 100 MG once a day
- ESCITALOPRAM (LEXAPRO) 20 MG at bedtime
- DICLOFENAC SODIUM 75 MG two times a day
- ACETAMINOPHEN 650 MG CR
- TYLENOL PM EXTRA STRENGTH TABS at bedtime as needed as directed
- OXYCODONE-ACETAMINOPHEN 10-650 MG two times a day
- TRAMADOL 50 MG as needed
- RAMIPRIL 10 MG two times a day
- LOSARTAN -HCTZ 100-12.5 MG once a day
- CLOPIDOGREL 75 MG once a day
- GLYCOPPYRROLATE 2 MG two times a day
- PENTOSAN POLYSULFATE SODIUM (ELMIRON) 200 MG twice a day
- IBANDRONATE (BONIVA) 150 MG once a month
- CALCIUM 600+D once a day
- MVI, VITAMIN B-12 once a day
Exam and Data

Exam

- T 98, BP 180/97, HR 72, RR 18, and O2 sat 93% on RA
- Patient is in no distress and is oriented to person, place, and year. No remarkable findings x dry membranes.
- MMSE 22/30 (-2 orientation, -3 recall, -1 conc, -1 pentagons, -1 sentence)

Labs: unremarkable, UA normal except SG 1.026

Imaging: CXR no pneumonia; Head CT: “No acute intracranial disease”

Admitted with Delirium, likely due to medications
What are anticholinergic medications?
Anticholinergics compete for binding at muscarinic or nicotinic cholinergic receptors
- Used as bowel and bladder antispasmodics
- To dry secretions
- To combat allergies

“Mad as a Hatter, Dry as a Bone, Red as a Beet, Blind as a Bat, Hot as a Hare”

ABCDs of anticholinergic side effects:
- Anorexia
- Blurry vision
- Constipation/ Confusion
- Dry mouth
- Sedation/ Stasis of urine
Acetylcholine (Ach) is an excitatory neurotransmitter found in both the central and peripheral nervous systems.

Integral to memory function.

Early loss of cholinergic neurons in patients with Alzheimer’s.
Acetylcholinesterase inhibitors increase acetylcholine in the synapse by preventing degradation of acetylcholine.
Acute effects of Anticholinergics on Cognition

The More I Think
The More Confused I Get
Scopolamine (0.4 mg) Reduces Hippocampal Activation During a Face-Name Memory Task

Similar reductions seen in the medial fusiform gyrus and inferior prefrontal cortex

Scopolamine effects on memory worse in older than young adults

**Selective Reminding Test Performance**

- Increased permeability of blood brain barrier
- Aging related loss of cholinergic neurons
- Changes in hepatic and renal clearance
- Changes in distribution of drugs

Terry and Buccafusco. J Pharm Experimental Ther. 2003
Cognitive and other Adverse Effects of Diphenhydramine Use in Hospitalized Older Patients

- 426 consecutive medical admissions in patients ≥70 yrs
- No baseline delirium or profound dementia

- 27% (n= 114) received diphenhydramine while hospitalized
  - Similar in demographics, comorbidities, baseline MMSE to those who did not get benadryl
- RR of delirium sx 1.7 (95% CI 1.3-2.3)
- Median length of stay 7 vs 6 days (p=0.009)
- Dose response relationship
- Inappropriate use in 24% of patients

- Atropine, scopolamine, diphenhydramine, amitryptiline...
Many drugs not thought to be “anticholinergic” do have anticholinergic activity (e.g., digoxin, diltiazem)

Older adults are at high risk of anticholinergic burden due to multiple drug therapy
Measuring Anticholinergic Activity

Solution + radio-labeled QNB
quinuclidinyl benzilate

Rat Brain Striatal membrane

Anticholinergic activity = amount QNB displaced from receptors by “sample” compared to amount of QNB displaced by a standard concentration of atropine.

Tune L and Coyle J. Arch Gen Psychiatry. 1980
Participants more likely to have low MMSE with higher serum anticholinergic activity

<table>
<thead>
<tr>
<th>Participants (%)</th>
<th>SAA Level</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>&lt;2.80 pmol/ mL</td>
<td>7.6%</td>
</tr>
<tr>
<td></td>
<td>≥2.80 pmol/ mL</td>
<td>28.6%</td>
</tr>
</tbody>
</table>

Serum Anticholinergic Activity associated with greater delirium risk and severity

67 Medical inpatients 75+ years old

Quintile 1=0–0.23; Q2=0.24–0.42; Q3=0.43–0.88; Q4=0.89–1.46; Q5=1.47–5.07 in nM atropine equivalents per 200-µL sample

Couple of different published lists
- “Short List”\(^1\): contains 52 drugs
  - Based on expert consensus
- “Long List”\(^2\): contains 117 drugs
  - Based on serum anticholinergic activity
- Drugs classified from 0 = not anticholinergic to 3 = highly anticholinergic

Anticholinergic Burden Scores

- Mildly anticholinergic = 1
  - Furosemide
  - Dilitiazem
- Moderately anticholinergic = 2
  - Cimetidine
  - Carbamazepine
- Highly anticholinergic = 3
  - Amitryptiline
  - Diphenhydramine
  - Diazepam
  - Paroxetine
  - Ranitidine
  - Oxybutynin
  - Tolterodine

Which of her medications are anticholinergic?

- DONEPEZIL 10 MG once a day
- MEMANTINE 10 MG two times a day
- ALPRAZOLAM 0.5 MG three times a day
- AMITRYPTILINE 50 MG QHS
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- IBANDRONATE (BONIVA) 150 MG once a month
<table>
<thead>
<tr>
<th>Medicine</th>
<th>ABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPRAZOLAM</td>
<td>1</td>
</tr>
<tr>
<td>AMITRYPTILINE</td>
<td>3</td>
</tr>
<tr>
<td>BUPROPION*</td>
<td>(1)</td>
</tr>
<tr>
<td>DIPHENHYDRAMINE</td>
<td>3</td>
</tr>
<tr>
<td>GLYCOPYPYRRROLATE^</td>
<td>(3)</td>
</tr>
<tr>
<td>Total Anticholinergic Burden</td>
<td>7-11</td>
</tr>
</tbody>
</table>

*Conflicting data; ^less likely to cross blood-brain barrier
Literature Review: 11/13 studies examining the relationship between anticholinergic burden and acute changes in cognition, including delirium, were positive.
Chronic Effects of Anticholinergics on Cognition
How might anticholinergics have chronic effects on cognition?
Dicyclomine exacerbates A-beta pathology in transgenic mice

Muscarinic Receptors are involved in APP processing

Klausner and Steers. Curr Urology Reports. 2007
Chronic Effects of Anticholinergics on Cognition

Autopsy data from 54 patients with Parkinson’s Disease by use of anticholinergics

Chronic anticholinergic use may increase Alzheimer’s pathology

Anticholinergics associated with incident MCI

- Longitudinal cohort study of 372 people >60 yo, free of dementia
- 14% were taking an anticholinergic drug
- Persistent users more likely to be diagnosed with MCI. Adjusted OR 5.12 (95% CI 1.94-13.5)
- No difference in dementia risk at 8 yrs

A look at our own data

- ~7500 women ≥65 years old enrolled in the Women's Health Initiative Memory Study (WHIMS)

- Determine the cumulative effects of anticholinergic drugs ("anticholinergic burden") on
  - trajectories of cognitive decline
  - the development of mild cognitive impairment (MCI) or dementia
WHIMS: Multi-center RCT of Estrogen (+ progestin) vs Placebo. Participants were free of dementia at baseline.

- Trial was stopped early due to unfavorable risk:benefit ratio on CVD
- Mean on-trial f/u 4.4 yrs (range 0-8)

Predictor: Anticholinergic exposure (y/n) and ABS

- Medication data was collected at baseline, year 1, 3, and 6
33% of WHIMS participants taking Anticholinergic medications at baseline
## Most Commonly Used Anticholinergics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamterene</td>
<td>1</td>
<td>11.6</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>3</td>
<td>8.5</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>1</td>
<td>6.2</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>1</td>
<td>5.9</td>
</tr>
<tr>
<td>Furosemide</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>2</td>
<td>4.0</td>
</tr>
</tbody>
</table>
### Strongest Correlates of Anticholinergic Use*

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (no)</td>
<td>0.53 (0.47-0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF (no)</td>
<td>0.32 (0.2-0.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td># Non-Anticholinergic meds</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-2 (vs &gt;6)</td>
<td>0.27 (0.21-0.34)</td>
<td></td>
</tr>
<tr>
<td>2-4 (vs &gt;6)</td>
<td>0.53 (0.41-0.68)</td>
<td></td>
</tr>
<tr>
<td>Self Reported Health</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Excellent (vs fair/poor)</td>
<td>0.28 (0.21-0.36)</td>
<td></td>
</tr>
</tbody>
</table>

- Also physical activity, race, CVD, hysterectomy

* Based on stepwise logistic regression
Mean 3MS scores over time by current AC *

- **Solid Line**: No AC Use
- **Dashed Line**: AC Use

* p<0.001

* adjusted for age and HT assignment
Anticholinergic Users at Greater Risk of Incident Cognitive Impairment

Time until MCI/PD

- No AC Use
- AC Use

\[ p = 0.03 \]
\[ HR = 1.27, \quad 95\% CI = [1.02, 1.59] \]
Conclusions

- In this population, the effects of anticholinergics on 3MS scores over time appear small.
- Baseline AC use is associated with greater risk of incident MCI/dementia:
  - Will need further adjustments for confounders.
  - Y/N predictor not likely to be as strong as a 3 level score predictor (0, 1, >=2).
3070 participants ≥75 years old and free of dementia at enrollment into the GEM Study

Aim: to determine the association between anticholinergic burden and

- Change in cognition over time (3MSE)
- Incident dementia

Participants followed q6 months for median 6 years.

- In clinic review of all medications
- Cognitive testing
## Results: Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>≥ 1 AC drug (N=1206)</th>
<th>No AC (N=1864)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age (yrs)</strong></td>
<td>78.8</td>
<td>78.5</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>50.8</td>
<td>43.2</td>
</tr>
<tr>
<td><strong>White (%)</strong></td>
<td>95.4</td>
<td>95.6</td>
</tr>
<tr>
<td><strong>Education ≥ 12 yrs (%)</strong></td>
<td>88.6</td>
<td>89.2</td>
</tr>
<tr>
<td><strong>HTN (%)</strong></td>
<td>59.5</td>
<td>50.8</td>
</tr>
<tr>
<td><strong>Mean 3MSE score</strong></td>
<td>93.1</td>
<td>93.5</td>
</tr>
<tr>
<td><strong>Self-reported health ≥ good</strong></td>
<td>88.6</td>
<td>96.0</td>
</tr>
<tr>
<td><strong>Mean number of medications</strong></td>
<td>8.9</td>
<td>6.1</td>
</tr>
</tbody>
</table>
Anticholinergic Use Increased Over Time

% of participants taking at least one anticholinergic

Visit Number

% of People
Anticholinergic burden NOT associated with change in 3MS

Adjusted 3MSE scores over time by ABS

P=0.41

P=0.09 difference between groups
## Anticholinergic Burden associated with increased risk of dementia

<table>
<thead>
<tr>
<th>Score</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>score = 0</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>score = 1</td>
<td>1.16</td>
<td>(0.91 – 1.48)</td>
</tr>
<tr>
<td>score &gt; 1</td>
<td>1.52</td>
<td>(1.20 – 1.93)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, education, alcohol use, body mass index, hypertension status, self-reported health status, and number of non-anticholinergic drugs.
Conclusions About Cognition

- Anticholinergic medications have acute effects on cognition in older adults
- Chronic use of anticholinergics may increase risk of cognitive impairment or dementia
- 3MSE is not very sensitive to change in populations of healthy older adults
Anticholinergics and physical Function
The use of anticholinergic drugs has been associated with lower muscle strength and poorer reaction time in older adults.

- Possibly related to central effects on psychomotor slowing, +/- peripheral side effects

Anticholinergic burden associated with falls in older psychiatric inpatients

- Mean Anticholinergic Burden of fallers 3.7 vs 2.1 for non-fallers (p<0.05)

Evaluation of Longitudinal changes in function

- Use GEMS population of >3000 participants 75 years and older, followed for 6 years

- To determine the association between anticholinergic burden and function
  - Self-reported (ADL and IADL)
  - Performance-based (gait speed)
Methods: Outcomes

- Incident Dependency in ≥1 ADL
  - eating, dressing, bathing, toileting, transferring, household ambulation
- Incident Dependency in ≥1 IADL
  - Meal preparation, money management, telephone use, shopping, light housework, and medication management
- Gait Speed
  - Usual pace over 15 ft
Covariates considered

- age, sex, race, education, income, clinic site
- Alcohol intake, BMI, HTN
- Baseline cognitive function (3MSE)
- Number of non-anticholinergic medications
- Self-reported health
Analyses

- ABS calculated for each participant and categorized as 0, 1, 2+ based on distribution of scores
- The effect of ABS on
  - Time to incident dependency in ADL or IADL was assessed using unadjusted and adjusted Hazards regression models.
  - Gait speed was assessed using mixed effects linear regression modeling
    - Accounting for within-person correlation
  - All models stratified by baseline MCI/normal status
- ABS updated every visit
ABS $\geq 2$ associated with increased odds of being dependent in ADL and IADL at baseline

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>ADL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td>reference</td>
<td>1.0</td>
<td>reference</td>
</tr>
<tr>
<td>1</td>
<td>0.98</td>
<td>0.75-1.28</td>
<td>0.80</td>
<td>0.60-1.06</td>
</tr>
<tr>
<td>$\geq 2$</td>
<td>1.79</td>
<td>1.40-2.29</td>
<td>1.31</td>
<td>1.00-1.72</td>
</tr>
<tr>
<td>IADL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td>reference</td>
<td>1.0</td>
<td>reference</td>
</tr>
<tr>
<td>1</td>
<td>1.18</td>
<td>0.96-1.46</td>
<td>0.97</td>
<td>0.78-1.22</td>
</tr>
<tr>
<td>$\geq 2$</td>
<td>1.83</td>
<td>1.48-2.28</td>
<td>1.35</td>
<td>1.07-1.72</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, educ, etoh, bmi, htn, clinic, health, number of other meds

Sink K, et al. JAGS 2008; 56(4 suppl)
Incident Dependence in IADL

Incident IADL Disability by Baseline ABS
Baseline Normal

Cumulative Incidence of Disability

Adjusted HRs
0  1.0 (ref)
1  1.23 (1.06 – 1.42)
2+ 1.58 (1.37 – 1.82)
P<0.0001
How meaningful are these HRs?

Compared to a person with an ABS of 0,

- a person with an ABS of 1 is like being 3.2 years older at baseline
- a person with an ABS of 2 is like being 7.3 years older at baseline
Incident Dependence in ADL

Incident ADL Disability by Baseline ABS
Baseline Normal

ABS
- 0
- 1
- 2+

Cumulative Incidence of Disability

Adjusted HR
0 1.0 (ref)
1 1.16 (0.96 – 1.39)
2+ 1.56 (1.31 – 1.84)

P<0.0001
How meaningful are these HRs?

Compared to a person with an ABS of 0,

- a person with an ABS of 2 is like being 8.1 years older at baseline
ABS Associated with Slower Gait at baseline

<table>
<thead>
<tr>
<th>ABS</th>
<th>Mean walk speed * (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.89</td>
</tr>
<tr>
<td>1</td>
<td>0.88</td>
</tr>
<tr>
<td>2+</td>
<td>0.86</td>
</tr>
</tbody>
</table>

P value 0.02

*Adjusted for age, sex, educ, etoh, bmi, htn, clinic, health, number of other meds, height
Taking an anticholinergic is like aging 4 yrs

Change in Gait Speed

Time (years)

0 1 2 3 4 5 6

Age effect: 0.01 m/s/year
0→1 -0.041 m/s
0→2+ -0.043 m/s
P<0.001
Conclusions about function

- Anticholinergic burden is negatively associated with both self-reported and performance based function.

- Having an ABS of 2 or more was associated with risk of IADL and ADL dependency to the same magnitude as 7-8 years of age.

- Exposure to any level of anticholinergics is associated with slower gait speed, comparable to the effect of 4 years of aging.
Mrs. S. in Follow-up

- Follow up in Memory Assessment Clinic 1 month post D/C
- Family reports she is subjectively much better than she was immediately prior to admission, and probably better than she has been in 6-9 months. Still c/o apathy.

Selected Meds
- ALPRAZOLAM 0.5 MG Q2-3 hrs prn
- BUPROPION HCL 100 MG once a day
- ESCITALOPRAM (LEXAPRO) 20 MG at bedtime
- ACETAMINOPHEN 650 MG CR 2 tabs 3 times a day
- OXYCODONE 5 MG q6 hrs prn
- GLYCOPPYRROLATE 2 MG two times a day

- MMSE 21/30; GDS 1/15
Many drugs have anticholinergic properties

Older adults may have significant anticholinergic burden even if not on classically anticholinergic drugs

Older adults are more sensitive to cognitive effects of anticholinergics

- Mild decrease in cognition to frank delirium
- Before start someone on cholinesterase Inhibitor, d/c all possible anticholinergics
  - To see if cognition improves
  - To avoid irrational polypharmacy
- Chronic use may increase risk of dementia
- Effects on physical function (slower gait speed, falls, decline in ADL) less studied
What should you do?

- Critically review med lists on admission and at least annually in outpatient practice
- Assess efficacy of each med and discontinue if no longer needed
- Substitute for less anticholinergic alternatives
  - Diphenhydramine → nasal steroid, loratidine
  - Paroxetine → sertraline or citalopram
  - Cimetidine/ranitidine → PPI
  - Oxybutynin/tolterodine → timed voiding, darifenacin
Acknowledgements

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  - WFU: David Goff, MD, PhD; Jeff Williamson, MD, MHS; Mark Espeland, PhD; Hal Atkinson, MD; James Lovato, MS; Karen Oles, PharmD
  - Johns Hopkins: Michelle Carlson, PhD
  - U Pitt: Oscar Lopez, MD; Steve DeKosky
  - NCCAM: Richard Nahin, PhD

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  - Hartford Geriatrics Health Outcomes Scholars Award
  - Claude D. Pepper Older Adults Independence Center
  - Kulynych Center for Memory and Cognition Research
Anticholinergics may make delirium worse

Use of Medications with Anticholinergic Effect Predicts Clinical Severity of Delirium Symptoms in Older Medical Inpatients

- 278 medical inpatients with delirium (mean age 83)
- Medications were recorded daily and AC scores were calculated
- Delirium symptoms assessed at least q3 days
  - Altered attention
  - Disorientation
  - Disturbances in consciousness
  - Memory
  - Perception
  - Motor activity
- Increases in AC burden associated with increased delirium symptoms, even after controlling for confounders

Han et al. Arch Int Med. 2001