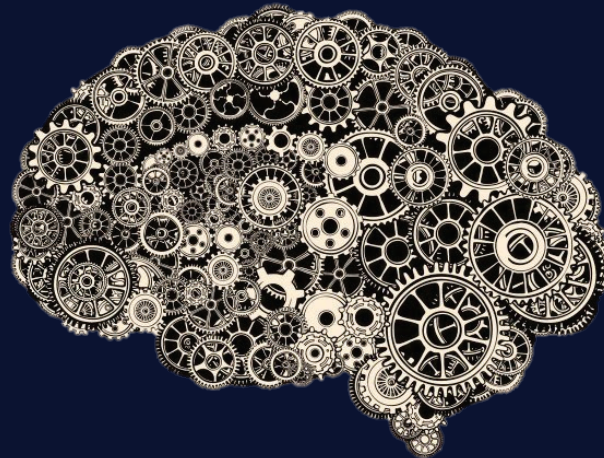


Anticholinergics and Risk of Dementia



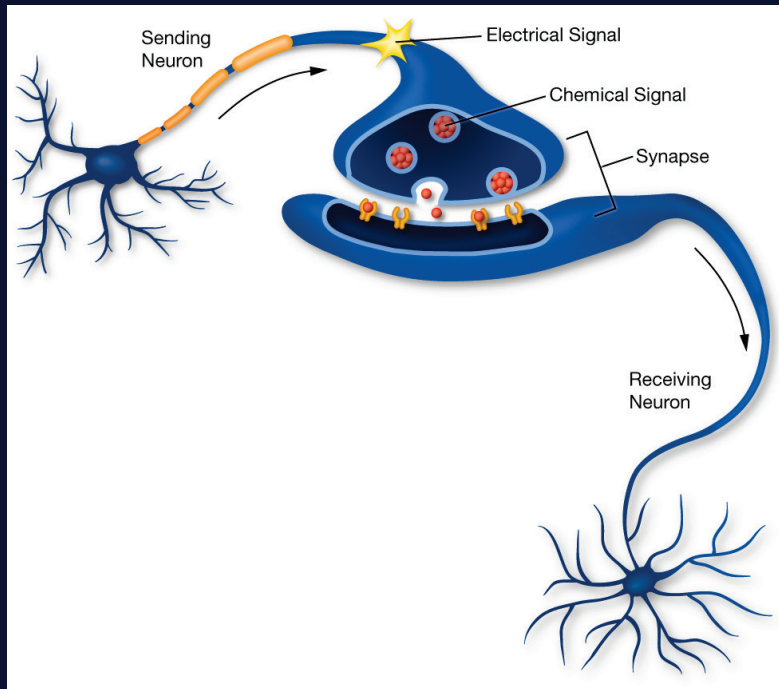
Shelly Gray, PharmD, MS
School of Pharmacy
University of Washington

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

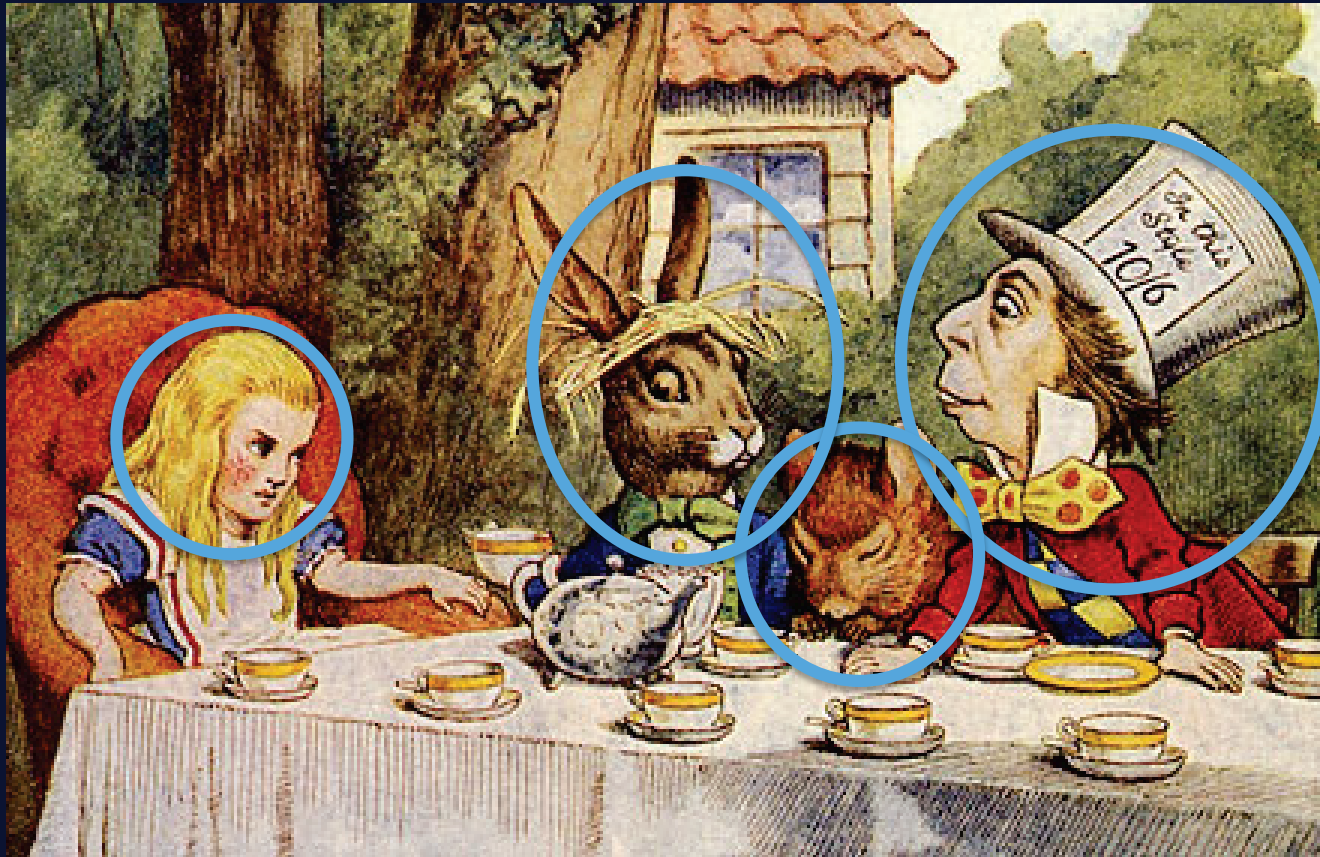
Anticholinergic Medications

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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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

<u>Class</u>	<u>Example Medications</u>
Antiarrhythmic	Disopyramide
Antihistamine (1 st gen)	Diphenhydramine, meclizine, hydroxyzine
Antiparkinson	Benztropine, trihexyphenidyl
Antipsychotics	Chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine
GI antispasmodic	Atropine, belladonna, clidinium
GU antispasmodics	Oxybutynin, solifenacin, tolterodine
Skeletal muscle relaxants	Cyclobenzaprine, orphenadrine
Antidepressants	Amitriptyline, desipramine, doxepin, paroxetine

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

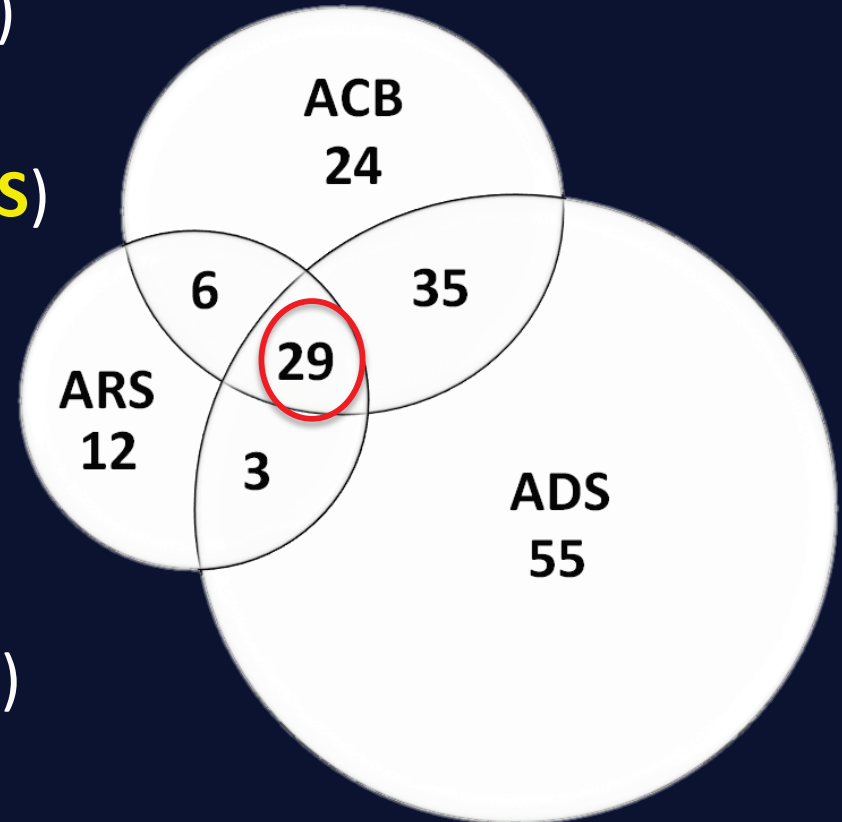
Universities of Pittsburgh, WA and UCSF; NIA; N.FL/S.GA VA GRECC

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

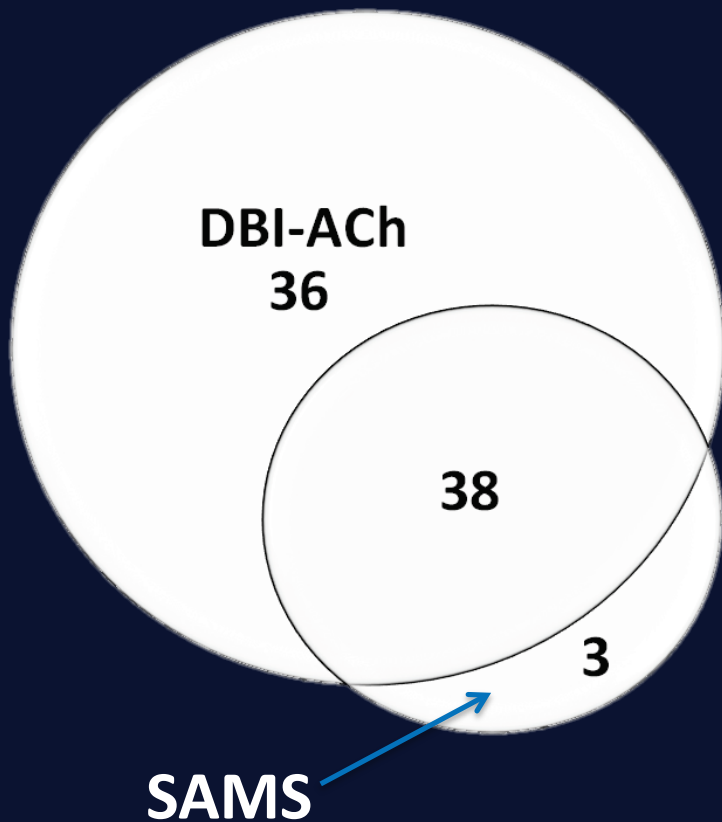
- Ranked from 1 (low) to 3 (high) AC activity
- Anticholinergic Drug Scale (**ADS**)
 - Original 2002, Updated 2014
- Anticholinergic Cognitive Burden Scale (**ACB**)
 - Original 2008, updated 2012
- Anticholinergic Risk Scale (**ARS**)
 - Original 2008



Example Calculation

<u>Drug</u>	<u>ADS</u>	<u>ACB</u>	<u>ARS</u>
Cimetidine	2	1	2
Paroxetine	2	3	1
Pramipexole	---	---	1
Total	4	4	4

Anticholinergic Scales Using Standardized Daily Doses (SDD)



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

Example Calculation

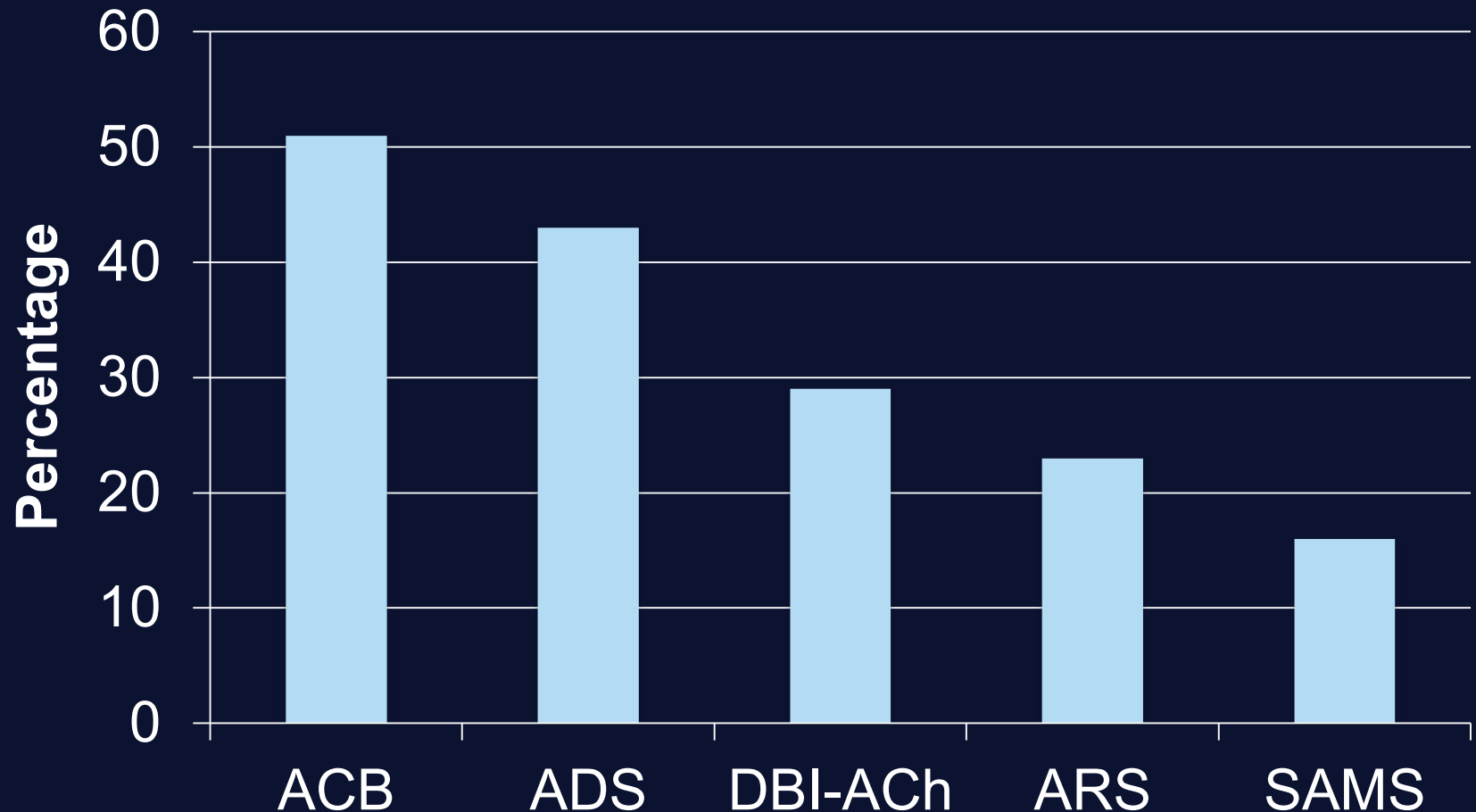
DBI-ACh

<u>Drug</u>	<u>TDD</u>	<u>MED</u>	<u>SDD</u>
Amitriptyline	50mg	40mg	1.25
Benadryl®	25mg	75mg	0.33
Oxybutynin	10mg	10mg	1.00
Total SDD			2.58

SAMS

<u>Drug</u>	<u>TDD</u>	<u>MED</u>	<u>SDD</u>
Amitriptyline	50mg	10mg	5.00
Benadryl®	25mg	50mg	0.50
Oxybutynin	10mg	5mg	2.00
Total SDD			7.50

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

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Original Investigation

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

JAMA Intern Med 2015; 175(3):401-407.

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

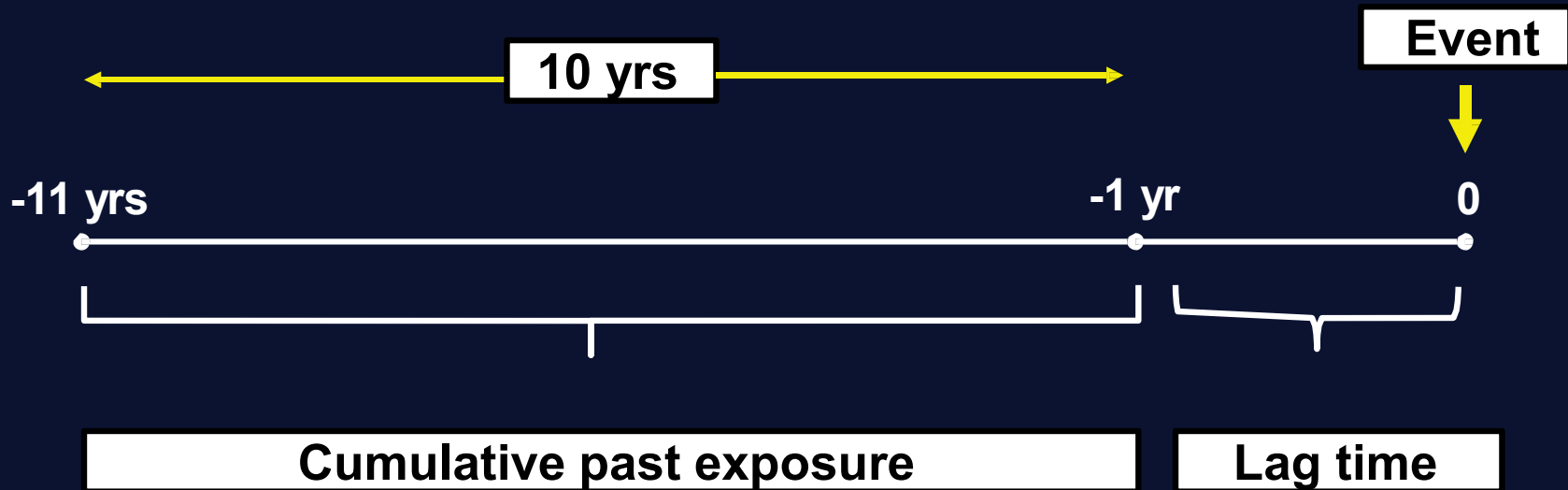
- Computerized pharmacy data
- Focused on highly-AC agents (i.e., SAMS)
 - Calculated SDD for each AC medication
 - SDD summed across all fills x 10 years to yield cumulative Total Standardized Dose (TSD)

<u>Drug</u>	<u>TDD</u>	<u>MED</u>	<u>SDD</u>	<u>Days</u>	<u>TSD</u>
Amitriptyline	10mg	10mg	1.00	730	730.0
Benadryl [®]	25mg	50mg	0.50	120	60.0
CumulativeTSD					790.0

- 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 *APOE* $\epsilon 4$

RESULTS

Select Baseline Participant Characteristics (n=3,434)

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

*637 (79.9%) dementia cases were Alzheimer's disease

Summary of Anticholinergic Use

<u>AC Medication Class</u>	<u>% of all TSD</u>	
Antidepressants	63%	} 91%
Antihistamines	17%	
GU antispasmodics	11%	
GI antispasmodics	5%	
Antivertigo/antiemetics	2%	

AC Exposure and Risk of Incident Dementia and Alzheimer's Disease (AD)

TSD Category	Dementia HR (95% CI)	AD HR (95% CI)
0	<i>Reference</i>	<i>Reference</i>
1-90	0.92 (0.74-1.16)	0.95 (0.74-1.23)
91-365	1.19 (0.94-1.51)	1.15 (0.88-1.51)
366-1095	1.23 (0.94-1.62)	1.30 (0.96-1.76)
> 1095	1.54 (1.21-1.96)	1.63 (1.24-2.14)

Sensitivity Analysis: Anticholinergic Medication Classes

Cumulative Use (TSD)	Dementia HR (95% CI)
Antidepressants	
0	<i>Reference</i>
1-365	1.12 (0.92-1.36)
366-1095	1.49 (1.12-1.98)
> 1095	1.29 (1.01-1.65)
Other AC classes	
0	<i>Reference</i>
1-365	0.98 (0.92-1.18)
366-1095	1.19 (0.90-1.58)
> 1095	1.31 (1.00-1.72)

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

Question from a 68 year old woman...

“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.

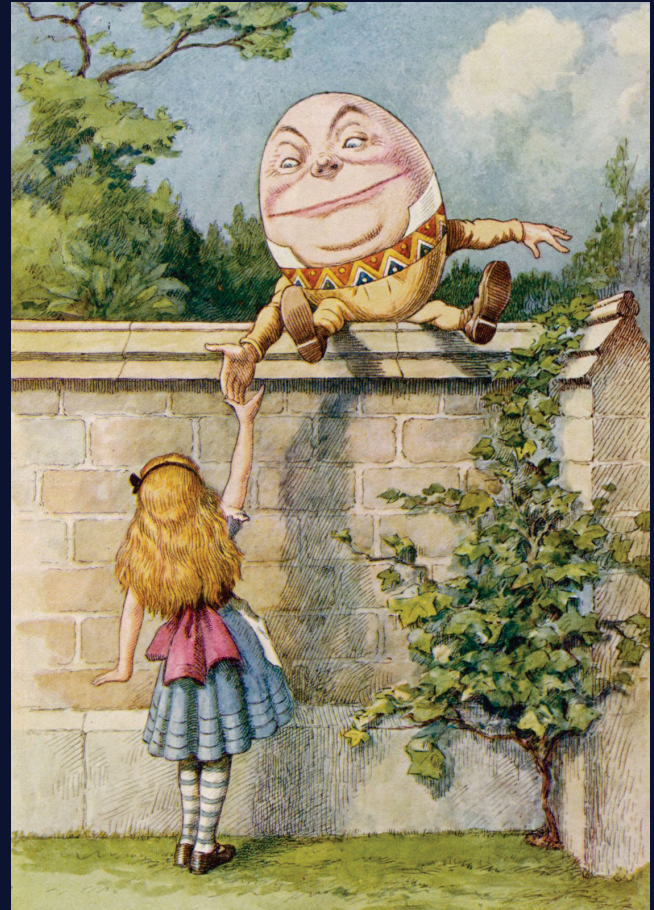
Implications for Healthcare Providers

- 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).

Marcum Z, Wirtz H, Pettinger M, LaCroix A, Carnahan R, Cauley J, Bea J, Gray SL (under prep)



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Common Reactions to Presentations about Potentially Inappropriate Medication Use

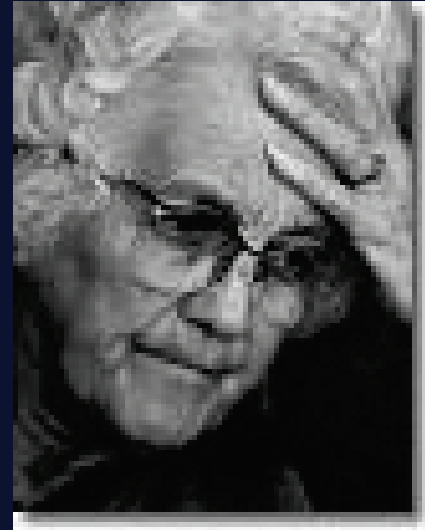


Me

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

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

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

Condition	AC Drug(s)	Alternative
Atrial fibrillation	Disopyramide	Diltiazem (<i>rate control</i>)
Allergies	1 st gen antihistamines	2 nd gen antihistamines Nasal steroids Leukotriene inhibitors
Depression	TCAs, paroxetine	SSRI/SNRI
Neuropathic pain	TCAs	SNRI Gabapentin Capsaicin topical Lidocaine patch
Parkinson's disease	Benzotropine Trihexyphenidyl	Carbidopa/levodopa
Acute back spasm	Cyclobenzaprine Orphenadrine	Acetaminophen Non-acetylated salicylate NSAID

Questions?

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

