Quality of life in frail and elderly patients – watch the anticholinergic burden

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Statement of interest

Financial:

Either I or my institution has received funding for research, consultancy or speaker honoraria from:

Astellas Pharma

Essity AB

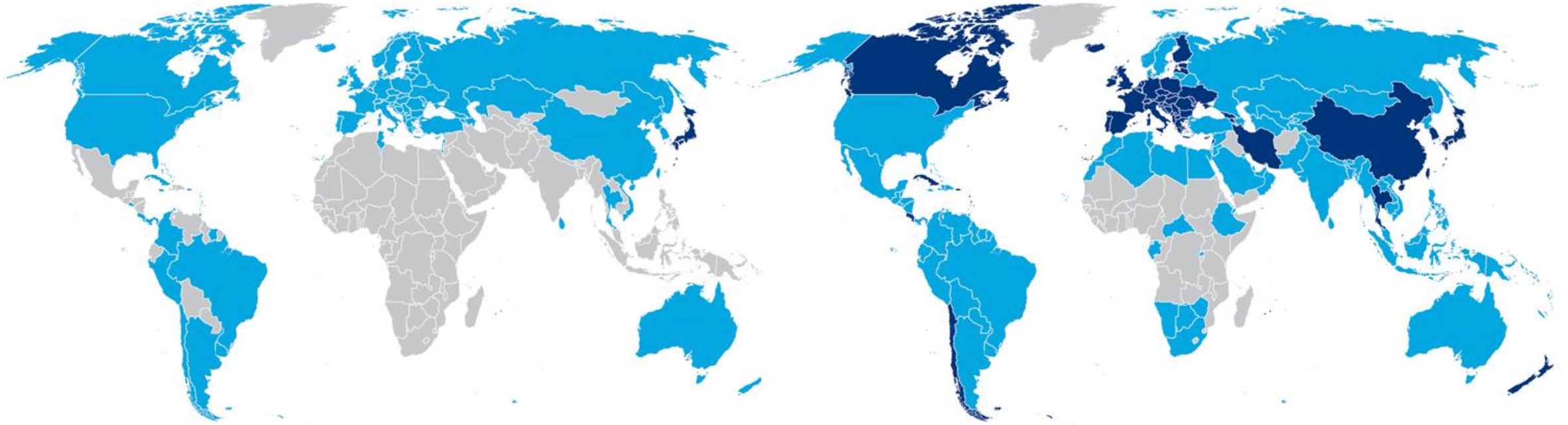
Pfizer Corp

Non-financial:

I am President of the Canadian Continence Foundation

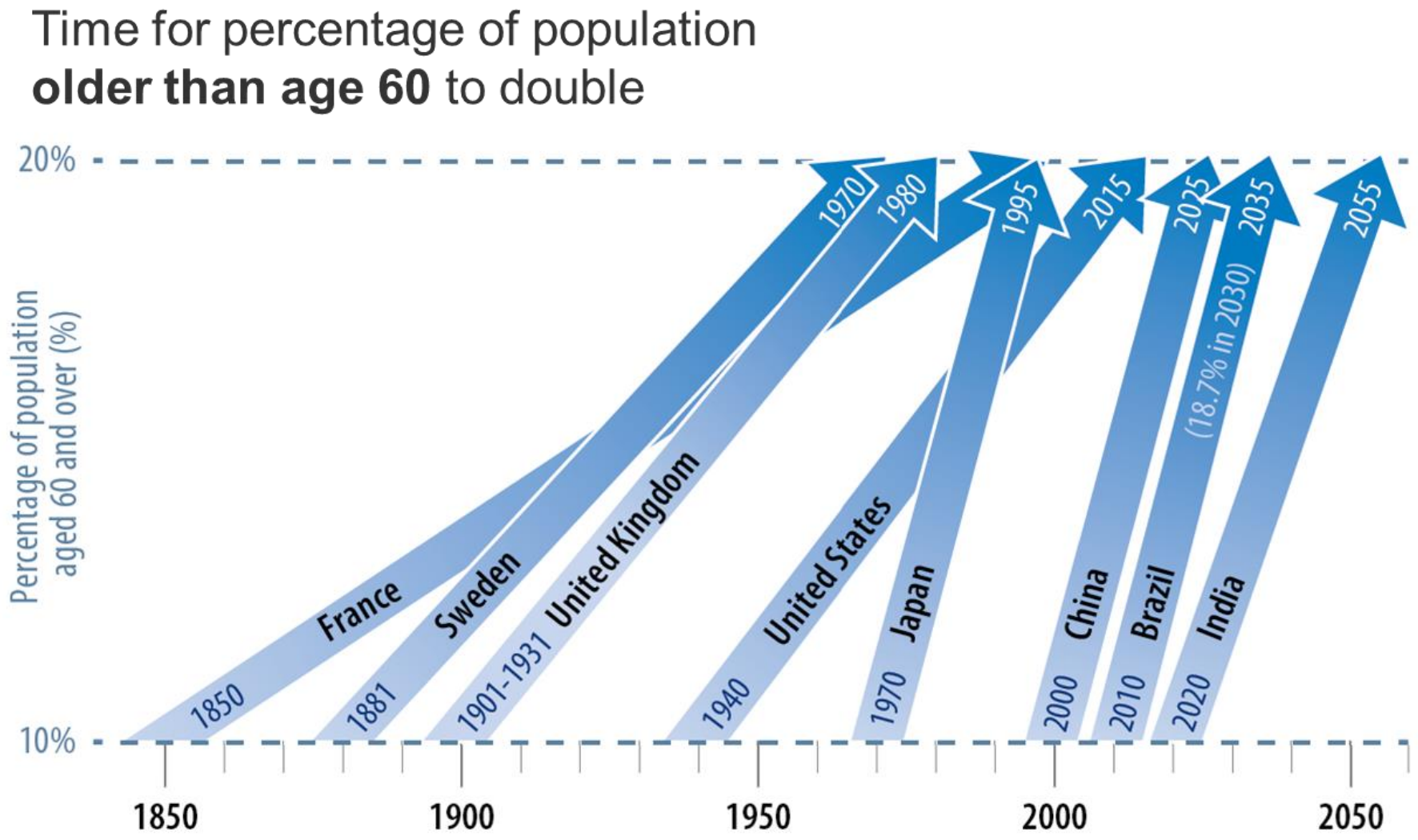
I am Co – Chair of the International Consultation on Incontinence

Populations are getting older



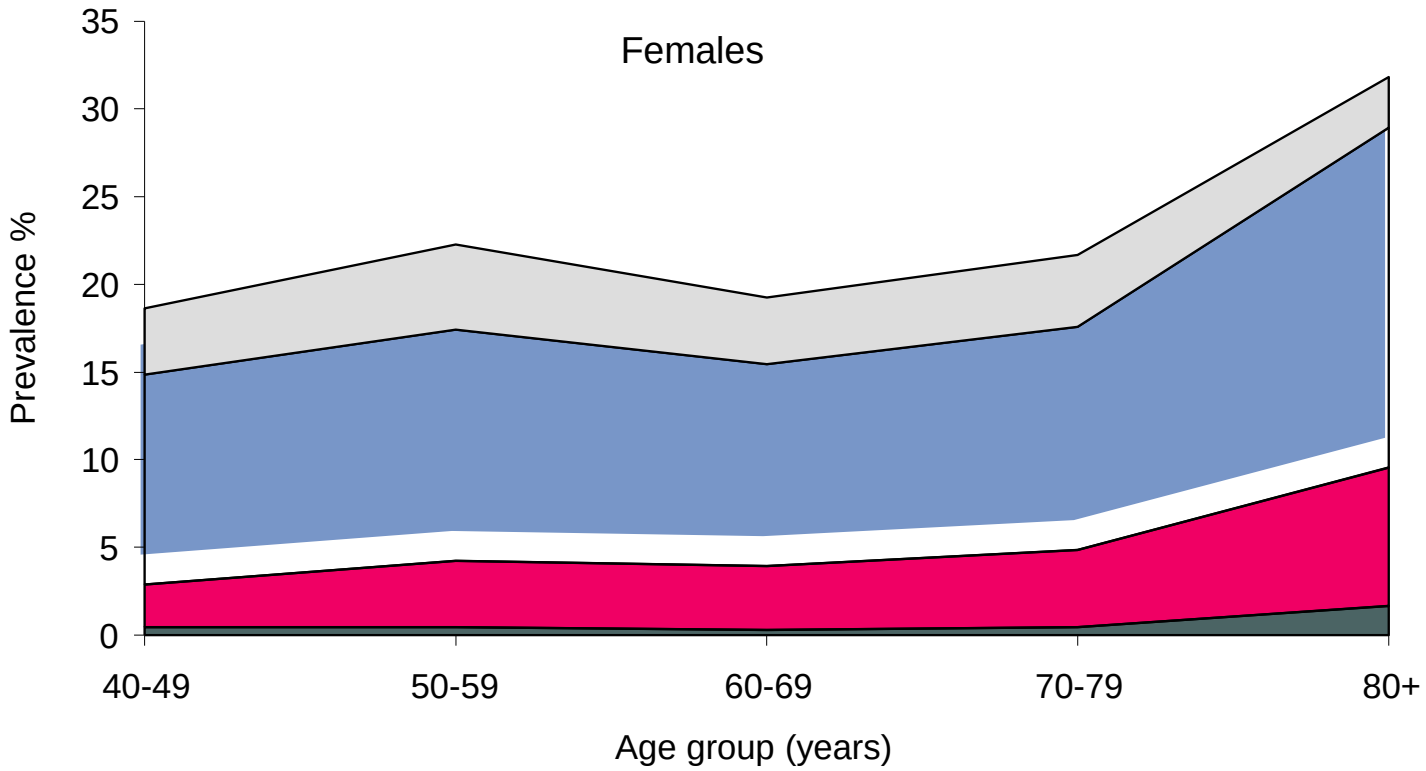
http://www.who.int/ageing/media/infographics/en/

Population aging is speeding up



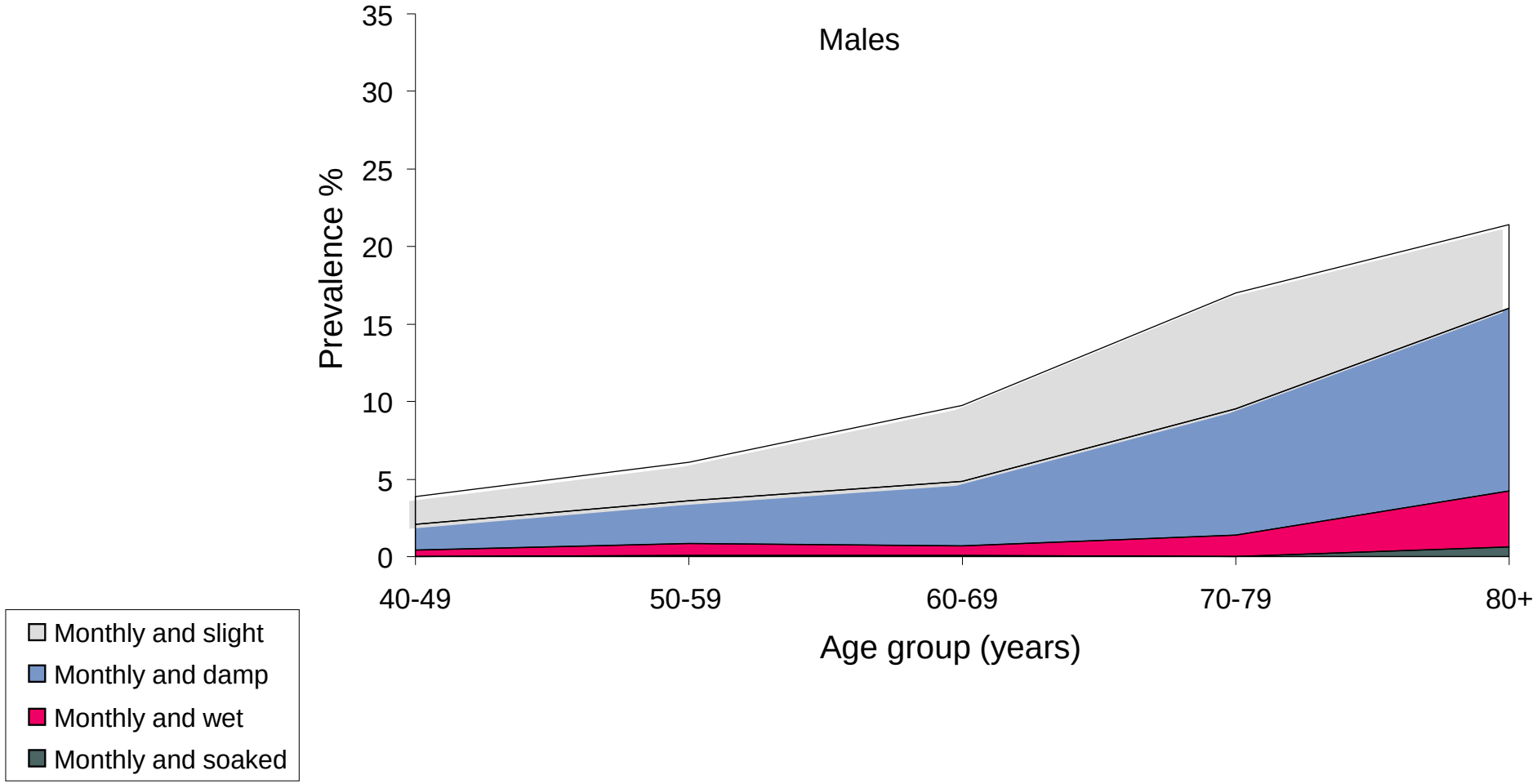
http://www.who.int/ageing/media/infographics/en/

Urinary incontinence prevalence and severity in women



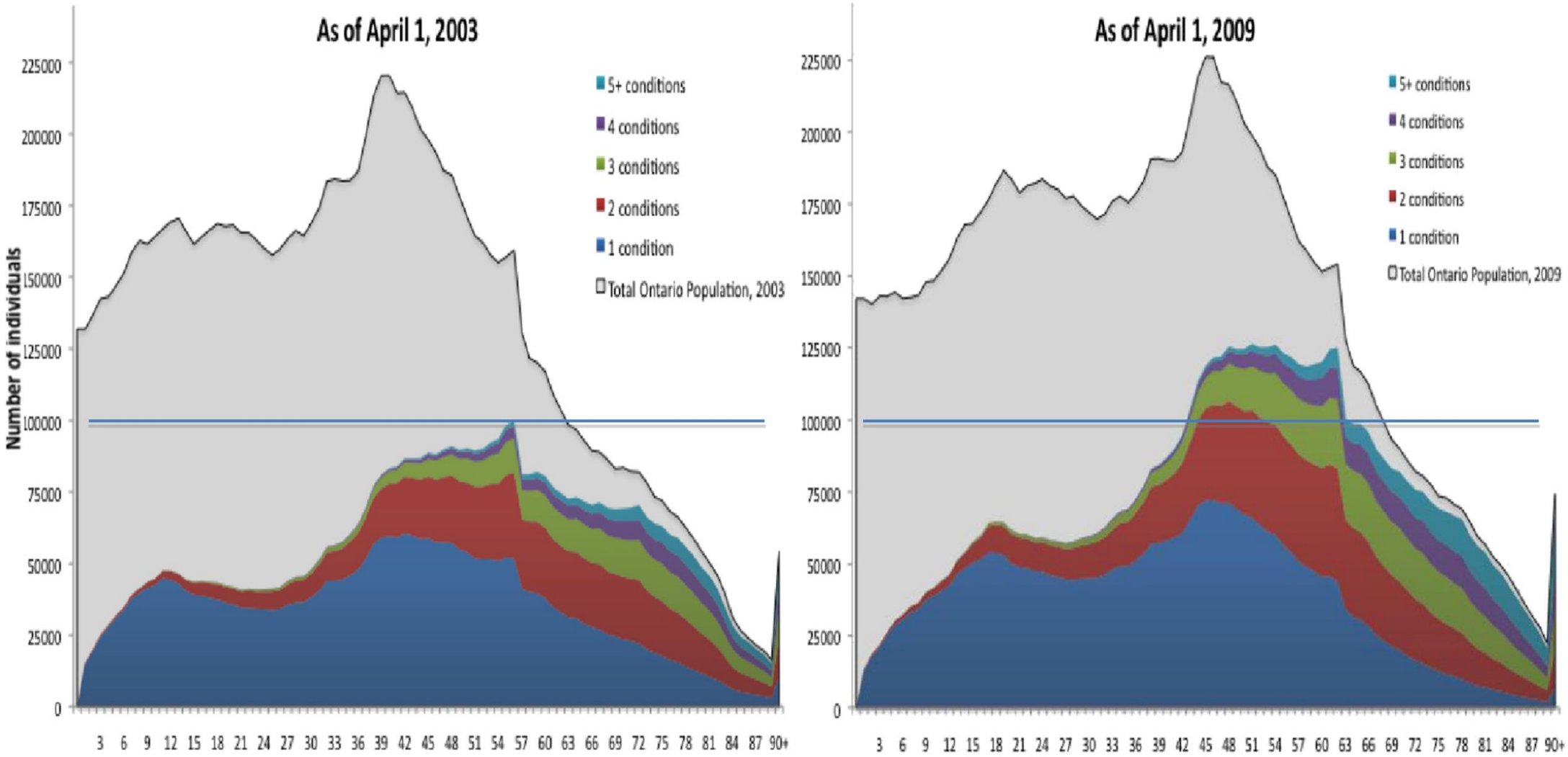
Perry S et al. J Public Health Med 2000; 22(3):427-34 (the Leicestershire MRC incontinence study)

Urinary incontinence prevalence and severity in men



Perry S et al. J Public Health Med 2000; 22(3):427-34 (the Leicestershire MRC incontinence study)

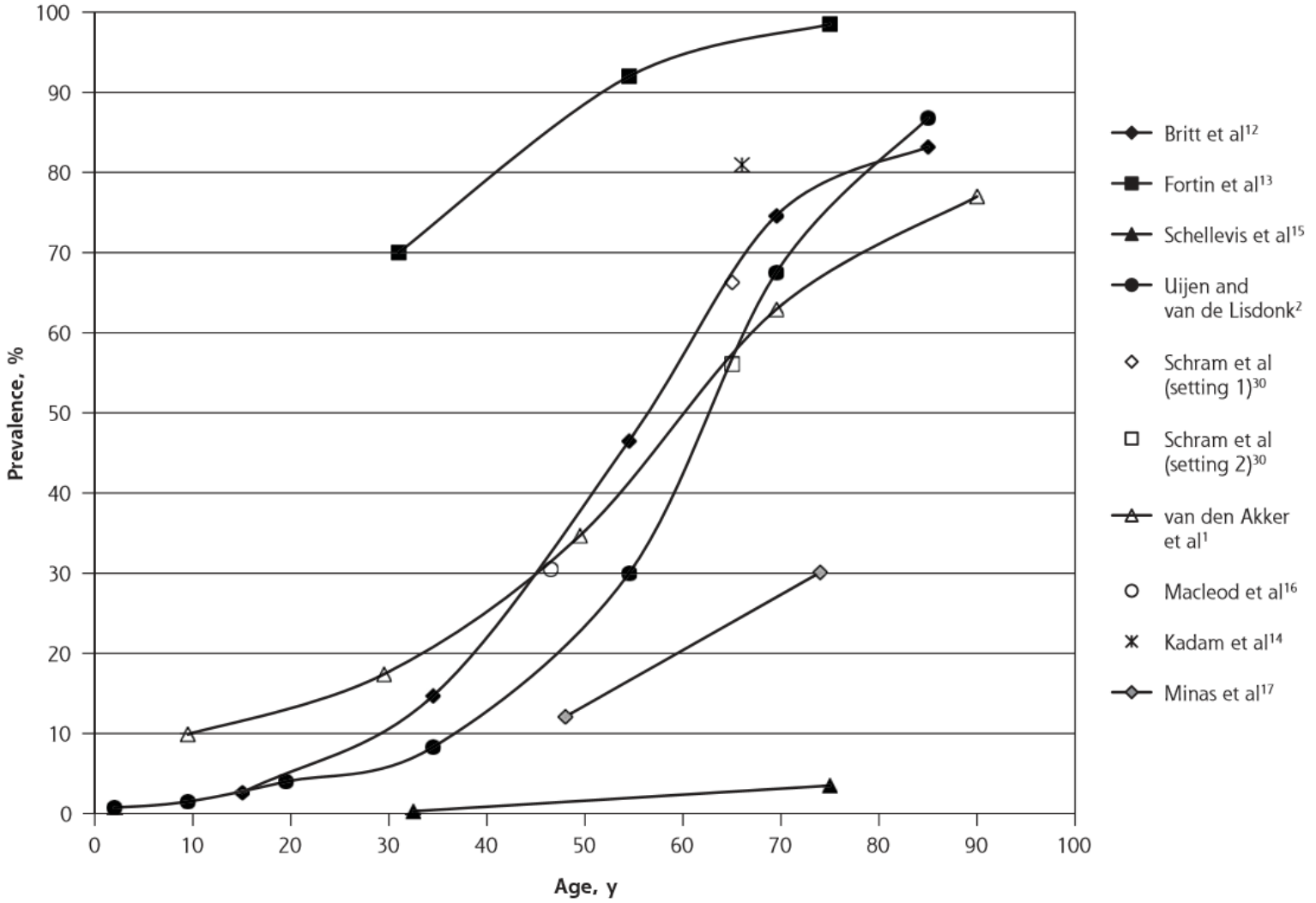
Multimorbidity



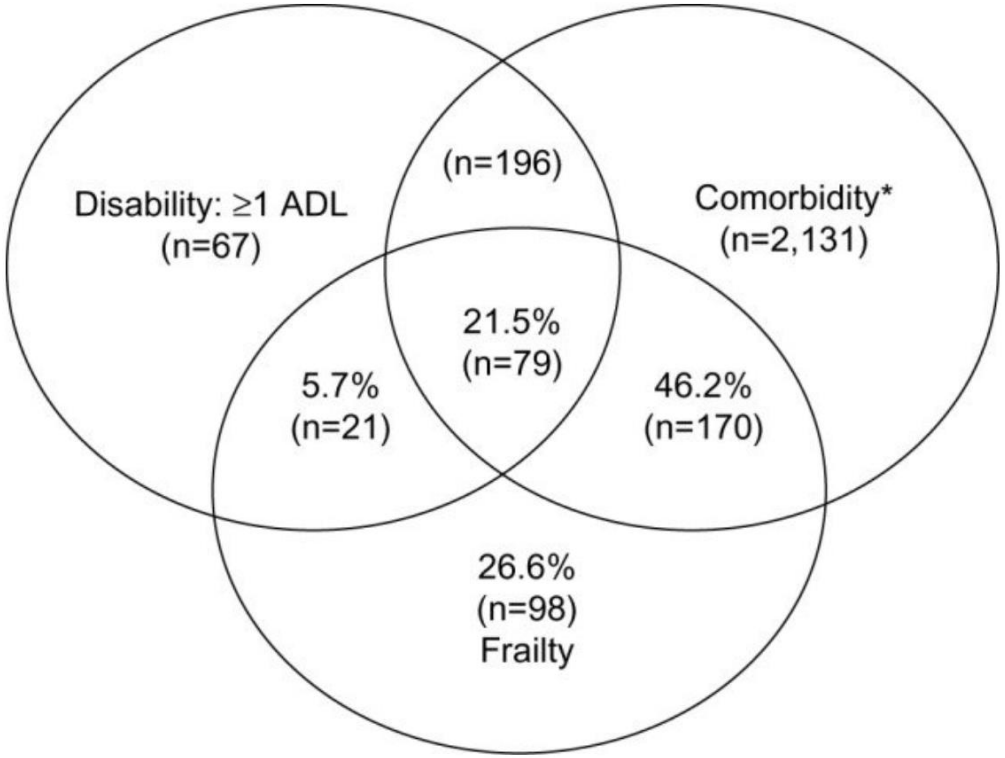
BMC Public Health (2015) 15:415

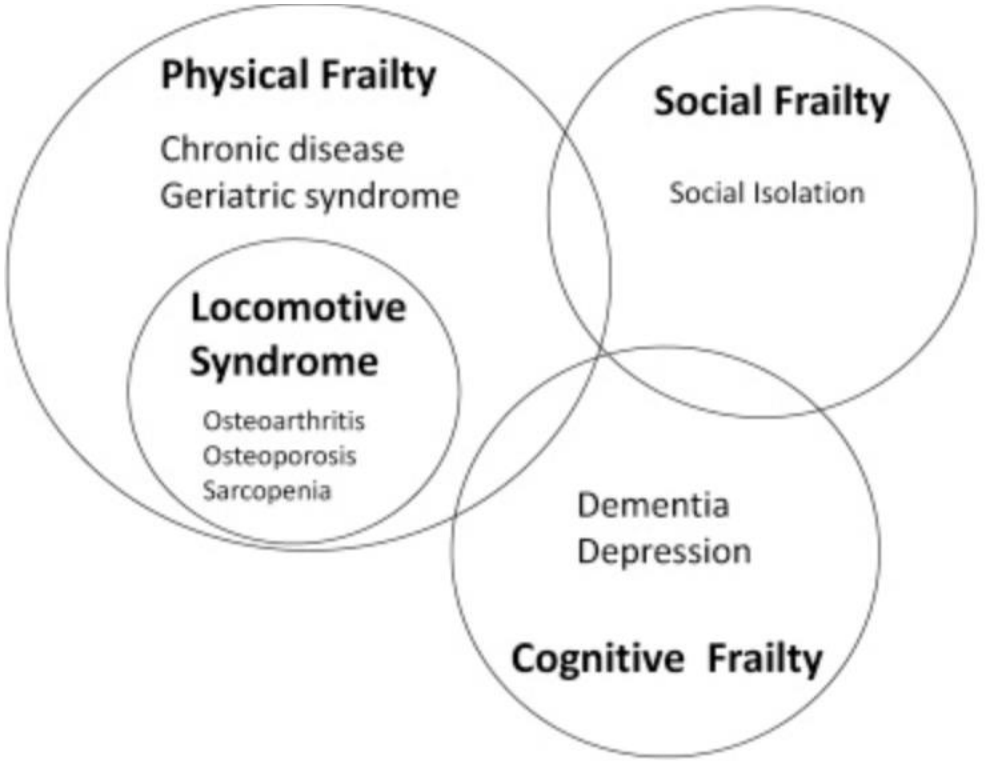
The rise of multimorbidity

Prevalence of multimorbidity (defined as ≥2 diseases) reported in primary care settings



A complex relationship





Osteoporosis and Sarcopenia 2016;2(3): 156-163
Clinical Interventions in Aging 2014;9(3):433-441

What is frailty?

Phenotypic model

- Involuntary weight loss (>10%)
- Weakness (grip strength <20th centile)
- Slowness (<1.0m/s)
- Exhaustion
- Decreased physical activity

J Gerontol Med Sci 2001

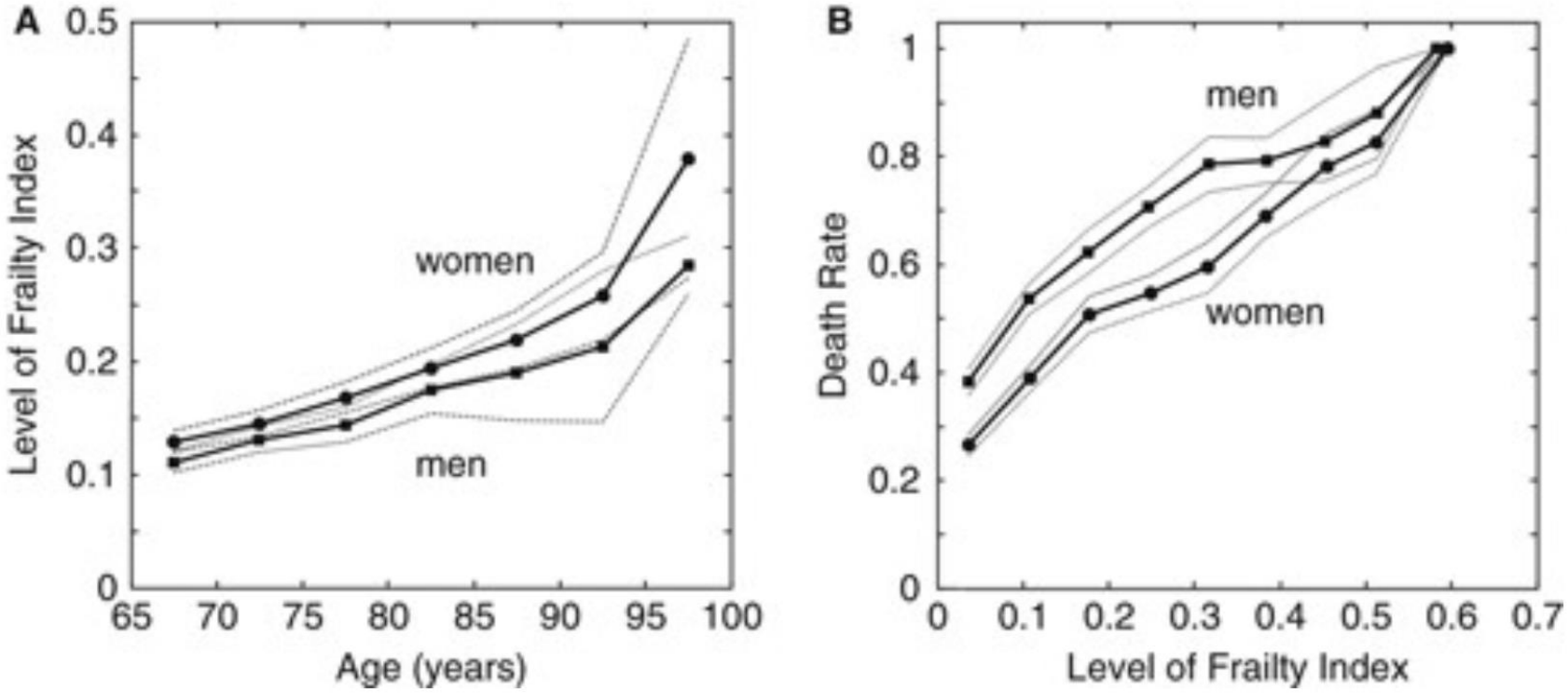
Accumulated deficits model

The more things wrong with you, the worse you do…**Frailty Index**
Independent of the exact number or nature of deficits

A continuous measure derived from Comprehensive Geriatric Assessment

Scientific World Journal. 2001 Aug 8;1:323-36

Frailty leads to bad things…



The age-specific distribution of the Frailty Index (A) grouped according to 5-year intervals from age 65 and the 10-year death rate as a function of the Frailty Index (B). Circles represent women, and squares represent men, with 95% confidence intervals (CIs) shown in thin lines

Journal of the American Geriatrics Society 2010;58(4):681-7

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house.** Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In severe dementia, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging. Revised 2008.
2. K Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173:489-495.

DALHOUSIE UNIVERSITY *Inspiring Minds*

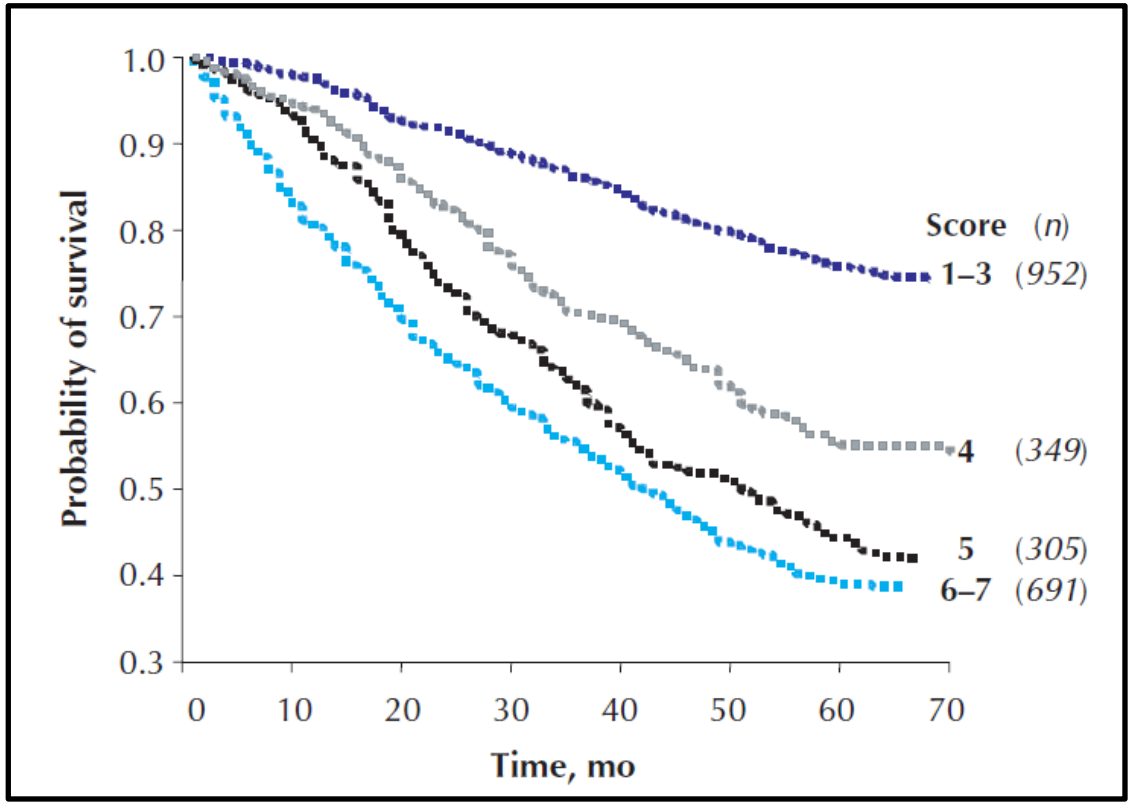
CFS score and mathematically derived FI highly correlated (Pearson 0.80, $p<0.01$)

Available at: http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm

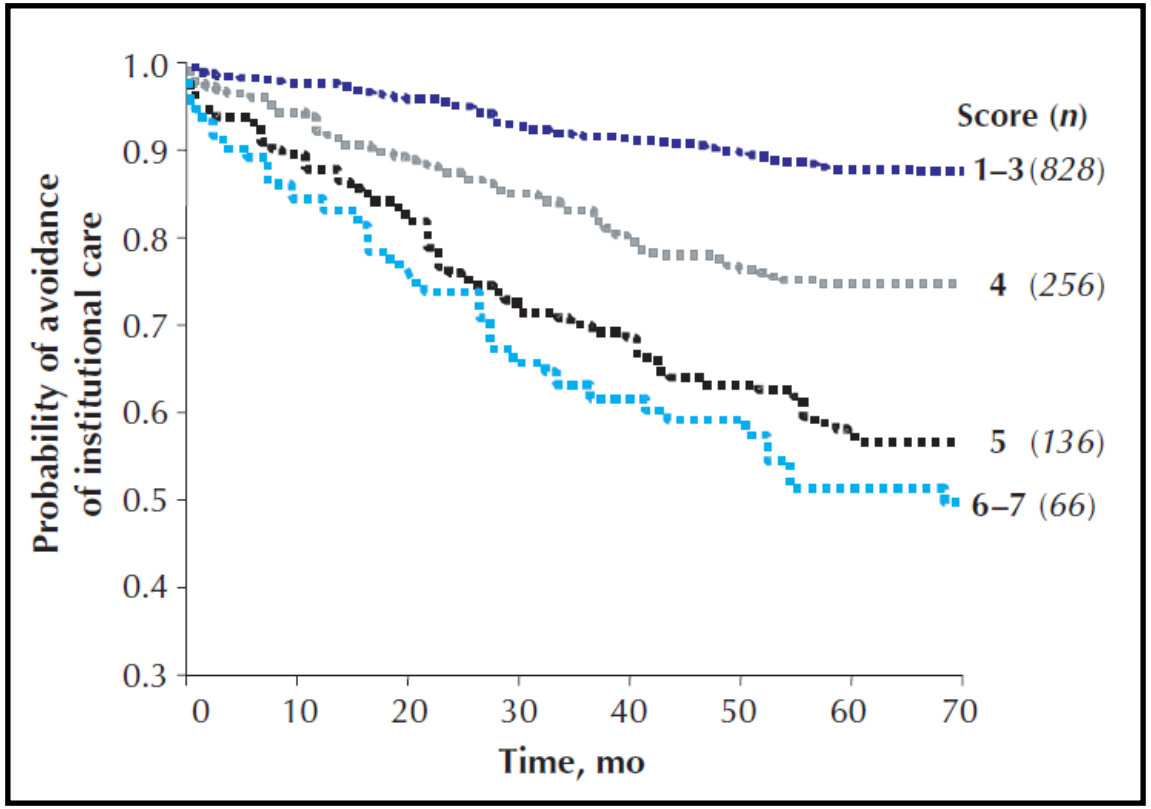
Rockwood et al CMAJ 2005

A global clinical measure of fitness and frailty in elderly people

Survival



Institutionalization

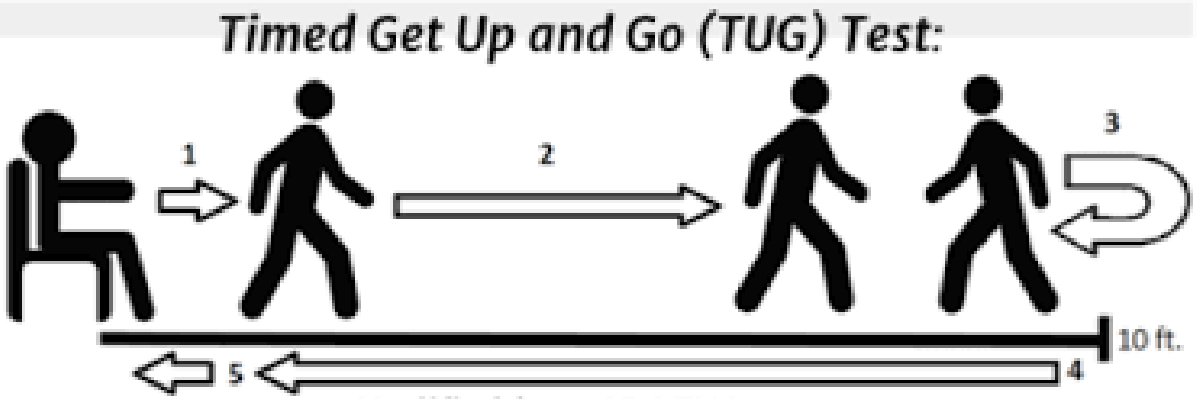


For each 1-category ↑ in CFS score ~ 21.2% ↑ death and 23.9% ↑ institutionalization

Rockwood et al CMAJ 2005

Frailty and OAB

- Timed Up and Go Test used in urology patients in US
- 201 and 1162 individuals with and without OAB
- Individuals with OAB had slower TUGT (13.7 ± 7.9 sec) than non-OAB counterparts (10.9 ± 5.2 sec), p<0.0001
- 32.3% and 11.0% of OAB and non-OAB individuals being categorized as slow (>15s) or frail.
- Slower TUGT was a significant predictor of OAB (adjusted OR 3.0; 95% CI 2.0-4.8).
- Age was not independently associated with this diagnosis (p values >0.05 for each age group)



Urology. 2017 Aug;106:26-31.

Frailty in Norway

Source	Frailty prevalence	Number of participants	Setting	Frailty definition	Age (years)	Women (%)
Langholz *et al.*, 2017 [71] Poland	3.7	736	Community	CHS	≥ 65	51.4
Matusik *et al.*, 2012 [17]	75.6	86	Nursing home	CFS	≥ 65	76.7
Theou *et al.*, 2013 [40]	42.0	2425	Community	SHARE FI	≥ 50	*Not reported*
Bieniek *et al.*, 2016 [72]	54.2	325	Hospital - Geriatric Ward	CHS	NA	67.0

Ann Ist Super Sanita. 2018 Jul-Sep;54(3):226-238.

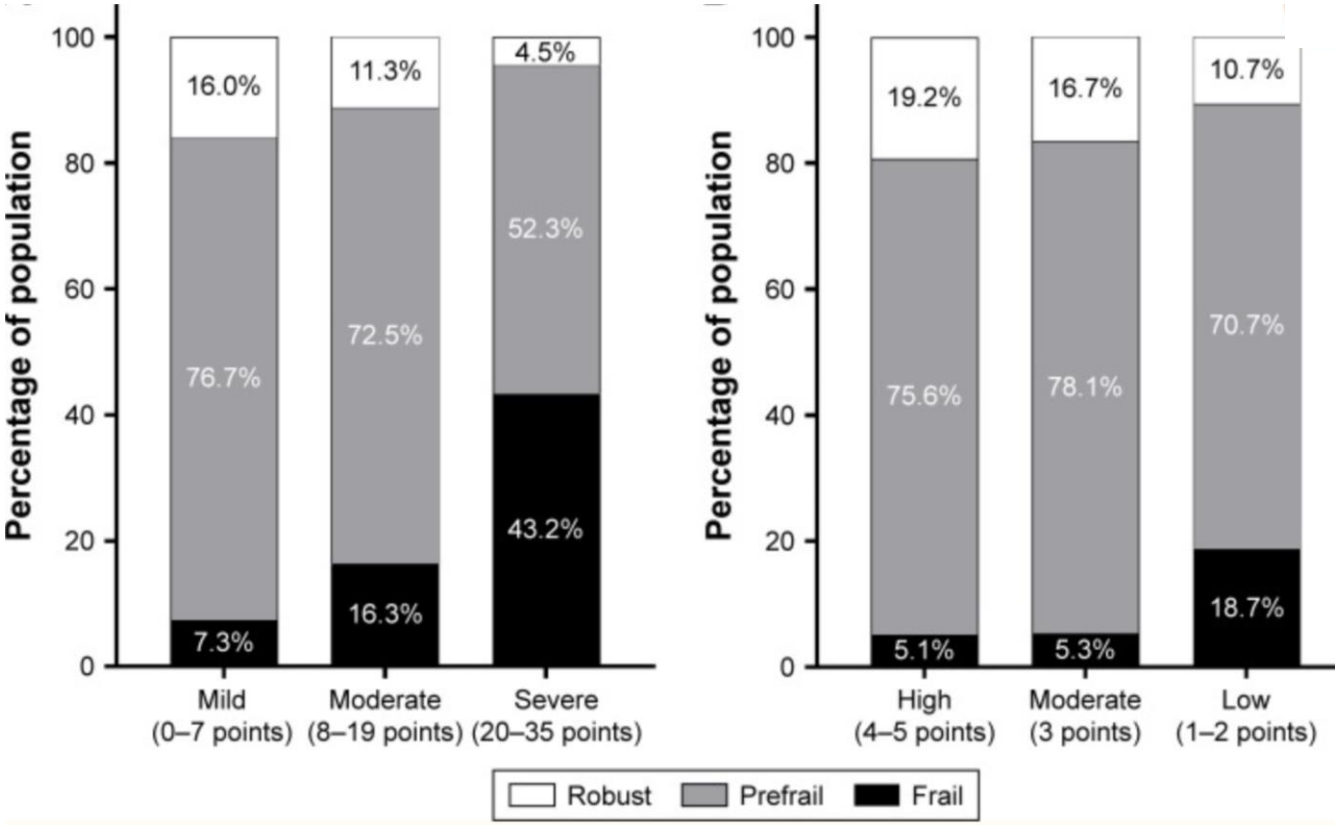
UI in frail older women

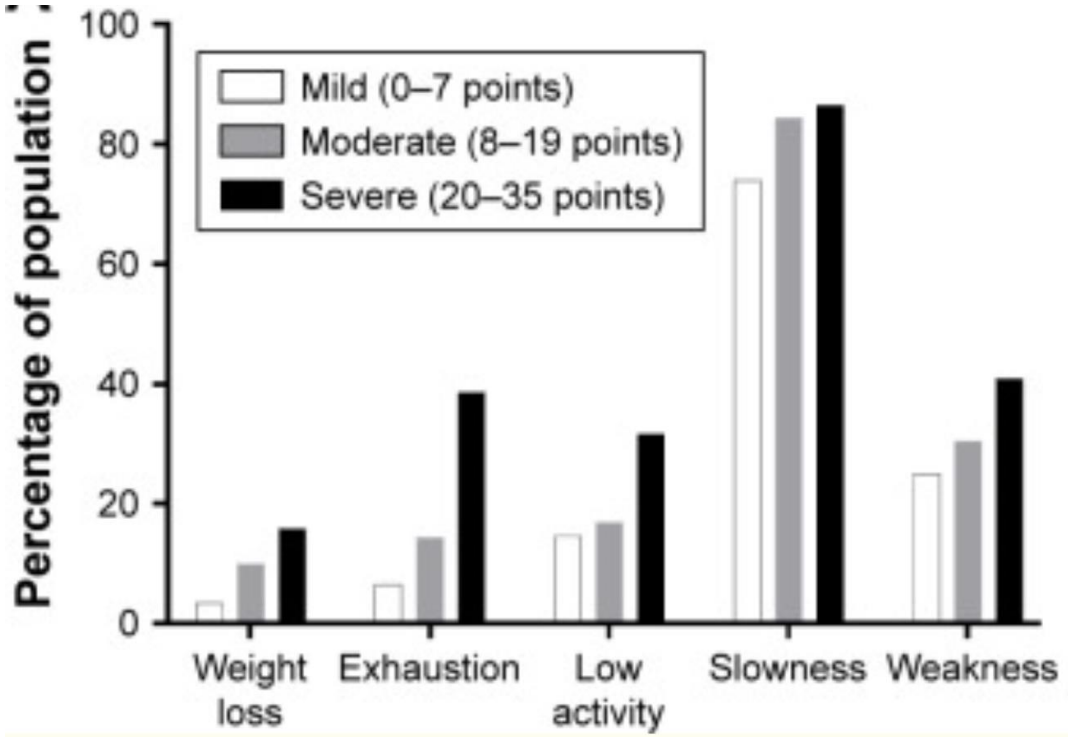
Variable	Non-frail		Pre-frail		Frail		P
	n = 159	%	n = 191	%	n = 35	%	
Heart diseases	15	9.4	24	12.6	9	25.7	0.09
Hypertension	70	44.0	91	47.6	17	48.6	0.81
Stroke	0	0	5	2.6	3	8.6	0.02
Diabetes	15	9.4	38	19.9	14	40.0	< 0.001
Cancer	3	1.9	4	2.1	4	11.4	0.02
Arthritis	22	13.8	32	16.7	9	2.6	0.51
Depression	8	5.0	12	6.3	6	1.7	0.10
Respiratory diseases	27	17.0	34	17.8	12	3.4	0.14
Osteoporosis	26	16.4	41	21.5	15	42.9	0.007
Urinary incontinence	33	20.8	71	37.2	15	42.9	0.001
Fecal incontinence	2	1.3	4	2.1	4	11.4	0.002
Number of medications per day							
0	25	15.7	18	9.4	2	5.7	
1	36	22.7	25	13.1	5	14.3	
2	26	16.3	31	16.2	6	17.2	0.54
3	23	14.5	30	15.7	4	11.4	
4+	49	30.8	87	45.6	18	51.4	
Number of doctor visits over the last 12 months							
0	18	11.3	15	7.9	0	0	
1 to 4	101	63.5	115	60.2	18	51.4	0.03
5 or more	40	25.2	61	31.9	17	48.6	
Hospitalization over the last 12 months							
Yes	22	13.8	37	19.4	15	42.8	< 0.001
No	137	86.2	154	80.6	20	57.2	

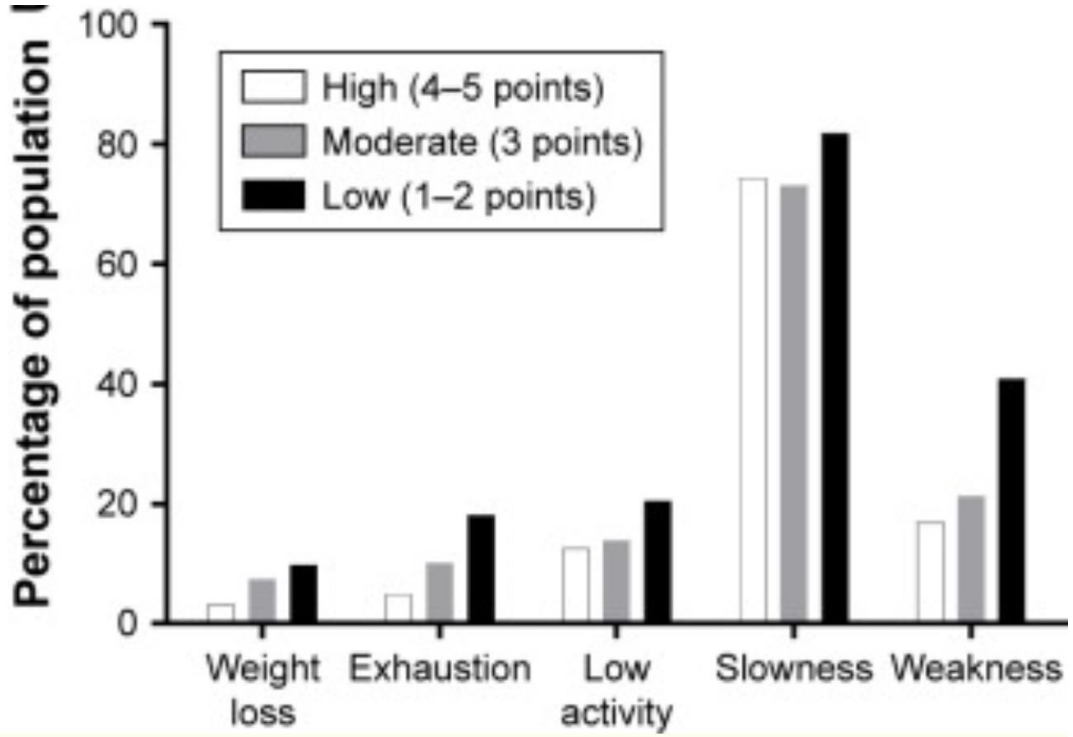
Sao Paulo Med. J. vol.134 no.5 São Paulo Sept./Oct. 2016 Epub Sep 19, 2016
http://dx.doi.org/10.1590/1516-3180.2016.0078180516

LUTS in men and frailty

- 492 men, mean (SD) age 74.2 (5.6) Most men were prefrail (73.2%) or frail (13.4%), and multimorbidity (32.5%), low cognition (16.7%), IADL disability (15.7%), and fall history (13.0%) were common.
- The most prevalent underlying diseases were hypertension (48.8%), arthritis (22.6%), diabetes (17.3%), heart disease (11.2%) and chronic lung disease (7.5%)

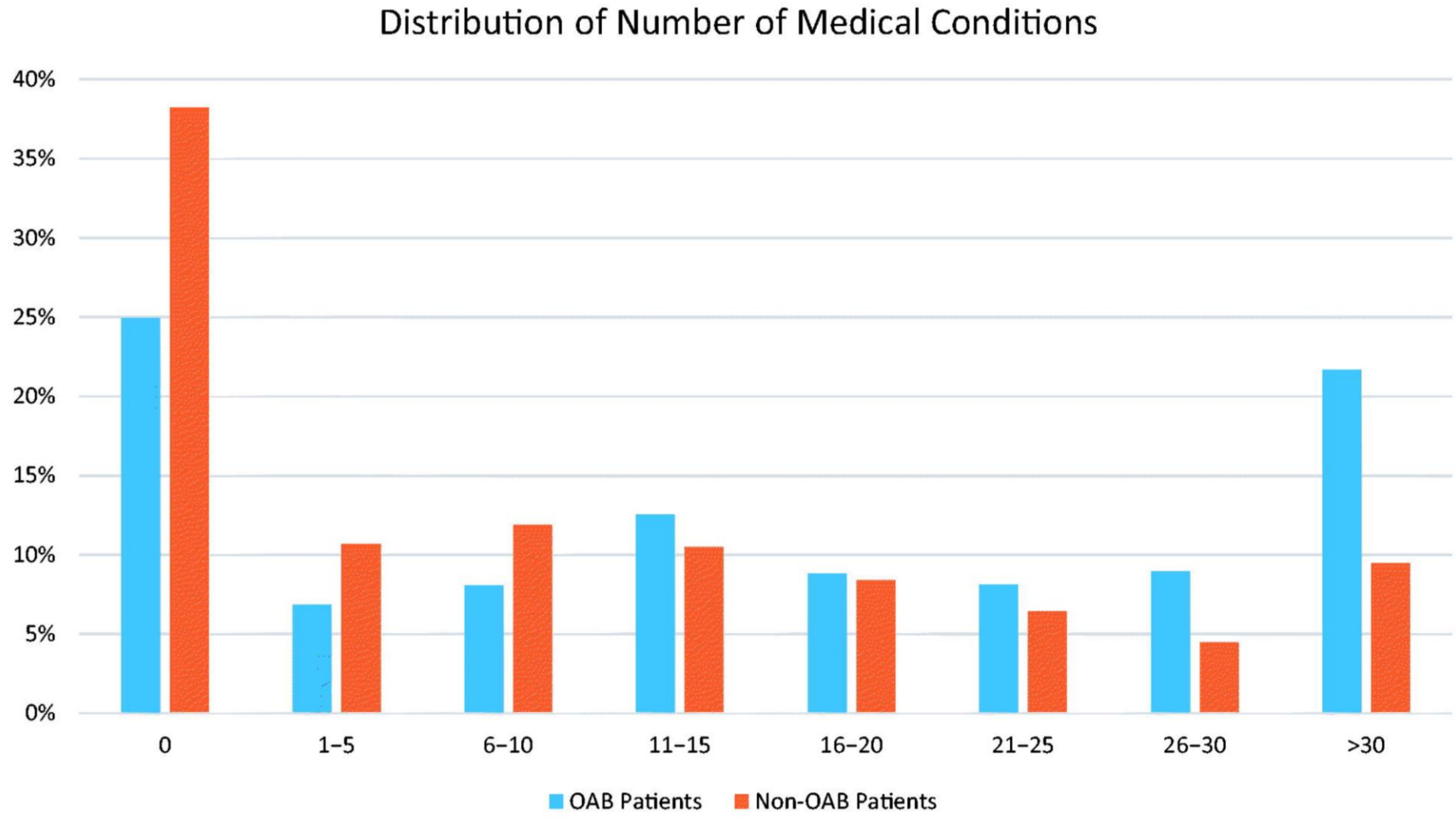



Percentage of population
100
80
60
40
20
0
Mild (0–7 points)
Moderate (8–19 points)
Severe (20–35 points)
Weight loss
Exhaustion
Low activity
Slowness
Weakness


Percentage of population
100
80
60
40
20
0
High (4–5 points)
Moderate (3 points)
Low (1–2 points)
Weight loss
Exhaustion
Low activity
Slowness
Weakness

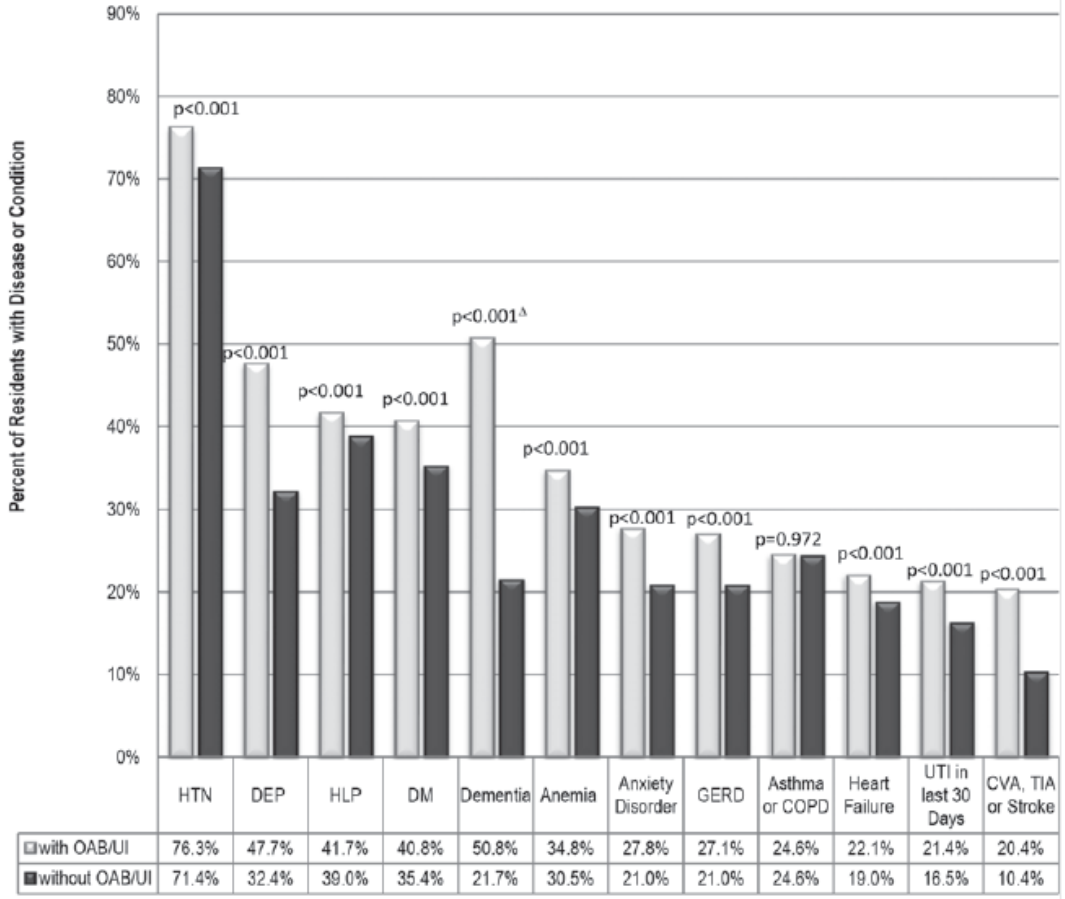
Elderly OAB patients have more comorbid conditions than those without

OAB, N=415
Non-OAB, N=6,868



CURRENT MEDICAL RESEARCH AND OPINION, 2016:32;1997–2005

Prevalent disease in residents with UI/ OAB compared with a matched cohort without UI/OAB in nursing homes



	HTN	DEP	HLP	DM	Dementia	Anemia	Anxiety Disorder	GERD	Asthma or COPD	Heart Failure	UTI in last 30 Days	CVA, TIA or Stroke
with OAB/UI	76.3%	47.7%	41.7%	40.8%	50.8%	34.8%	27.8%	27.1%	24.6%	22.1%	21.4%	20.4%
without OAB/UI	71.4%	32.4%	39.0%	35.4%	21.7%	30.5%	21.0%	21.0%	24.6%	19.0%	16.5%	10.4%

Abbreviations: COPD = Chronic obstructive pulmonary disease, CVA = Cerebrovascular accident, DEP = Depression, DM = Diabetes mellitus, GERD = Gastroesophageal reflux disease, HTN = Hypertension, HLP = Hyperlipidemia, OAB = Overactive bladder, TIA = Transient ischemic attack, UI = Urinary incontinence, UTI = Urinary tract infections.

Consultant pharmacist 2015;30: 533-542

and are more impaired in ADL

Table 1. Baseline demographic characteristics and functional impairment measures, MCBS respondents, by OAB status.

	OAB Patients (Unweighted $N = 415$, Weighted $N = 1{,}019{,}946$)	Non-OAB patients (Unweighted $N = 6868$, Weighted $N = 17{,}768{,}956$)	*P* Value
Age, years	78.5 (0.4)	76.9 (0.1)	<.01
Age Group, %			<.01
<75 years	34.6	46.1	
≥75 years	65.4	53.9	
Sex, %			
Female	71.2	61.7	<.01
Male	28.9	38.3	
Race, %			
White	75.9	75.8	0.87
Black	8.2	9.0	
Hispanic	10.2	10.2	
Other/Unknown	5.8	5.0	
Activities of Daily Living Limitations, %			
0 items	56.0	67.4	<.01
1–2 items	20.5	18.7	
≥3 items	22.4	13.3	
Missing	1.0	0.7	
Instrumental Activities of Daily Living Limitations, %			
0 items	46.7	60.2	<.01
1–2 items	25.1	21.3	
≥3 items	16.0	11.9	
Missing	12.2	6.6	
Physical Functioning Limitations, %			
0 items	9.8	18.6	<.01
1–2 items	27.5	37.2	
≥3 items	50.4	37.4	
Missing	12.4	6.8	
VES-13 Score	5.9 (0.15)	4.7 (0.05)	<.01
VES-13 Score <3	22.7	37.4	<.01
VES-13 Score ≥3	77.3	62.6	

Data presented are the means (standard error of the mean) or percentages.
MCBS, Medicare Current Beneficiary Survey; OAB, overactive bladder; VES; Vulnerable Elders Survey.

CURRENT MEDICAL RESEARCH AND OPINION, 2016:32;1997–2005

What is anticholinergic burden?

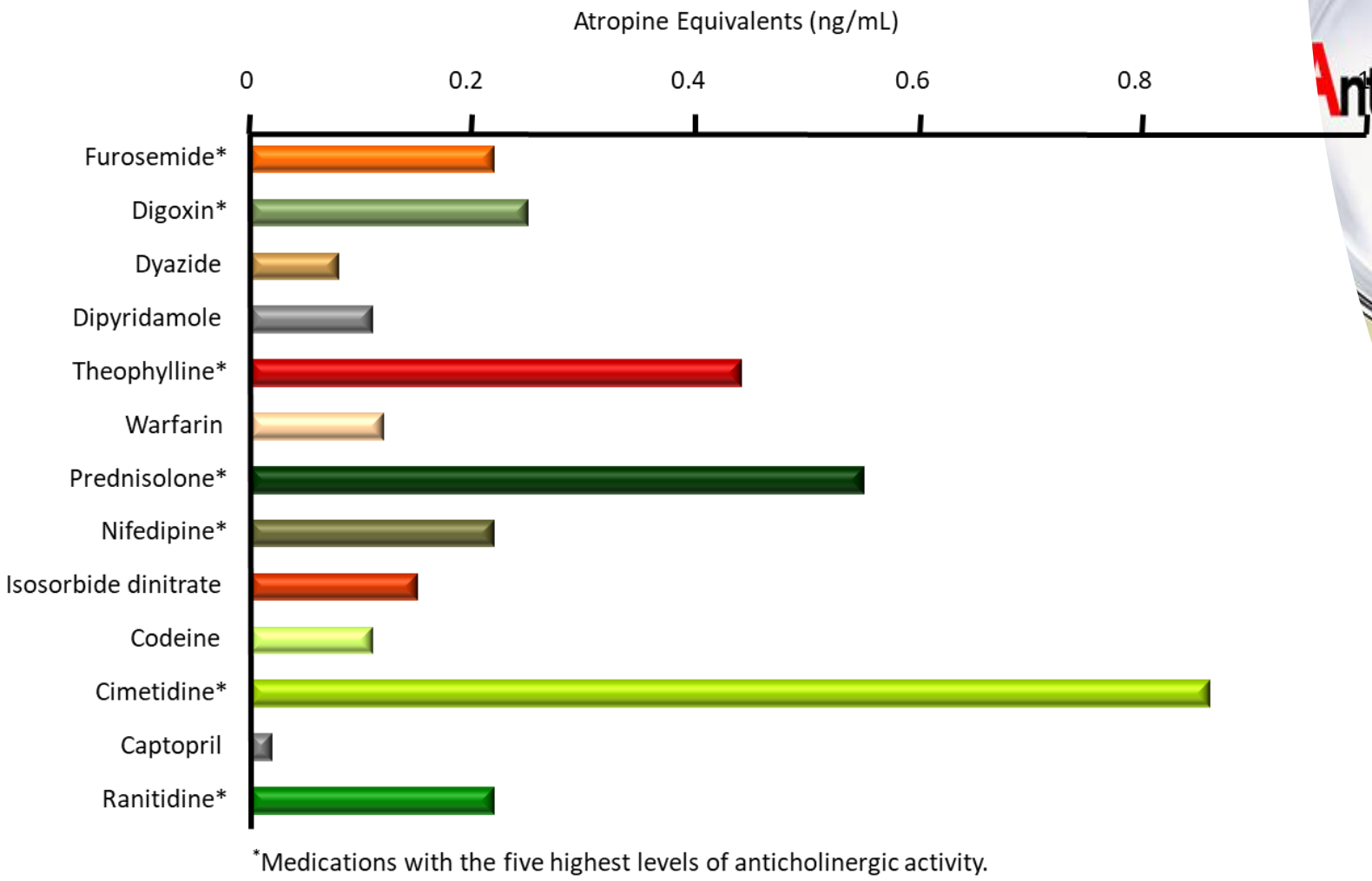
the cumulative exposure to one or more anticholinergic medications and the associated increased risk of adverse effects

How is ACB calculated? – the scores and scales

- A number of scales have been designed to quantify the level of anticholinergic burden: e.g.
  - Anticholinergic Cognitive Burden (ACB) Scale
  - Anticholinergic Risk Scale (ARS)
  - Anticholinergic Drug Scale (ADS)
  - Anticholinergic Component of the Drug Burden Index (DBIAC)
- These scales typically categorize anticholinergic medications as well as medications with anticholinergic side effects into groups based on their level of anticholinergic activity

British Journal of Clinical Pharmacology. 2015;80(2):209-220
Archives of Internal Medicine. 2008;168(5):508-513.
Aging Health 2008; 4(3): https://doi.org/10.2217/1745509X.4.3.311
The Journal of Clinical Pharmacology. 2006;46(12):1481-1486.
The American Journal of Medicine. 2009;122(12):1142-1149.e1142.

Serum anticholinergic levels ranked according to frequency of prescriptions in older adults



*Medications with the five highest levels of anticholinergic activity.

Tune LE et al. *Am J Psychiatry* 1992; 149: 1393–94.

There are 16….

- Anticholinergic Cognitive Burden Scale
- Anticholinergic Risk Scale
- Anticholinergic Drug Scale
- Anticholinergic Component of the Drug Burden Index
- Anticholinergic Burden Classification
- Clinician-rated Anticholinergic Score
- Anticholinergic Activity Scale
- Anticholinergic Loading Scale
- Scale reported by Chew *et al*. (2008)
- Scale reported by Duran *et al*. (2013)
- Pharmacological Index
- Clinical Index
- Scale reported by Cancelli *et al*. (2008)
- Scale reported by Whalley *et al*. (2012)
- Anticholinergic Burden Score
- Summated Anticholinergic Medications Scales

Aging Health 2008; 4(3): https://doi.org/10.2217/1745509X.4.3.311
Arch Intern Med. 2008;168(5):508-513
The Journal of Clinical Pharmacology. 2006;46(12):1481-1486.
Arch Intern Med. 2007;167(8):781-787.
BMJ (Clinical research ed). 2006;332(7539):455-459.
J Am Geriatr Soc. 2008;56(12):2203-2210.
JNNP 2010;81(2):160-165.
Dementia and geriatric cognitive disorders. 2011;31(3):173-178
J Am Geriatr Soc. 2015;63(10):2120-2124.
J Am Geriatr Soc. 2008;56(7):1333-1341.
Eur J Clin Pharmacol. 2013;69(7):1485-1496.
The American journal of psychiatry. 2004;161(1):116-124.
Clinical pharmacology and therapeutics. 2008;84(1):63-68.
Journal of Alzheimer's disease : JAD. 2012;30(2):253-261.
International psychogeriatrics. 2002;14(3):307-310.

They have been variably tested and validated

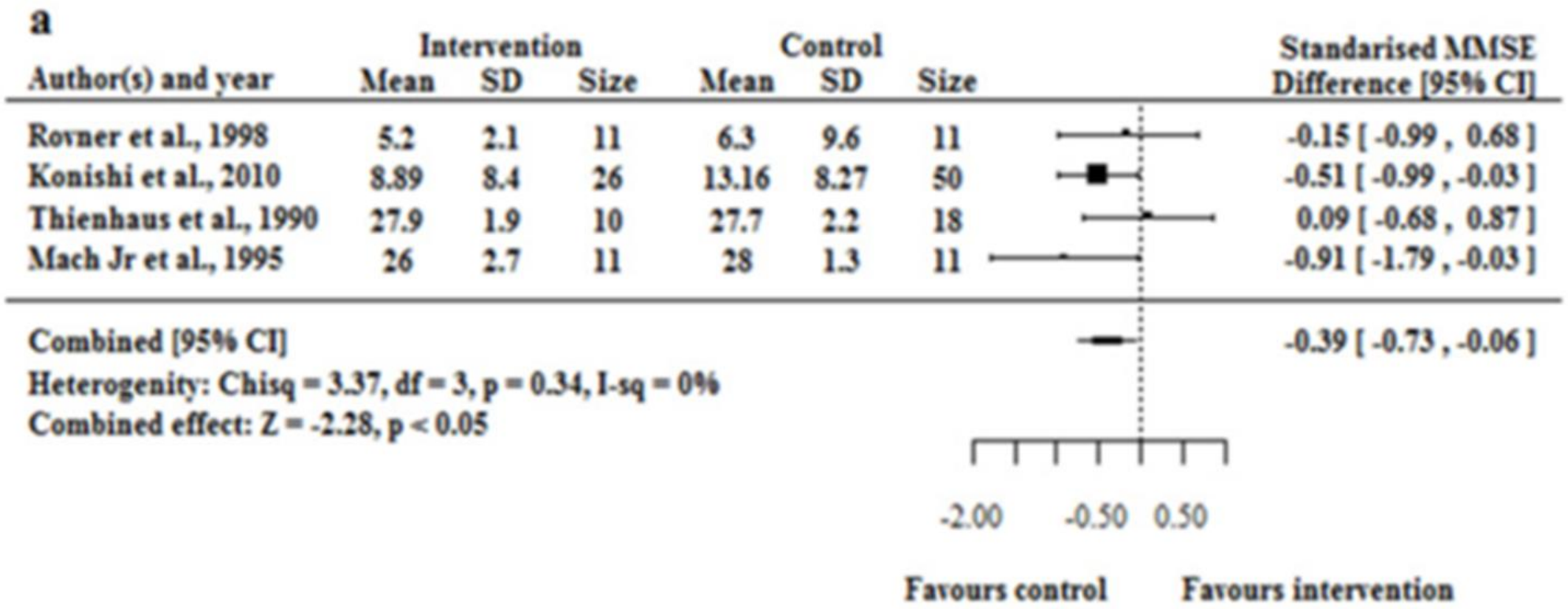
- AAS - Anticholinergic Activity Scale
- ABS - Anticholinergic Burden Score
- ACB - Anticholinergic Cognitive Burden
- ADS - Anticholinergic Drug Scale
- ALS - Anticholinergic Loading Scale
- ARS - Anticholinergic Risk Scale

Derivation

- ACB and ARS were derived from expert opinion and literature review.
- The ABC, ALS, and AAS were based on a combination of expert opinion, literature review and assessment of serum anticholinergic activity (SAA).
- The ADS was developed based on assessment of SAA only.

Caution

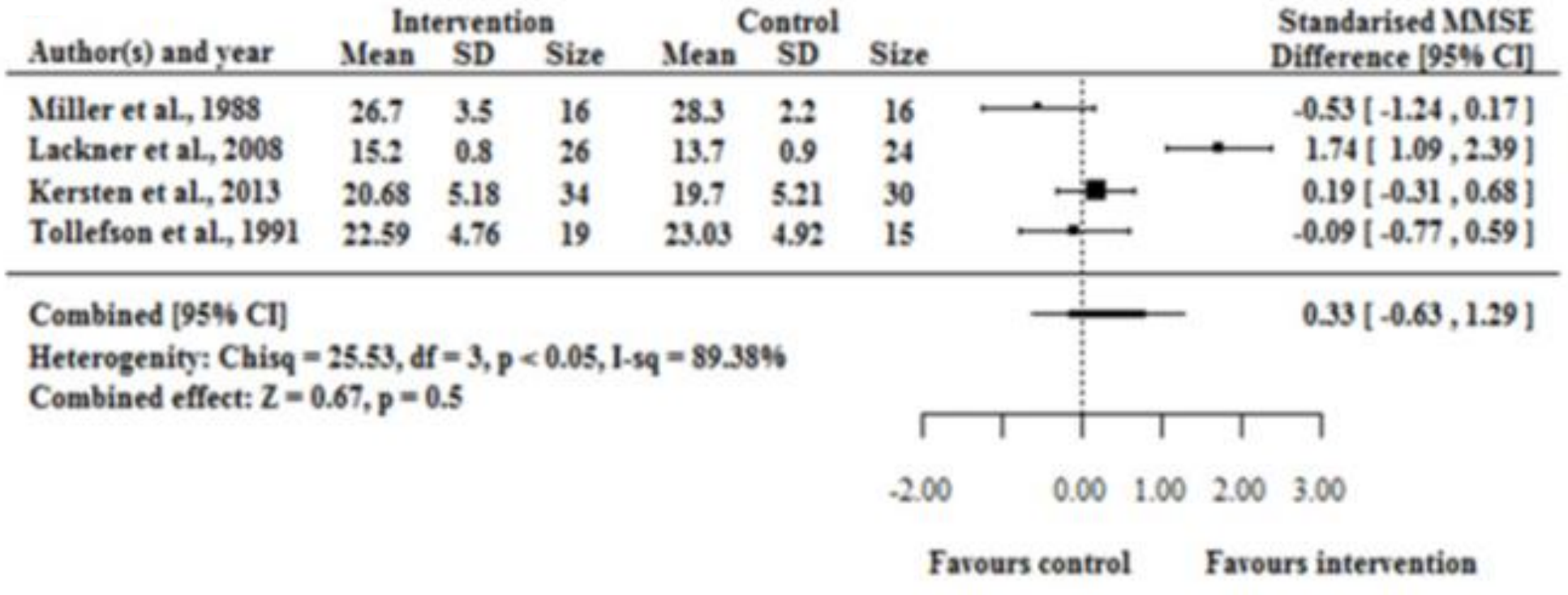
RCTs failed to confirm an association between SAA and impaired cognitive performance



Salahudeen SM. PLoS One 2016;11(3):e0151084

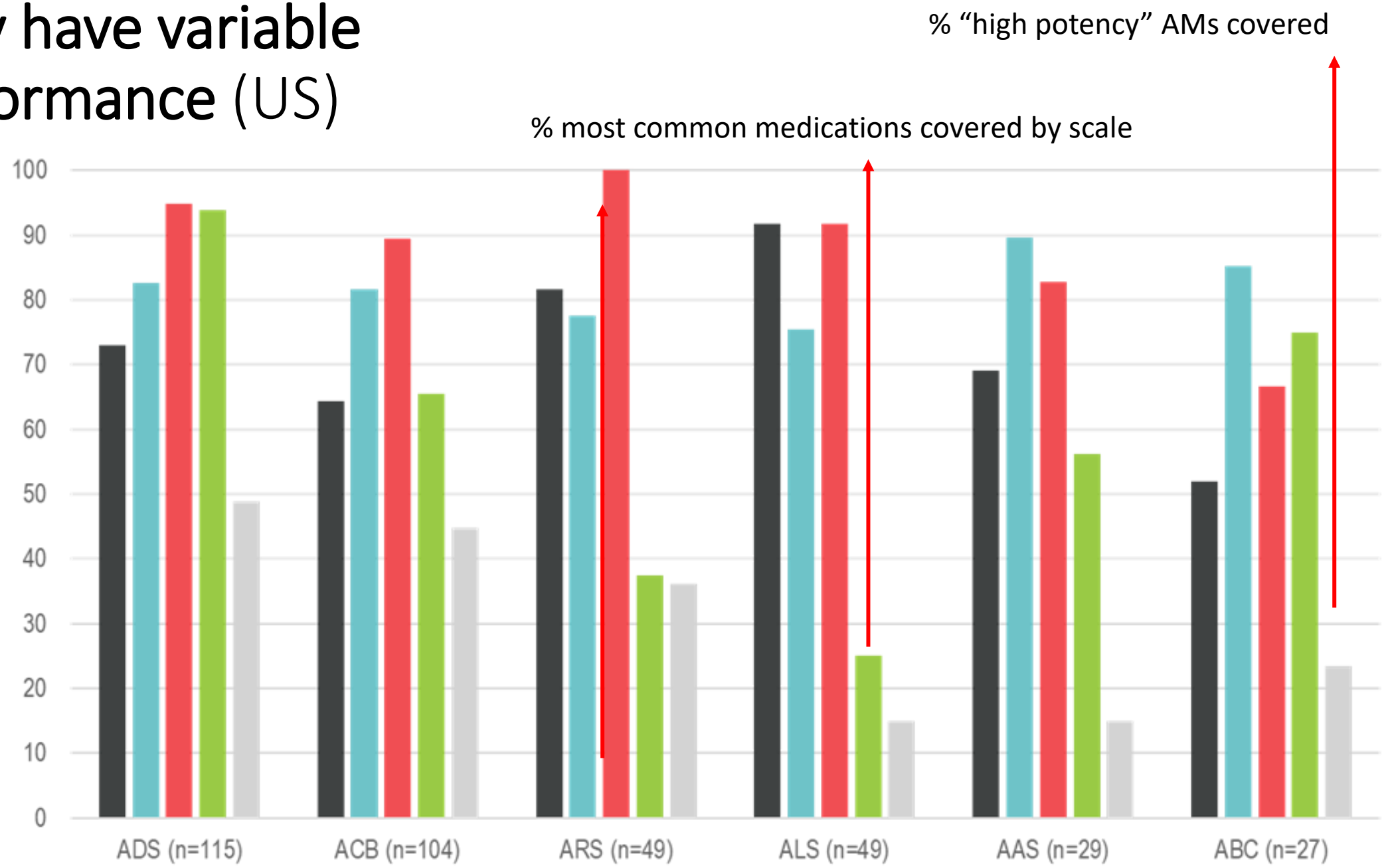
Caution

Increasing SAA associated with lower MMSE scores ($p < 0.05$) for **observational** studies



Salahudeen SM. PLoS One 2016;11(3):e0151084

They have variable performance (US)



Anticholinergic Cognitive Burden Scale

Drugs with ACB Score of 1

Generic Name	Brand Name
Alimemazine	Theralen™
Alverine	Spasmonal™
Alprazolam	Xanax™
Aripiprazole	Abilify™
Asenapine	Saphris™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Cetirizine	Zyrtec™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clidinium	Librax™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Desloratadine	Clarinex™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Iloperidone	Fanapt™
Isosorbide	Isordil™, Ismo™
Levocetirizine	Xyzal™
Loperamide	Immodium™, others
Loratadine	Claritin™
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	Procardia™, Adalat™
Paliperidone	Invega™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Venlafaxine	Effexor™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
Meperidine	Demerol™
Methotrimeprazine	Levoprome™
Molindone	Moban™
Nefopam	Nefogesic™
Oxcarbazepine	Trileptal™
Pimozide	Orap™

Categorical Scoring:
- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:
- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:
- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. [3]
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. [4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. [4]

Aging Brain Care

www.agingbraincare.org

Drugs with ACB Score of 3

Generic Name	Brand Name
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Doxylamine	Unisom™, others
Fesoterodine	Toviaz™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Propiverine	Detrunorm™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Solifenacin	Vesicare™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™
Trospium	Sanctura™

Medications Reviewed in 2012 Update

Medications Added with Score of 1:
Aripiprazole (Abilify™)
Asenapine (Saphris™)
Cetirizine (Zyrtec™)
Clidinium (Librax™)
Desloratadine (Clarinex™)
Iloperidone (Fanapt™)
Levocetirizine (Xyzal™)
Loratadine (Claritin™)
Paliperidone (Invega™)
Venlafaxine (Effexor™)

Medications Added with Score of 2:
Nefopam (Nefogesic™)

Medications Added with Score of 3:
Doxylamine (Unisom™, others)
Fesoterodine (Toviaz™)
Propiverine (Detrunorm™)
Solifenacin (Vesicare™)
Trospium (Sanctura™)

Medications Reviewed But NOT Added:
Fexofenadine (Allegra™)
Gabapentin (Neurontin™)
Topiramate (Topamax™)
Levetiracetam (Keppra™)
Tamoxifen (Nolvadex™)
Nizatidine (Axid™)
Duloxetine (Cymbalta™)

Criteria for Categorization:
Score of 1: Evidence from in vitro data that chemical entity has antagonist activity at muscarinic receptor.

Score of 2: Evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect.

Score of 3: Evidence from literature, expert opinion, or prescribers information that medication may cause delirium.

Complete References:

1. Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and practical application. Aging Heatlh. 2008;4(3):311-320.
2. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. Clinical Interventions in Aging. 2009;4(1):225-233.
3. CampbellN,BoustaniM,LaneK,etal.Useofanticholinergics and the risk of cognitive impairment in an African-American population. Neurology. 2010;75:152-159.
4. Fox C, Richardson K, Maidment I, et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing Study. Journal of the American Geriatric Society. 2011; 59(8): 1477-1483.
5. Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. Alzheimers Dementia. 2012; epub ahead of print.

Aging Brain Care

ANTICHOLINERGIC COGNITIVE BURDEN SCALE

2012 Update

Developed by the Aging Brain Program of the Indiana University Center for Aging Research

Regenstrief Institute

IDND FROM DISCOVERY TO DELIVERY

THE NEW WISHARD ESKENAZI HEALTH

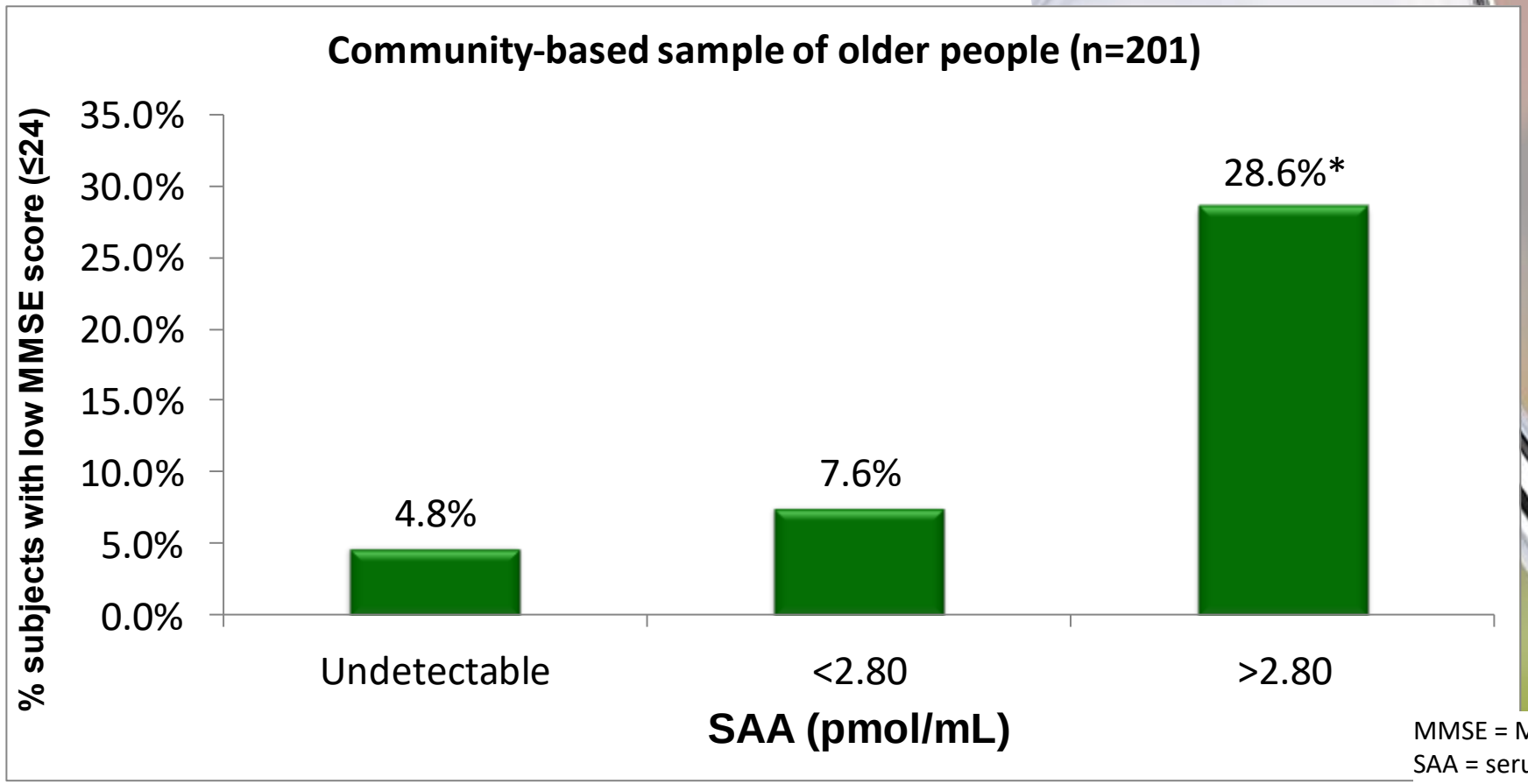
http://www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf

So what…?

A high level of anticholinergic burden is associated variably with decreased physical function, cognitive decline, falls, hospital admission and increased all-cause mortality

Aging Health 2008; 4(3): https://doi.org/10.2217/1745509X.4.3.311
Journal of the American Geriatrics Society. 2011;59(8):1477-1483
Drugs & aging. 2013;30(5):321-330
The American Journal of Geriatric Pharmacotherapy. 2012;10(4):251-257
Journal of the American Medical Directors Association. 2011;12(8):565-572.
The American Journal of Geriatric Psychiatry. 2013;21(8):785-793.

Anticholinergic burden and MMSE scores



MMSE = Mini-mental state examination
SAA = serum anticholinergic activity
*p<0.05 vs undetectable SAA (logistic regression)

1. Mulsant BH et al. *Arch Gen Psychiatry* 2003;**60:** 198–203.

Drugs With Anticholinergic Properties, Cognitive Decline, and Dementia in an Elderly General Population

The 3-City Study

- 520/ 6912 participants (7.5%) were taking anticholinergic drugs at baseline
- 36 participants (6.9%) were taking 2 anticholinergic drugs
- 8 (1.5%) were taking 3 drugs.
- 1.6% of the participants were taking bladder drugs

Arch Intern Med. 2009;169(14):1317-1324

women reporting use of anticholinergic drugs at baseline showed greater decline over 4 years in

- verbal fluency scores (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.11-1.79)
- global cognitive functioning (OR, 1.22; 95% CI, 0.96-1.55)

- In men, decline in
  - visual memory (OR, 1.63; 95% CI, 1.08-2.47)
  - executive function (OR, 1.47; 95% CI, 0.89- 2.44).

- A 1.4- to 2-fold higher risk was observed for those who continuously used anticholinergic drugs but not for those who had discontinued use.

- The risk of incident dementia over the 4-year follow-up period was also increased in continuous users (hazard ratio [HR], 1.65; 95% CI, 1.00-2.73)

Arch Intern Med. 2009;169(14):1317-1324

- Fox *et al* examined medication use between 1991 – 1993 in 12,423 men and women over the age of 65 years.
- The most commonly used drugs in this cohort were furosemide, dextropropoxyphene, atenolol and nifedipine
- Over 2 years, use of medications with anticholinergic properties was associated with
- greater decline (0.33 points, 95%CI 0.03 – 0.64) in MMSE score than those not taking anticholinergics.
- mortality was greater for those taking medications with definite anticholinergic properties (OR 1.68; 95% CI 1.30 – 2.16).

Journal of the American Geriatrics Society, 2011;59:1477-83.

Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study

- 3,434 participants aged 65 and older with no dementia at study entry. Initial recruitment occurred between 1994 and 1996 or 2000 and 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants received follow-up every two years

= Oxybutynin 5mg od for 3 years

	All participants (N=3434)		TSDD [a]	
Medication Class	**N[b]**	**%**	**Total TSDD filled**	**% of all TSDD**
Antihistamines	2,224	64.8	1,158,404	17.2
Gastrointestinal antispasmodics	1,566	45.6	365,141	5.4
Antivertigo/antiemetics	1,433	41.7	154,488	2.3
Antidepressants	1,352	39.4	4,241,590	63.1
Bladder antimuscarinics	668	19.5	702,825	10.5
Skeletal muscle relaxants	175	5.1	20,274	0.3
Antipsychotics	38	1.1	45,888	0.7
Antiarrhythmic	22	0.6	31,249	0.5
Antiparkinson agents	12	0.3	1,615	0.0
Total			6,721,473	100.0

			Unadjusted[c,d]		Adjusted[d,e]	
TSDD[b]	**Follow-up time (person-years)**	**Number of Events**	**HR**	**95% CI**	**HR**	**95% CI**
Dementia						
0	5618	136	1.00	Reference	1.00	Reference
1-90	7704	203	0.96	0.77-1.20	0.92	0.74-1.16
91-365	5051	172	1.31	1.04-1.65	1.19	0.94-1.51
366-1095	2626	102	1.39	1.07-1.82	1.23	0.94-1.62
>1095	4022	184	1.77	1.40-2.23	1.54	1.21-1.96
Alzheimer's Disease						
0	5618	112	1.00	Reference	1.00	Reference
1-90	7704	168	0.96	0.75-1.24	0.95	0.74-1.23
91-365	5051	128	1.21	0.93-1.58	1.15	0.88-1.51
366-1095	2626	83	1.38	1.03-1.85	1.30	0.96-1.76
>1095	4022	146	1.73	1.34-2.24	1.63	1.24-2.14

JAMA Intern Med. 2015 Mar;175(3):401-7.

Crude and adjusted odds ratios of dementia by prescription of any, defined daily doses (DDDs), and total burden of anticholinergics measured with the Anticholinergic Cognitive Burden (ACB) score

Exposure during DEP	No of cases (%)	No of controls (%)	Odds ratio (95% CI)		
			Unadjusted	Adjusted at start of DEP[*] [†]	Adjusted at end of DEP[*] [‡]
Any use					
Prescriptions (ACB score):					
None	4295 (10.5)	36 329 (12.8)	1.00	1.00	1.00
1	36 437 (89.4)	247 406 (87.1)	1.25[§] (1.21 to 1.29)	1.11[§] (1.07 to 1.15)	1.10[§] (1.06 to 1.15)
2	1429 (3.5)	7909 (2.8)	1.27[§] (1.20 to 1.35)	1.10[§] (1.03 to 1.17)	1.10[§] (1.03 to 1.16)
3	14 453 (35.5)	86 403 (30.4)	1.27[§] (1.24 to 1.30)	1.16[§] (1.13 to 1.19)	1.11[§] (1.08 to 1.14)

- The results of the study found a small effect size, with odds ratios between the prescription of any drug with an ACB score of 1,2 or 3 (increasing potency) and an incident dementia diagnosis of between 1.06 and 1.11 with no clear increase in association with anticholinergic potency.
- There were inconsistent associations between ACB scale and class of medication, for example, antipsychotic drugs with a score of 3 showed no association whereas antidepressant and urological agents with the same classification did show such an association.
- These relationships were seen even for exposures 15-20 years before the diagnosis of dementia

BMJ, 2018. **361**: p. k1315

Associated effects of AM use with cognition in older persons

Study	Design	Exposure	Summary	
1 [64]	Prospective observational study of community-dwelling adults with ADD[85]	High vs. low anticholinergic burden score	No increased cognitive decline in participants with ADD receiving established doses of anticholinergic medications	+
2 [28]	Prospective observational study of community-dwelling and institutionalized older adults	Definite vs. possible anticholinergic medications, vs. no exposure	Anticholinergic medication use increased cumulative risk of cognitive impairment and mortality	-
3 [29]	Prospective observational study of community-dwelling cognitively normal older African Americans	Definite anticholinergic medications vs. no exposure	Anticholinergic medication use associated with an increased risk of cognitive impairment	-
4 [55]	Cross-sectional study of participants with probable ADD[85] referred to a psycho-geriatric Unit	SAA positive vs. negative	Positive SAA was associated with lower global cognitive performance	-
5 [56]	Prospective observational study of community-dwelling and institutionalized older adults	Exposure to anticholinergic medications vs. no exposure	Anticholinergic medication use was associated with decreased cognitive performance in older females	-
6 [53]	RCT, placebo controlled trial in institutionalized older adult females with mild-to-severe dementia	Oxybutynin ER 5 mg QD vs. placebo	Oxybutynin was safe and well-tolerated for the short-term treatment of urinary incontinence	+
7 [18]	Prospective observational study in community-dwelling and institutionalized older adults	Anticholinergic medications vs. no exposure	Adults exposed to anticholinergic medications had significant declines in cognitive performance, and were more likely to be classified as MCI	-
8 [51]	RCT, placebo controlled trial in cognitively normal older adults	Oxybutynin ER 20 mg QD vs. Darifenacin 15 mg QD, vs. placebo	Oxybutynin was associated with significant impairment in delayed recall; darifenacin was not	-/+
9 [41]	Cross-sectional study in patients with moderate-to-severe dementia admitted to a psycho-geriatric Inpatient Unit	SAA positive vs. negative	Higher SAA associated with lower cognitive performance	-
10 [54]	Retrospective cohort study in participants with ADD[85] selected from ADC database	Anticholinergic medications vs. no exposure	Anticholinergic medication use was associated with a greater decline in global cognitive performance	-
11 [27]	Cross-sectional study in community-dwelling cognitively normal older adults	High vs. low, vs. undetectable SAA	Higher SAA was associated with lower MMSE scores	-
12 [52]	RCT, placebo controlled cross-over study in cognitively normal older adults	Oxybutynin 10 mg vs. diphenhydramine 50 mg, vs. placebo	Oxybutynin and diphenhydramine caused impairment of cognition within 90 minutes of administration	-
13 [57]	Cross-sectional study in cognitively normal older adults with major depressive disorder	SAA positive vs. negative	SAA was associated with lower delayed recall scores, even at very low levels	-
14 [26]	RCT, placebo controlled cross-over study in cognitively normal adults	Scopolamine 0.5 mg IV vs. placebo	Older participants were more sensitive to the cognitive effects of scopolamine	-
15 [34]	Dose-response trial, placebo controlled in individuals with ADD[86] vs. age-matched controls	Scopolamine IV titration (0.1, 0.25, 0.5 mg and placebo)	Patients with ADD were more sensitive to the cognitive effects of cholinergic blockade	-

SD = standard deviation; RCT = randomized control trial; ADD = Alzheimer disease dementia; MMSE = Mini Mental State Examination [62]; ADC = Alzheimer Disease Center; SAA = serum anticholinergic activity; MCI = Mild Cognitive Impairment

*A detailed summary of Table 1 results is available upon email request (lfleenor@msma.org)

Mo Med. 2016 May-Jun; 113(3): 207–214.

- In most studies, anticholinergics have had no effect on working memory
- The results concerning anticholinergics and visuomotor functions, executive functions, verbal memory, and fluency as well as implicit and visual memory are mixed, ranging from no effect to a decrease.

References	Residence	Age (years)	Global cognition	Working memory	Visuomotor speed/ psychomotor processing	Complex attention/ executive functions	Verbal memory and learning	Language functions/verbal fluency	Implicit memory	Visual memory
Curran et al. [67]	Healthy	Mean 27		↓/0	↓		↓	0		
Sittironnarit et al. [6]	Healthy	>60	0	0	0	↓/0	0	↓/0		
Wojtalik et al. [46]	Schizophrrenia/ schizoaffective disorder patients	Mean 26		↓		↓	0			
Minzenberg et al. [33]	Schizophrenic outpatients	Mean 40	0	0	0	↓/0	↓	↓/0		↓
Lechevallier-Michel et al. [2]	Community	≥70	↓					↓		↓
Mulsant et al. [28]	Community	≥65	↓							
Han et al. [43]	Community	>65					↓			
Fox et al. [68]	Community	>65	↓							
Uusvaara et al. [69]	Community	75–90	0				0	↓		0
Hilmer et al. [5]	Community	70–79			↓					
Nebes et al. [53]	Community	>65		0	↓	↓			↓	
Lampela et al. [29]	Community	Mean 82	↓							
Ancelin et al. [3]	Outpatients	>60				↓/0		↓	0	
Sittironnarit et al. [6]	AD/MCI	>60	0	0	0	0	0	0		
Hori et al. [37]	Hospitalized AD patients	Mean 79 (SAA+), 78 (SAA−)	↓							
Mulsant et al. [63]	Dementia	63–96		0	↓					
Lu and Tune [31]	AD patients	Mean 76 (AchD+), 77 (AchD−)	↓							
Miller et al. [32]	Presurgical patients	Mean 67	0		0		↓			
Plaschke et al. [70]	Cardiac surgery patients	≥55		0	0	0	0	0		

Drugs Aging (2015) 32:963–974

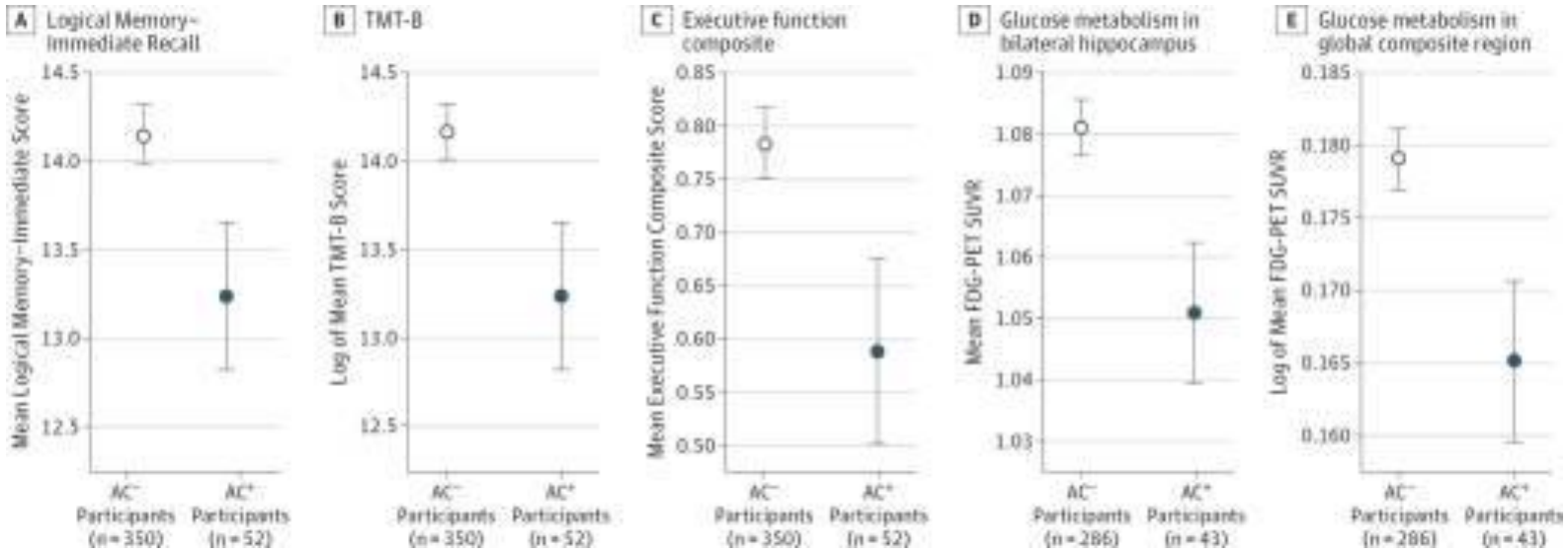
AM use and cognition

- Community-dwelling older adults (N = 7351) aged 60+ years with Clinical Dementia Rating-Sum of Boxes score between 0.5 and 2.5
- Participants who took AC medications were older, largely female, and had a higher prevalence of incontinence than those without AC exposure.
- Global cognition was significantly greater in the moderate/high-AC group than the no-AC group (-0.23 ± 0.53 vs. -0.32 ± 0.53).
- Multivariable linear regression showed that the global cognition score among the low- and moderate/high-AC groups, compared with the no- AC group, was 0.064 higher ($p = 0.006$ and $p = 0.12$, respectively).
- older adults might experience some beneficial cognitive effects from AC drugs, possibly due to the therapeutic effects of these medications in controlling comorbidities, outweighing any adverse effects on cognition.

Drugs Aging. 2016 Nov;33(11):809-818.

Association between AM use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults

- Use of medications with medium or high AC effects in the Alz Dis Neuroimaging Initiative cohort was associated with
- poorer cognition (particularly in immediate memory recall and executive function)
- reduced glucose metabolism
- whole-brain and temporal lobe atrophy
- and clinical decline.



301 participants without significant memory concerns
and 101 participants with significant memory concerns

JAMA Neurol. 2016 Jun 1; 73(6): 721–732

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Drugs Aging. 2016 Nov;33(11):809-818.

- Different populations
- Different assessments
- Different comorbidities

In clinical practice, anticholinergic burden should minimized to reduce the impact associated with excessive cholinergic inhibition

However, there is no standardized consensus on how to quantify the anticholinergic burden

The current anticholinergic drug scales simplify complex pharmacological mechanisms, which is particularly problematic in geriatric risk assessment

Salahudeen MS. Drugs Aging 2016;33:305–313.
Kersten H. Basic Clin Pharmacol Toxicol 2014;114(2):151-9.
Salahudeen MS. BMC Geriatr 2015;15:31.
Collamati A. Aging Clin Exp Res 2016;28(1):25-35.
Kelly M. Pharmacotherapy 2005;25(11):1592–1601.

What about the effect of stopping AM?

- In 87 NH residents ADS score of greater than or equal to 3 from 22 nursing homes, with a pharmacist led intervention
  - median ADS score reduced by 2 units ($p < .0001$) in the intervention group and remained unchanged in the control group.
- After 8 weeks, the adjusted mean difference in immediate recall was 0.54 words between the intervention and control group (95% confidence interval [*CI*]: −0.91, 2.05; $p = .48$).
- The study groups did not differ significantly in any of the other cognitive end points or SAA at either follow-up ($p > .18$).

J Gerontol A Biol Sci Med Sci. 2013 Mar;68(3):271-8.

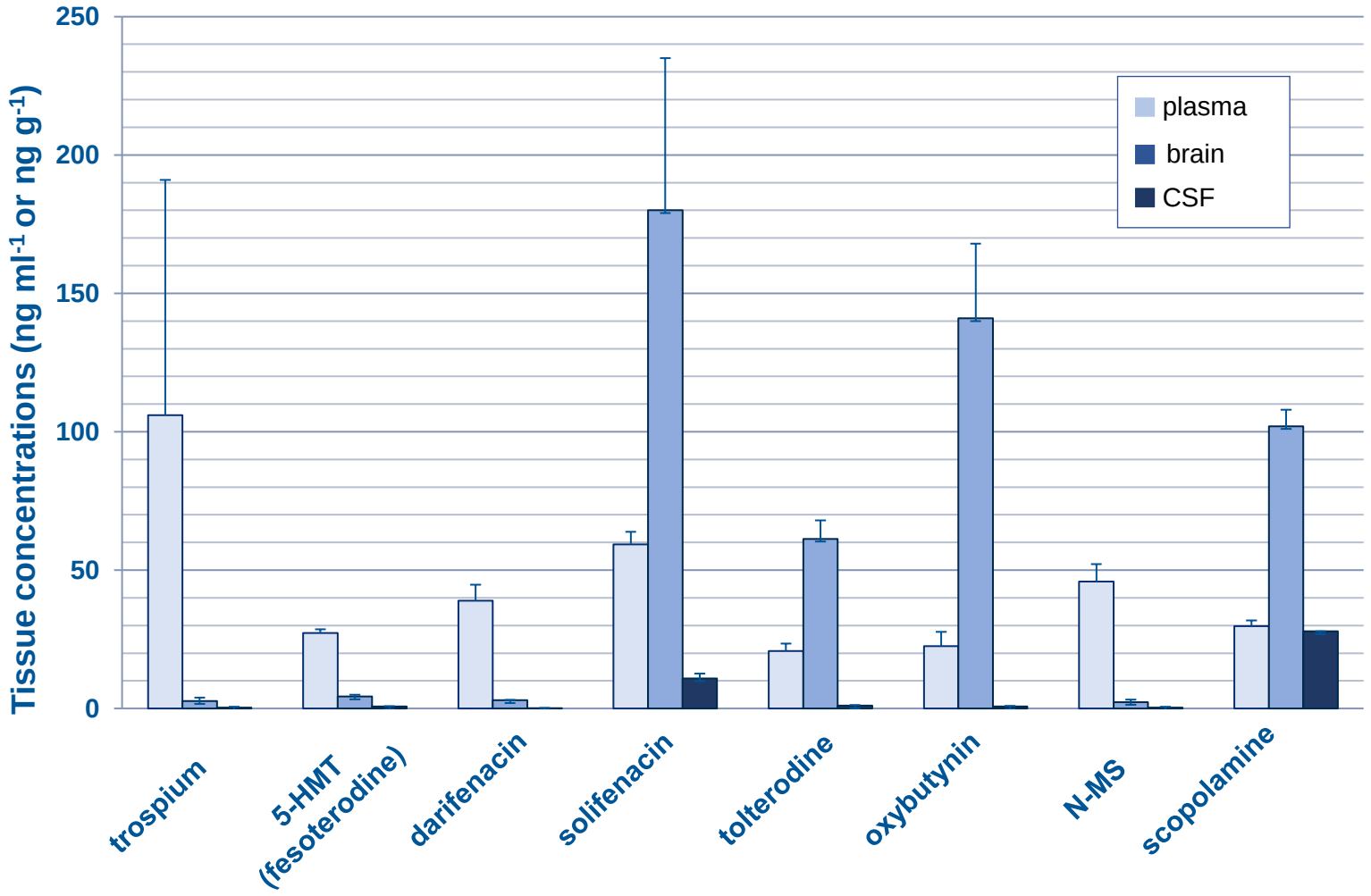
And for bladder antimuscarinics..?

- Community-dwelling men and women aged 65 and older (N = 24,106
- Overall, 5.2% (95% confidence interval (CI) = 4.9-5.5%) took a bladder antimuscarinic.
- Participants with impaired cognition were more likely to be taking an antimuscarinic than those with normal cognition.
- Rates of bladder antimuscarinic use were:
  - 4.0% (95% CI = 3.6-4.4%) for participants with normal cognition
  - 5.6% (95% CI = 4.9-6.3%) for those with mild cognitive impairment
  - 6.0% (95% CI = 5.5-6.4%) for those with dementia
- Of 624 participants with dementia who took antimuscarinics, 16% (95% CI 13-19%) were simultaneously taking other medicines with anticholinergic properties.

J Am Geriatr Soc. 2017 Feb;65(2):390-394.

Antimuscarinic concentrations in rat plasma, brain and CSF: *in vivo* study

Antimuscarinic concentrations in plasma, brain and CSF following subcutaneous dosing in rats



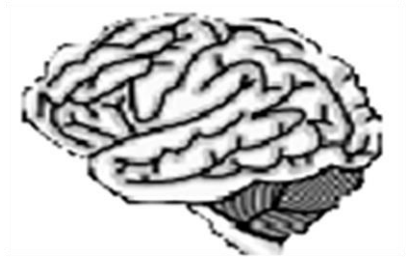
Error bars represent SDs. N=3.

Brain penetration was low for antimuscarinics that were P-glycoprotein substrates:
- 5-HMT (fesoterodine)
- trospium
- darifenacin[1]

Brain penetration was significant for those that were not P-glycoprotein substrates:
- oxybutynin
- solifenacin
- tolterodine[1]

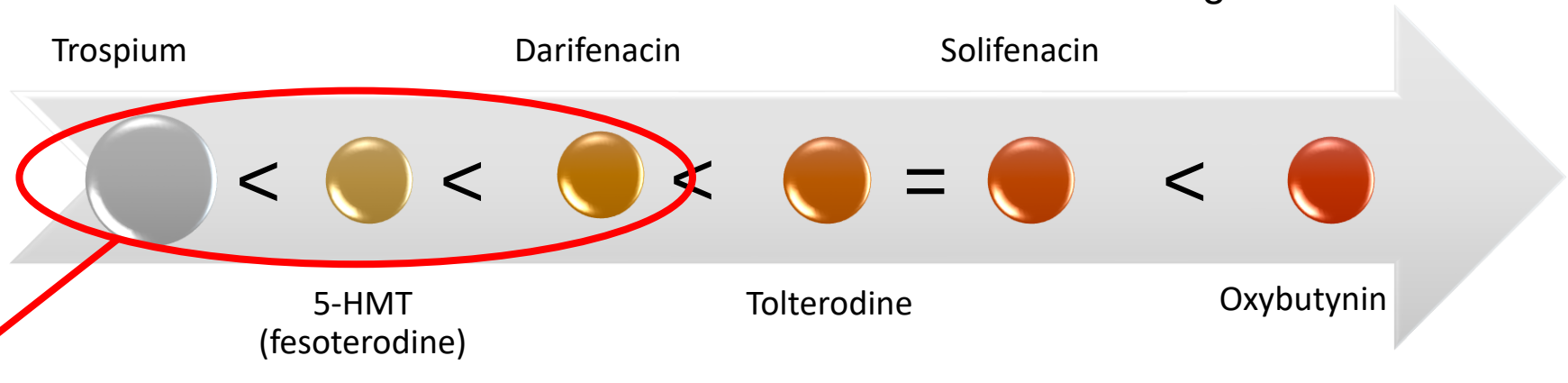
Callegari E *et al*., *Br. J. Clin. Pharm.* 2011;72: 235-246.

CNS Penetration Potential



Low Penetration

High Penetration

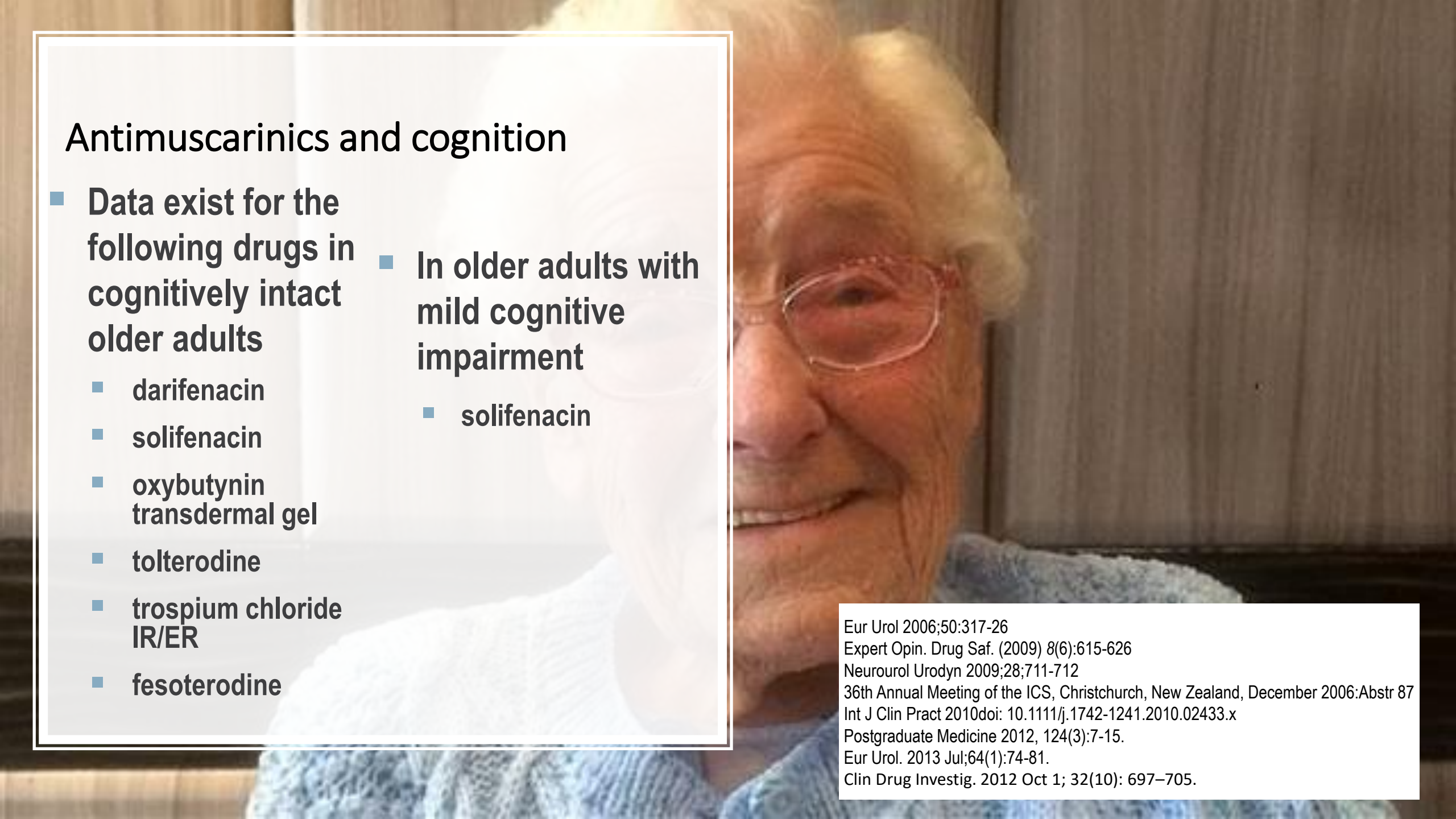


P-gp substrates – probably mitigates adverse effect

Callegari et al. *Br J Clin Pharmacol*. 2011; 72:2: 235-246.

Antimuscarinics and cognition

- Data exist for the following drugs in cognitively intact older adults
  - darifenacin
  - solifenacin
  - oxybutynin transdermal gel
  - tolterodine
  - trospium chloride IR/ER
  - fesoterodine
- In older adults with mild cognitive impairment
  - solifenacin



Eur Urol 2006;50:317-26
Expert Opin. Drug Saf. (2009) *8*(6):615-626
Neurourol Urodyn 2009;28;711-712
36th Annual Meeting of the ICS, Christchurch, New Zealand, December 2006:Abstr 87
Int J Clin Pract 2010doi: 10.1111/j.1742-1241.2010.02433.x
Postgraduate Medicine 2012, 124(3):7-15.
Eur Urol. 2013 Jul;64(1):74-81.
Clin Drug Investig. 2012 Oct 1; 32(10): 697–705.

Observational studies

- No effect on cognition (MMSE) in older persons, associated with
  - Solifenacin
  - oxybutynin, darifenacin, tolterodine, trospium v control
  - propiverine

Urol Int. 2017;98(3):350-357.
Aging Ment Health. 2015;19(3):217-23.

Pharmacological treatment – recommendations from the 6th ICI

- Fesoterodine is effective in ameliorating the symptoms of OAB in robust community dwelling and medically complex older people, identified by VES-13 **(level 1).**
- There is insufficient evidence to determine the efficacy, tolerability, and safety of the following agents in the frail elderly **(Level 4)**:
- **a)** Intravesical oxybutynin
- **b)** Transdermal oxybutynin
- **c)** Trospium
- **d)** Tolterodine
- **e)** Darifenacin
- **f)** Solifenacin
- **g)** Mirabegron
- **h)** Duloxetine
- **i)** Oral and topical oestrogen

Wagg, A. et al. “Incontinence in frail older persons” in Incontinence, Report of the 6th ICI 2017. ICS. Bristol

Pharmacological interventions

- Short-term treatment with oxybutynin-IR has small to moderate efficacy in reducing urinary frequency and urgency UI when added to behavioural therapy in long term care residents. **(Level 2)**
- Low dose oxybutynin-ER does not cause delirium in cognitively impaired nursing home residents **(Level 1)**
- Oxybutynin IR has been associated with cognitive adverse effects in persons with dementia and/or Parkinson's disease **(Level 3)**, although the incidence and prevalence are unknown **(Level 4)**
- Oxybutynin has been associated with tachycardia **(Level 3)**, but not associated with QTc prolongation **(Level 3)** or ventricular arrhythmia **(Level 2)**
- Oxybutynin is less effective in persons with impaired orientation, cerebral cortical under-perfusion, and reduced bladder sensation **(Level 2)**
- Oxybutynin is less well tolerated, versus solifenacin, in older people **(level 2)**

Wagg, A. et al. "Incontinence in frail older persons" in Incontinence, Report of the 6th ICI 2017. ICS. Bristol

Pharmacological treatment

- Tolterodine has been associated with cognitive impairment and tachycardia (**Level 3)**, although the incidence and prevalence are unknown. **(Level 4)**
- Solifenacin (5mg/day) is associated with no impairment of cognition in older persons with mild cognitive impairment versus placebo **(level 2)**
- Excessive anticholinergic load is associated with cognitive impairment in frail older adults **(level 3)**
- Anticholinerigc agents should be prescribed with due regard to underlying anticholinergic load in older persons **(level 3)**
- The effect of cholinergic load on persons with mild dementia is uncertain **(level 3)**

Wagg, A. et al. “Incontinence in frail older persons” in Incontinence, Report of the 6th ICI 2017. ICS. Bristol

Prospectively gathered data on old (65+) and oldest old (75+)

Darifenacin

STUDY:

n = 400, mean age 72 years randomized (2:1) to receive 12 weeks of double-blind treatment with darifenacin (7.5 mg once daily for 2 weeks, then optional titration to 15 mg daily) or placebo

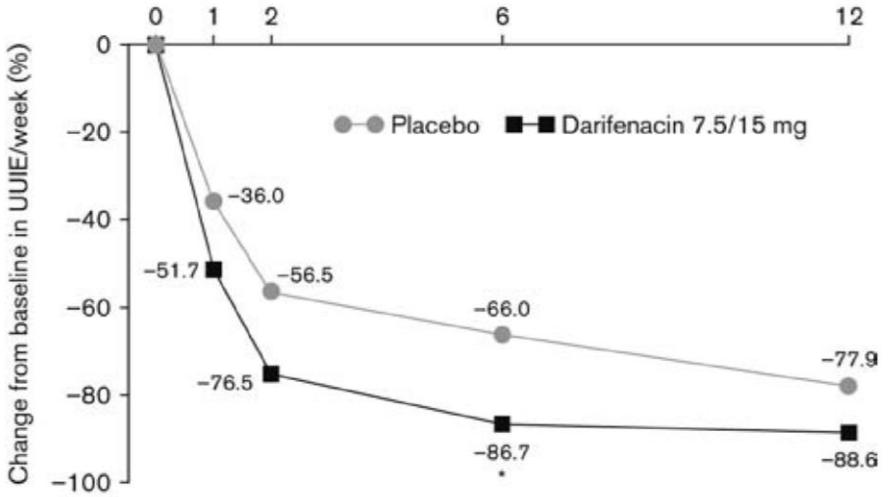
AE:

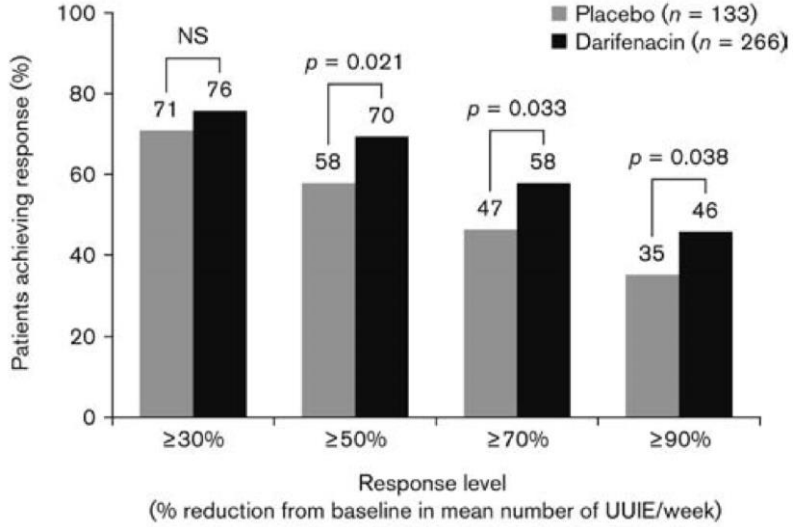
149 patients (56.0%) receiving darifenacin and 60 patients (45.1%) receiving placebo, of which 99 (37.2%) and 24 (18.0%) were considered to be related to the study drug, respectively

dry mouth – darifenacin 59 (22.2%), placebo 5 (3.8%) and constipation, darifenacin, 41 (15.4%) placebo, 11 (8.3%)

PROM:

Total OAB-q score treatment differences of 7.6 and 8.1 at Weeks 6 and 12, respectively in favour of darifenacin, $p < 0.001$ at both time points





Curr Med Res Opin. 2007 Oct;23(10):2347-58

Prospectively gathered data on old (65+) and oldest old (75+)

Fesoterodine

STUDY:

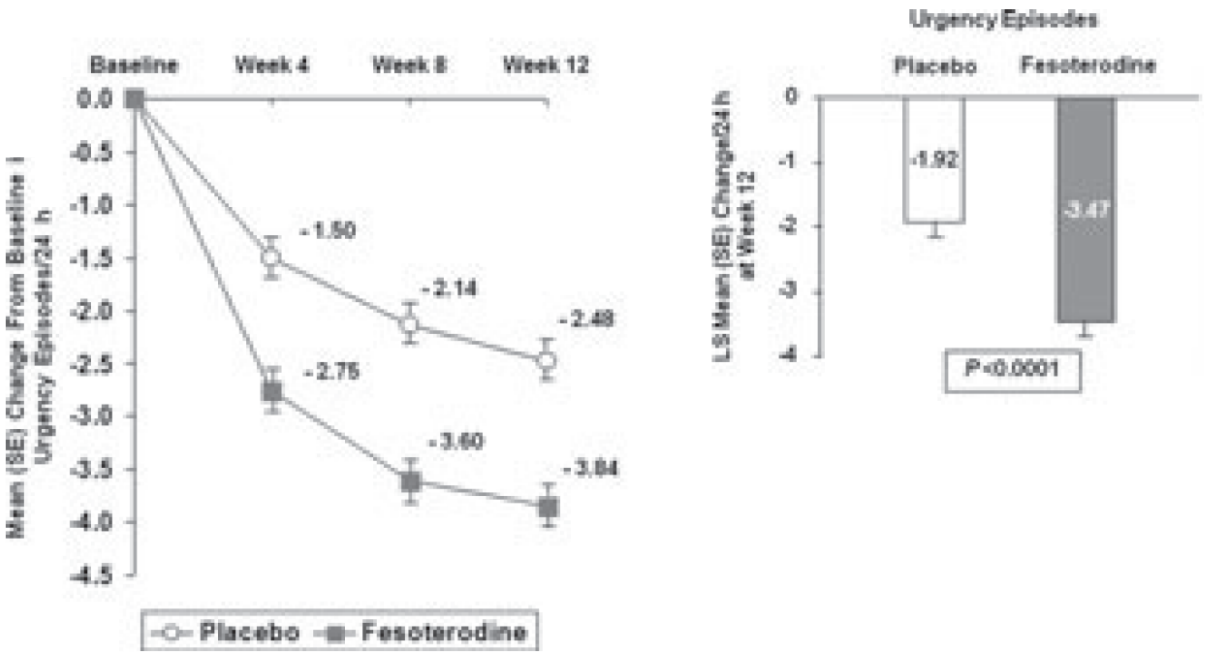
Fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs ≤75) and dosing time. Participants started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8

AE:

Any AE – 36.1% placebo, 62.2% fesoterodine. Dry mouth fesoterodine 33.9%, placebo 5.3% (76% mild-moderate). No change in MMSE scores.

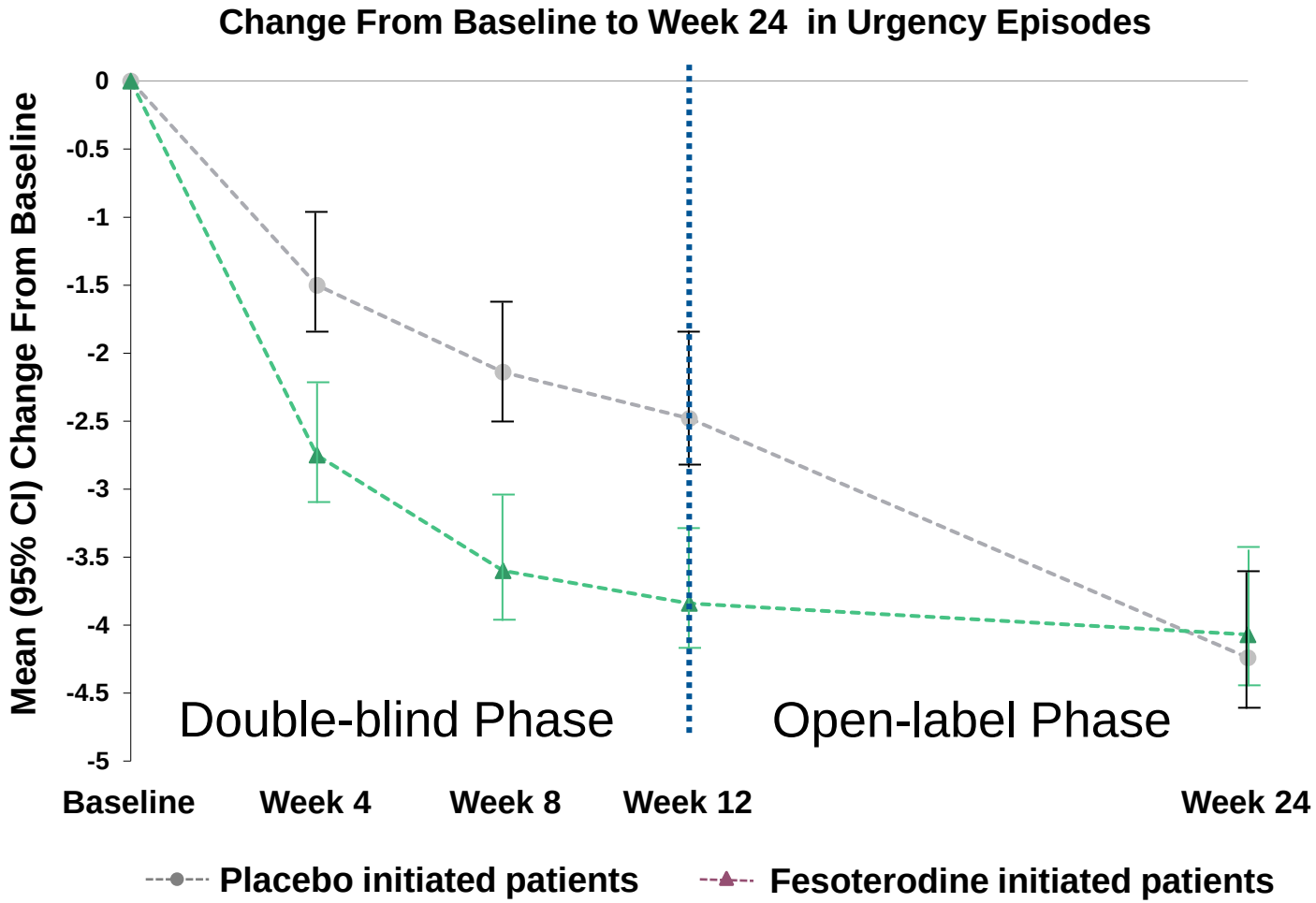
PROM:

The odds of response on the TBS, OAB-S, PPBC, and UPS were significantly greater in the fesoterodine group than placebo (P < .001 for TBS, OAB-S, and PPBC



J Am Geriatr Soc. 2013 Feb;61(2):185-93

SOFIA: Fesoterodine
Urgency Episodes *(Primary endpoint)*



- **By week 8, 64% of fesoterodine-treated participants opted for dose escalation.**
- **At week 12, all patients received fesoterodine**

Wagg et al. Neurourol Urodynam 2014;33:106–114.

Prospectively gathered data on old (65+) and oldest old (75+)

Fesoterodine in the vulnerable elderly

STUDY:

566 patients, mean age 75 (65-91) randomized 1:1 fesoterodine: placebo. All pts VES-13 >3. 50% of subjects in each group demonstrated significant levels of exhaustion and fatigue on the CES-D, 42% demonstrated impaired mobility on the TUG.

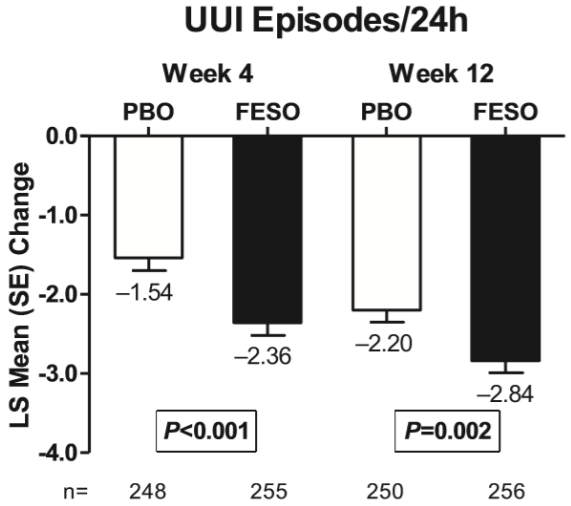
AE:

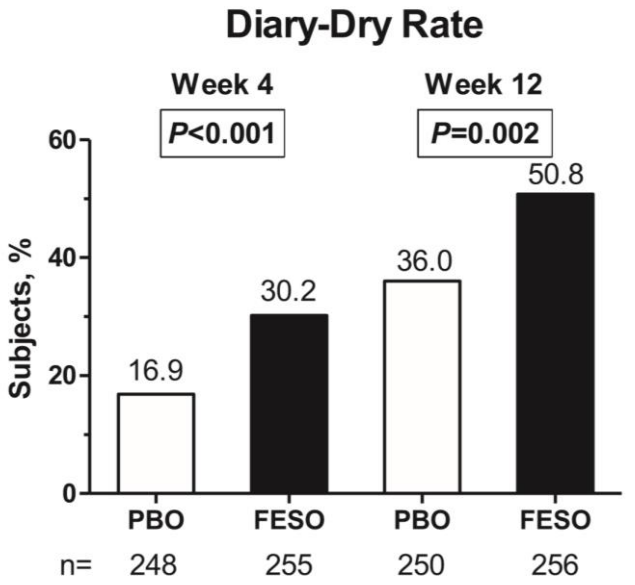
TEAE: placebo 42.7% fesoterodine 56.2%. Dry mouth, p:6.0% fesoterodine 23.5%, constipation, p: 4.3%, fesoterodine 11.1% urinary retention p: 0 fesoterodine 3.2% - 1/3 required catherization

No change in MMSE.

PROM:

12 week change in OAB symptom bother: placebo: -20.1(1.6), fesoterodine: -28.1 (1.6), p<0.005

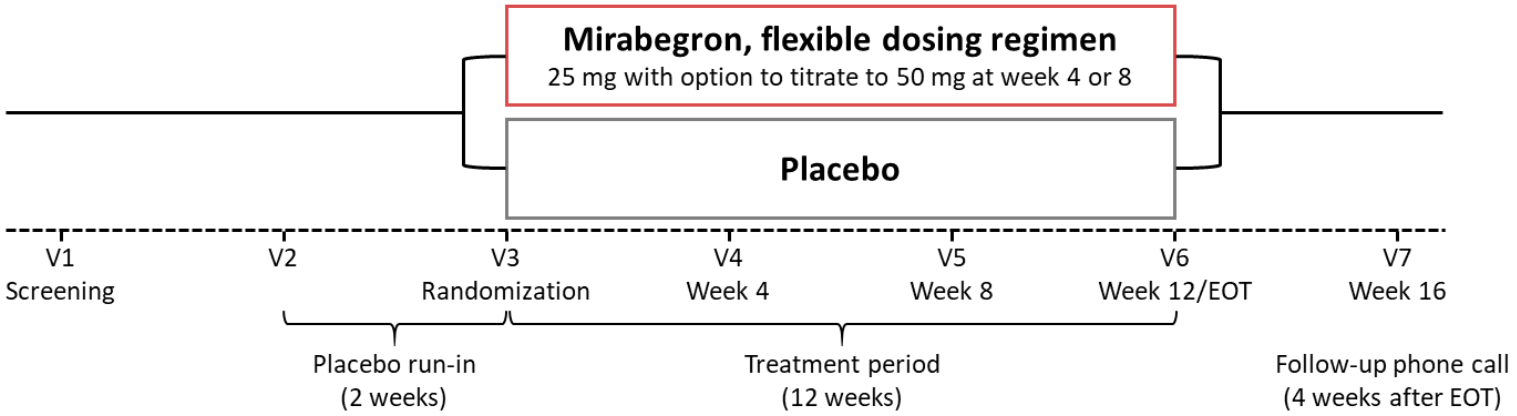




J Urol 2014;191(2):395-404

PILLAR: mirabegron efficacy and safety in patients aged ≥65 years with OAB symptoms

- Phase 4, double-blind, randomized, placebo-controlled study
- 3-day micturition diaries completed at baseline and before week 4, 8, and 12 (EOT)
- Patients with ≥1 incontinence episode, ≥3 urgency episodes (PPIUS grade 3 or 4), and ≥8 micturitions/24 h on average at baseline randomized 1:1 to mirabegron/placebo, stratified by age <75/≥75 years



Co-primary endpoints:
Change from baseline to EOT in mean number of micturitions and incontinence episodes/24 h for mirabegron total (25/50 mg) vs. placebo

EOT, end-of-treatment; OAB, overactive bladder syndrome; PPIUS, Patient Perception of Intensity of Urgency Scale.

No significant change in Montreal Cognitive Assessment score during the study
Mean (SD) score change from baseline to EOT: Placebo: 0.2 (2.3) Mirabegron Total: 0.1 (2.4)

Prospectively gathered data on old (65+) and oldest old (75+)

MIRABEGRON

STUDY:

12 week phase 4, double-blind, randomized, placebo-controlled study. Randomized 1:1 to mirabegron/placebo, stratified by age <75/≥75 years, 442 placebo, 445 mirabegron. Co-primary endpoints of micturition frequency and incontinence episodes/24h. Population "equivalent" to community dwelling elderly

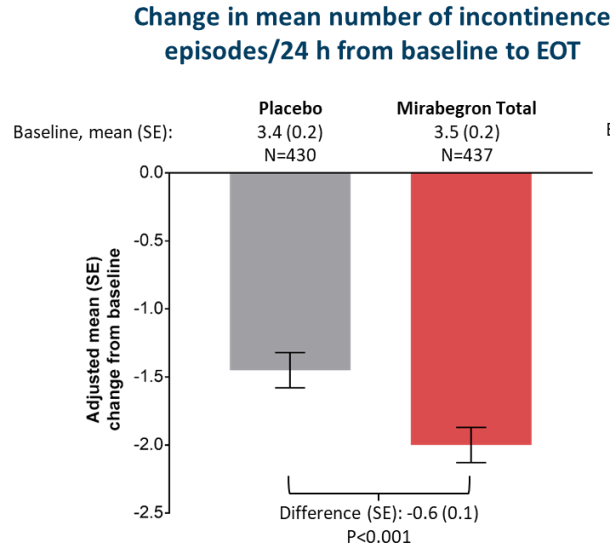
AE:

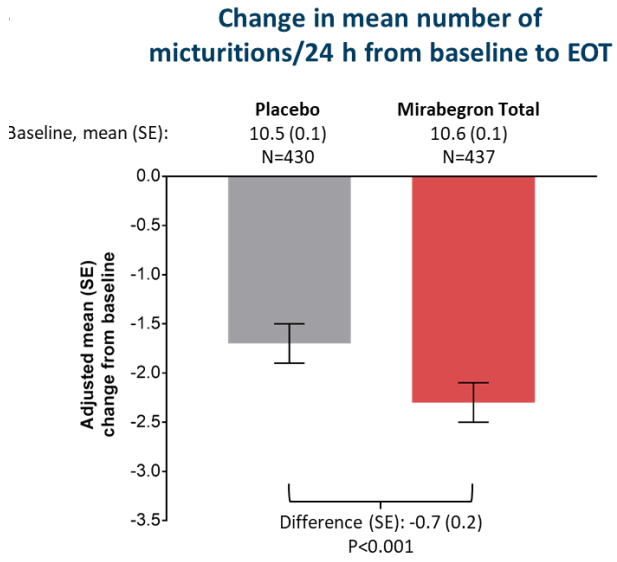
All TEAE: placebo, 39.4%, mirabegron, 47.0%. UTI 5.6% (P:7.0%), headache 5.2% (P:2.7%) Mean (SD) score change from baseline to EOT: Placebo: 0.2 (2.3) Mirabegron Total: 0.1 (2.4)

PROM:

Change in OAB-q symptom bother score from baseline to EOT Difference (SE): -5.2 (1.4)

P<0.001

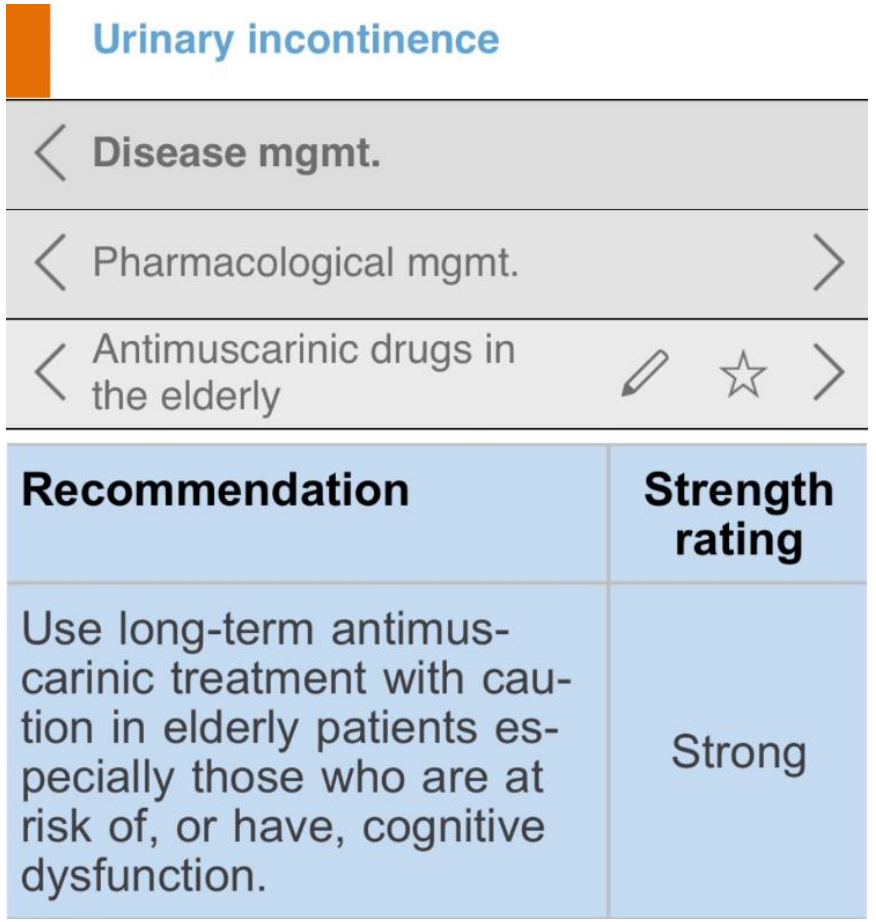




Wagg et al. Presented at ICS 2018

EAU guidelines

- Note:
  - Lumps all antimuscarinics together – evidence?
  - The result of AM use in those with CI is unclear



Urinary incontinence

Disease mgmt.

Pharmacological mgmt.

Antimuscarinic drugs in the elderly

Recommendation	Strength rating
Use long-term antimuscarinic treatment with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction.	Strong

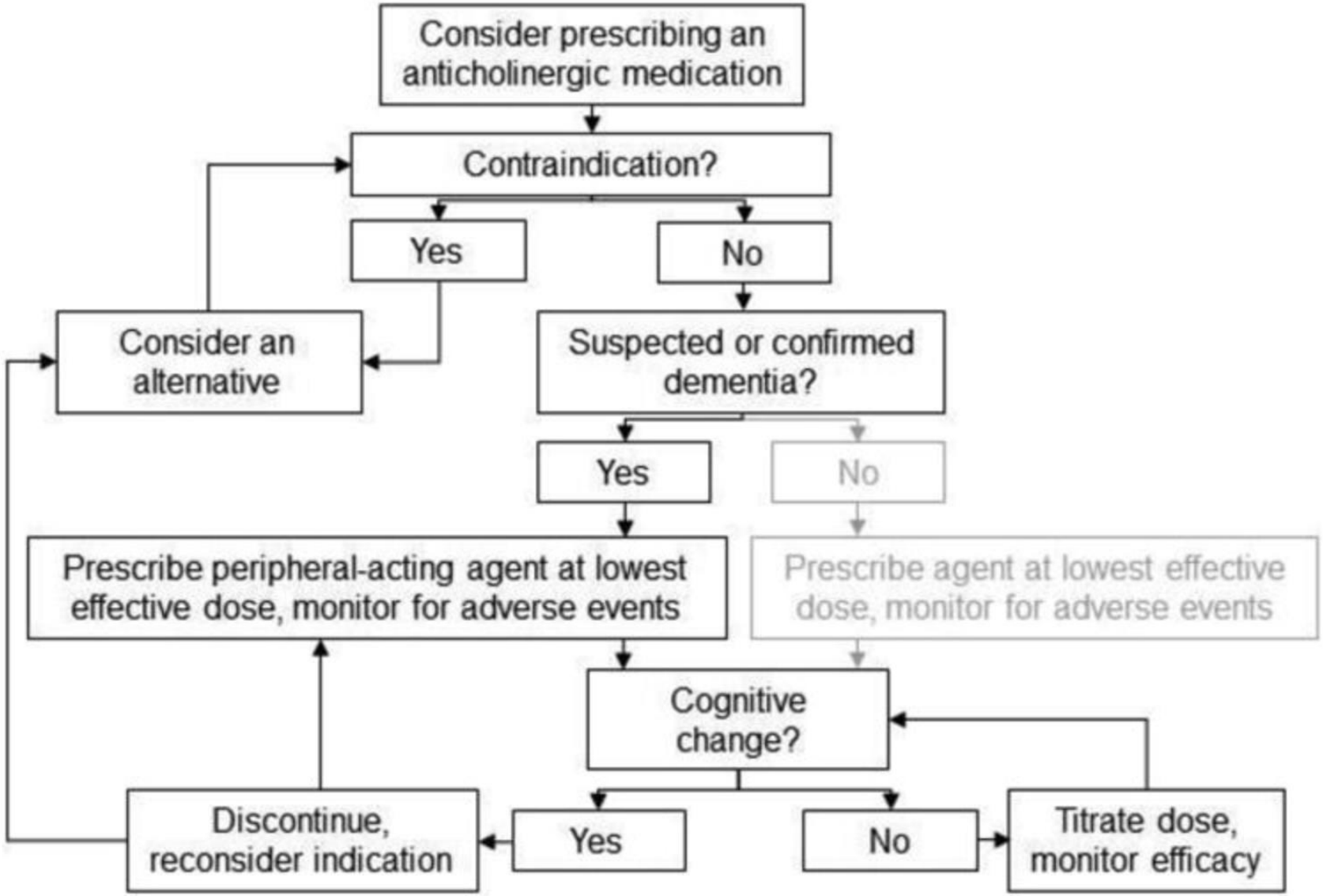
Eur Urol. 2018 Apr;73(4):596-609.

Patients with an increased risk of cognitive deficit

- Alzheimer's disease and related dementias (including mild cognitive impairment, age-associated memory impairment)[1]
- Parkinson’s disease and other akinetic rigid syndromes[2]
- Type 2 diabetes in the elderly[3]
- Poorly controlled hypertension[4]
- Multiple sclerosis[5]
- Alcohol dependence[6]
- (Multiple pre-existing anticholinergic medications)

1. Sunderland T et al. *Arch Gen Psychiatry* 1987; 44: 418–46.
2. Koller WC . *Cortex* 1984; 20: 307–11.
3. Perlmuter LC et al. *Am J Med* 1984; 77: 1043–48.Goldstein FC. J Am Geriatr Soc. 2013 Jan;61(1):67-73. doi: 10.1111/jgs.12067
4. Gaudino EA et al. *Neuropsychiatry Neuropsychol Behav Neurol* 2001; 14: 32–44.
5. Duka T et al. *Alcohol Clin Exp Res* 2003; 10: 1563–72.

Suggested strategy for anticholinergic medication prescribing and monitoring in older adults with (black) and without dementia (gray).



Mo Med. 2016 May-Jun; 113(3): 207–214.

Take home messages:

ONE

There is a weak association between anticholinergic load and cognitive impairment at the highest exposure levels over a minimum of 2-3 years

Take home messages:

TWO

Anticholinergic burden scales variably capture the true nature of anticholinergic load; even high scores often have no relationship with either cognitive or functional impairment, sometimes even in vulnerable older adults

Take home messages:

THREE

There is a dearth of data concerning long term effects of newer AM on cognition – we should be open, careful and overall, remember that active treatment of OAB-UUI in older people is better than none

Don’t forget….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ICS 2019
GOTHENBURG
Poseidon, the sea God
by Carl Milles
One of Gothenburg's
most famous landmarks,
situated at the top of
the main boulevard
Avenyn at the square
Götaplatsen.
www.ics.org/2019
#ICSMeeting