Impact evaluation of Anticholinergics and Antihypertensives exposure on Dementia Prognosis using Pharmacoepidemiology & Stem Cell–Based Approach

Inez K. A. Pranoto, PhD

Postdoctoral Scholar (Jessica Young's Lab)
UW Department of Laboratory Medicine and Pathology

Onchee Yu, MS

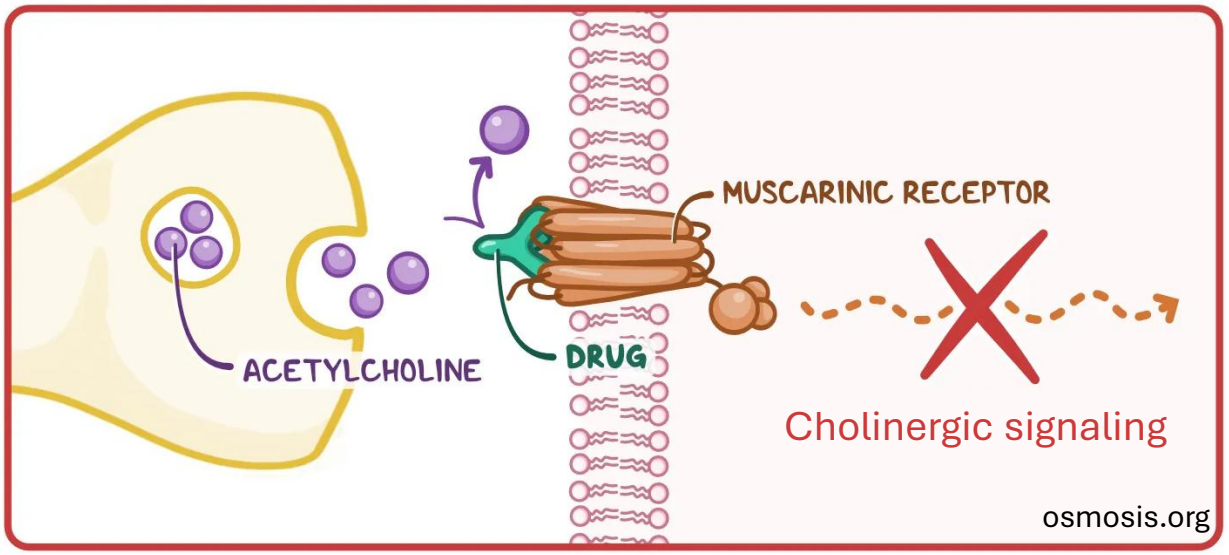
Principal Collaborative Biostatistician
Kaiser Permanente Washington Health Research Institute

ACT U19 Project 3 Objectives

Aim 1: To directly test mechanisms of neurotoxicity from anticholinergics (ACMs) and address confounding by indication by deploying human stem cell-based molecular assays

Aim 2: To determine comparative associations of antihypertensives (AHTs) with neuropathology, dementia and AD, and neuroimaging outcomes. Test cellular mechanisms of neuroprotection.

Anticholinergic medications (ACMs) inhibit cholinergic signaling to manage various health conditions



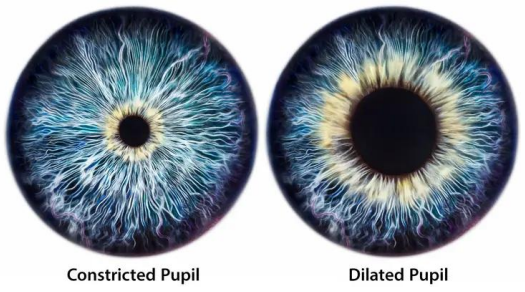
Acetylcholine:
neurotransmitter that normally binds to the muscarinic receptors for cholinergic signaling activation

Prescribed to treat various health conditions:

Depression
(Antidepressants)

Overactive bladder
(Urological)

Allergy
(Antihistamines)



Pupil dilator during eye exam
(Mydriatics)

Prolonged use of certain ACMs is correlated to an increased risk in dementia

Drug Type	Study Participants, No. (%)		Odds Ratio (95%CI)		
	Case Patients (n = 58 769)	Controls (n = 225 574)	Unadjusted	Adjusted for the Other Drug Types[a]	Fully Adjusted[b]
Antihistamines, TSDDs					
Nonuse	52 312 (89.0)	202 429 (89.7)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	4987 (8.5)	18 187 (8.1)	1.05 (1.02-1.09)	1.02 (0.98-1.05)	1.03 (0.99-1.07)
91-365	923 (1.6)	3105 (1.4)	1.14 (1.06-1.23)	1.06 (0.99-1.15)	1.03 (0.95-1.12)
366-1095	280 (0.5)	1022 (0.5)	1.06 (0.93-1.22)	0.98 (0.85-1.12)	1.02 (0.88-1.18)
>1095	267 (0.5)	831 (0.4)	1.22 (1.06-1.41)	1.14 (0.99-1.31)	1.14 (0.98-1.34)
Antidepressants, TSDDs					
Nonuse	42 831 (72.9)	173 014 (76.7)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	5098 (8.7)	19 402 (8.6)	1.08 (1.04-1.11)	1.04 (1.01-1.08)	1.02 (0.98-1.06)
91-365	3463 (5.9)	11 931 (5.3)	1.20 (1.15-1.24)	1.14 (1.10-1.19)	1.12 (1.07-1.17)
366-1095	2227 (3.8)	6749 (3.0)	1.35 (1.29-1.42)	1.27 (1.20-1.33)	1.25 (1.18-1.32)
>1095	5150 (8.8)	14 478 (6.4)	1.47 (1.42-1.52)	1.34 (1.29-1.39)	1.29 (1.24-1.34)
Antivertigo/Antiemetics, TSDDs					
Nonuse	44 800 (76.2)	176 584 (78.3)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	11 427 (19.4)	41 159 (18.3)	1.10 (1.07-1.12)	1.06 (1.03-1.08)	1.05 (1.02-1.08)
91-365	1574 (2.7)	5026 (2.2)	1.23 (1.16-1.31)	1.14 (1.08-1.21)	1.14 (1.07-1.21)
366-1095	617 (1.1)	1659 (0.7)	1.47 (1.34-1.61)	1.33 (1.21-1.47)	1.41 (1.27-1.56)
>1095	351 (0.6)	1146 (0.5)	1.20 (1.06-1.35)	1.06 (0.94-1.20)	1.08 (0.94-1.24)
Antiparkinson Agents, TSDDs					
Nonuse	58 477 (99.5)	225 047 (99.8)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	68 (0.1)	179 (0.1)	1.43 (1.08-1.90)	1.04 (0.78-1.38)	1.01 (0.73-1.39)
91-365	50 (0.1)	59 (0)	3.29 (2.25-4.81)	2.07 (1.40-3.05)	1.68 (1.09-2.58)
366-1095	39 (0.1)	71 (0)	2.08 (1.40-3.09)	1.29 (0.86-1.94)	1.03 (0.66-1.61)
>1095	135 (0.2)	218 (0.1)	2.39 (1.93-2.97)	1.61 (1.29-2.03)	1.52 (1.16-2.00)
Antipsychotics, TSDDs					
Nonuse	56 957 (96.9)	222 174 (98.5)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	388 (0.7)	882 (0.4)	1.71 (1.51-1.93)	1.56 (1.38-1.76)	1.44 (1.25-1.66)
91-365	332 (0.6)	695 (0.3)	1.90 (1.66-2.17)	1.67 (1.46-1.91)	1.41 (1.21-1.65)
366-1095	304 (0.5)	490 (0.2)	2.45 (2.12-2.83)	2.15 (1.85-2.49)	2.09 (1.76-2.47)
>1095	788 (1.3)	1333 (0.6)	2.29 (2.09-2.50)	1.89 (1.72-2.07)	1.70 (1.53-1.90)
Bladder Antimuscarinics, TSDDs					
Nonuse	51 905 (88.3)	206 796 (91.7)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	2139 (3.6)	7005 (3.1)	1.21 (1.15-1.27)	1.18 (1.12-1.24)	1.19 (1.13-1.26)
91-365	1417 (2.4)	4078 (1.8)	1.38 (1.30-1.47)	1.33 (1.25-1.41)	1.35 (1.27-1.45)
366-1095	1244 (2.1)	2941 (1.3)	1.71 (1.59-1.83)	1.63 (1.52-1.74)	1.65 (1.53-1.78)
>1095	2064 (3.5)	4754 (2.1)	1.73 (1.64-1.82)	1.65 (1.57-1.74)	1.65 (1.56-1.75)
Skeletal Muscle Relaxants, TSDDs					
Nonuse	58 340 (99.3)	224 006 (99.3)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	372 (0.6)	1380 (0.6)	1.08 (0.96-1.22)	1.01 (0.89-1.14)	0.98 (0.86-1.11)
91-365	39 (0.1)	115 (0.1)	1.38 (0.95-1.99)	1.17 (0.81-1.70)	1.12 (0.77-1.65)
366-1095	9 (0)	41 (0)	0.90 (0.44-1.88)	0.84 (0.40-1.75)	0.99 (0.46-2.10)
>1095	9 (0)	32 (0)	1.09 (0.52-2.29)	0.90 (0.42-1.91)	1.10 (0.47-2.55)
Gastrointestinal Antispasmodics, TSDDs					
Nonuse	54 733 (93.1)	210 093 (93.1)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	2765 (4.7)	10 914 (4.8)	0.97 (0.93-1.01)	0.90 (0.86-0.94)	0.90 (0.85-0.94)
91-365	722 (1.2)	2686 (1.2)	1.05 (0.96-1.14)	0.94 (0.86-1.02)	0.93 (0.85-1.02)
366-1095	267 (0.5)	938 (0.4)	1.11 (0.97-1.27)	0.98 (0.85-1.12)	0.93 (0.80-1.09)
>1095	282 (0.5)	943 (0.4)	1.19 (1.04-1.36)	1.03 (0.90-1.18)	1.04 (0.90-1.20)
Antiarrhythmics, TSDDs					
Nonuse	58 720 (99.9)	225 402 (99.9)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	9 (0)	37 (0)	0.88 (0.42-1.84)	0.88 (0.42-1.84)	0.74 (0.33-1.64)
91-365	7 (0)	20 (0)	1.38 (0.58-3.28)	1.35 (0.57-3.22)	1.25 (0.44-3.53)
366-1095	10 (0)	27 (0)	1.22 (0.58-2.56)	1.16 (0.55-2.46)	1.22 (0.56-2.66)
>1095	23 (0)	88 (0)	0.97 (0.61-1.55)	0.99 (0.62-1.58)	0.94 (0.56-1.55)
Antiepileptics, TSDDs					
Nonuse	57 358 (97.6)	221 082 (98)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	630 (1.1)	2459 (1.1)	0.98 (0.90-1.07)	0.89 (0.81-0.97)	0.88 (0.80-0.97)
91-365	202 (0.3)	592 (0.3)	1.31 (1.12-1.54)	1.17 (1.00-1.38)	1.14 (0.95-1.36)
366-1095	135 (0.2)	359 (0.2)	1.42 (1.16-1.74)	1.25 (1.02-1.53)	1.13 (0.90-1.41)
>1095	444 (0.8)	1082 (0.5)	1.58 (1.41-1.77)	1.44 (1.28-1.61)	1.39 (1.22-1.57)
Antimuscarinic Bronchodilators, TSDDs					
Nonuse	54 891 (93.4)	211 578 (93.8)	1 [Reference]	1 [Reference]	1 [Reference]
1-90	1228 (2.1)	4326 (1.9)	1.10 (1.03-1.17)	1.05 (0.99-1.13)	0.99 (0.92-1.07)
91-365	786 (1.3)	2885 (1.3)	1.05 (0.97-1.14)	1.01 (0.93-1.09)	0.97 (0.89-1.06)
366-1095	742 (1.3)	2719 (1.2)	1.07 (0.99-1.16)	1.02 (0.94-1.11)	0.97 (0.88-1.06)
>1095	1122 (1.9)	4066 (1.8)	1.08 (1.01-1.16)	1.05 (0.98-1.13)	0.97 (0.90-1.05)

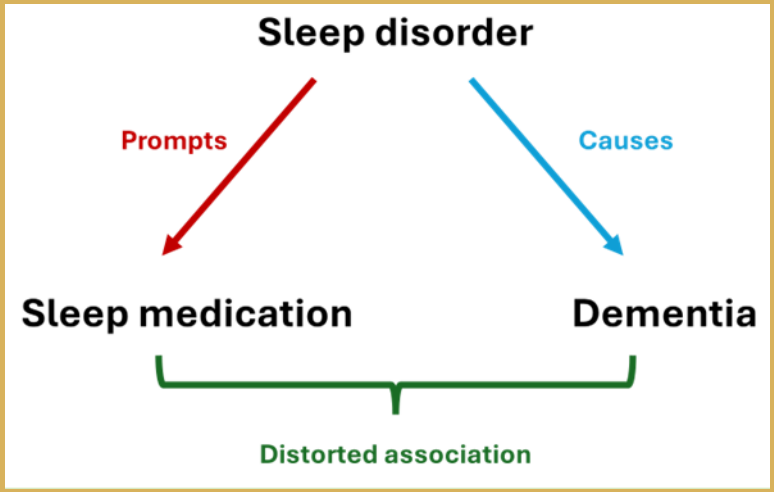
Gray, S. L. et al., *JAMA Intern Med*. 2015
Coupland, C et al., *JAMA Intern Med*. 2019
Richardson, K. et al. *BMJ*. 2018
Iyen, B. et al. *BMJ Medicine*. 2024

Pharmacoepidemiology studies are confounded by biases & incapable of dissecting molecular mechanism

Multimorbidity
participants suffer from multiple illnesses

Polypharmacy
participants take multiple medications simultaneously

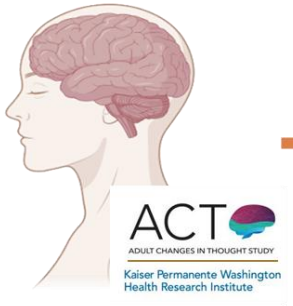
Confounding by indication bias
A bias where the reason for initiating a treatment is also associated with the observed outcome



Human iPSC-derived cortical neurons model!

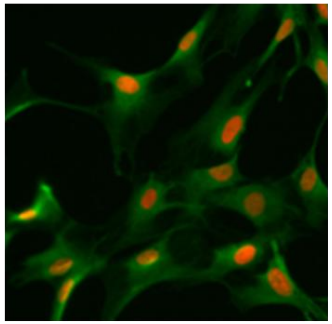
Elucidating the mechanisms by which ACMs drive neurotoxicity using hiPSC-neurons from ACT cohort

Post-mortem brains



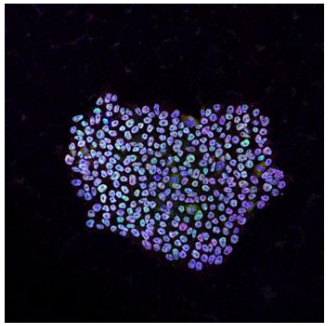
12 ACT donors:
6 males & 6 females

Leptomeningeal cells



Reprogram

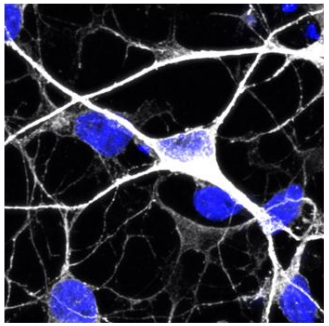
hiPSCs



12 hiPSC lines

Differentiate

hiPSC-derived cortical neurons



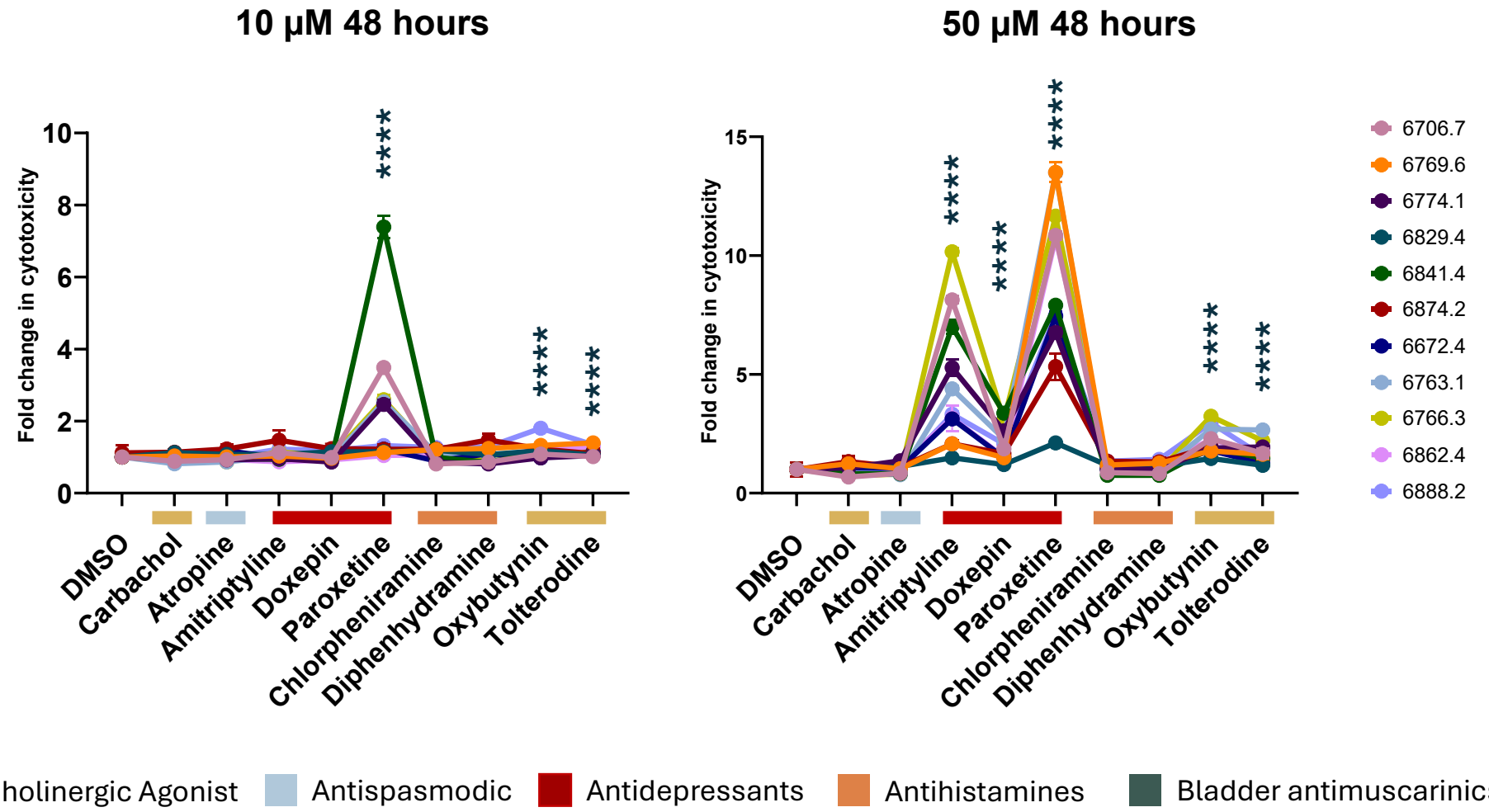
ACMs classifications		Drug name
Cholinergic agonist control		*Carbachol*
ACMs **NOT associated with dementia**	Antispasmodic	*Atropine*
	Antihistamines	*Chlorpheniramine* *Diphenhydramine*
ACMs **associated with dementia**	**Antidepressants**	*Amitriptyline* *Doxepin* *Paroxetine*
	Bladder antimuscarinics	*Oxybutynin* *Tolterodine*
Non-ACM alternatives	Antidepressants	*Mirtazapine*
	Urologics	*Mirabegron*

Screening assessments:

1. **Neurotoxicity**
2. **Tau hyperphosphorylation**
3. **$A\beta^{42}/A\beta^{40}$ ratio**
4. **Neuronal firing activity**

Antidepressants & bladder antimuscarinics consistently induce neurotoxicity across ACT cell lines

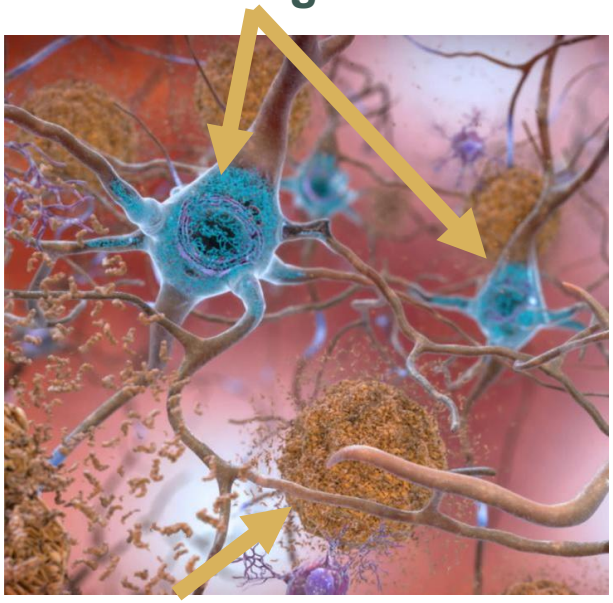
1 Neurotoxicity



Tau tangles and amyloid plaque are pathological hallmarks of Alzheimer's disease

2 **Tau hyperphosphorylation**
No consistent changes

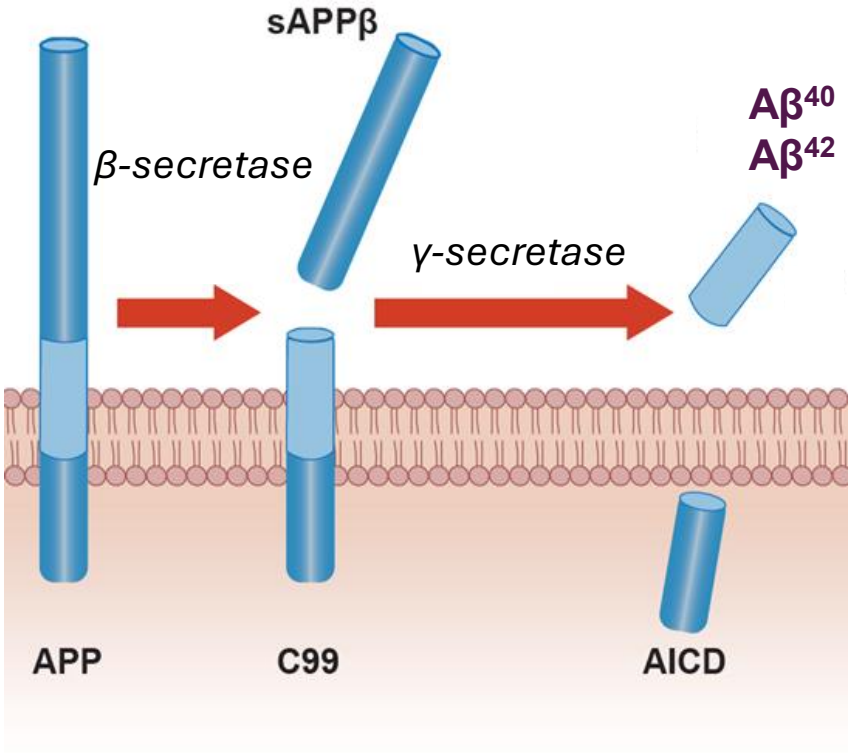
Tau tangles



NIH

Amyloid plaque

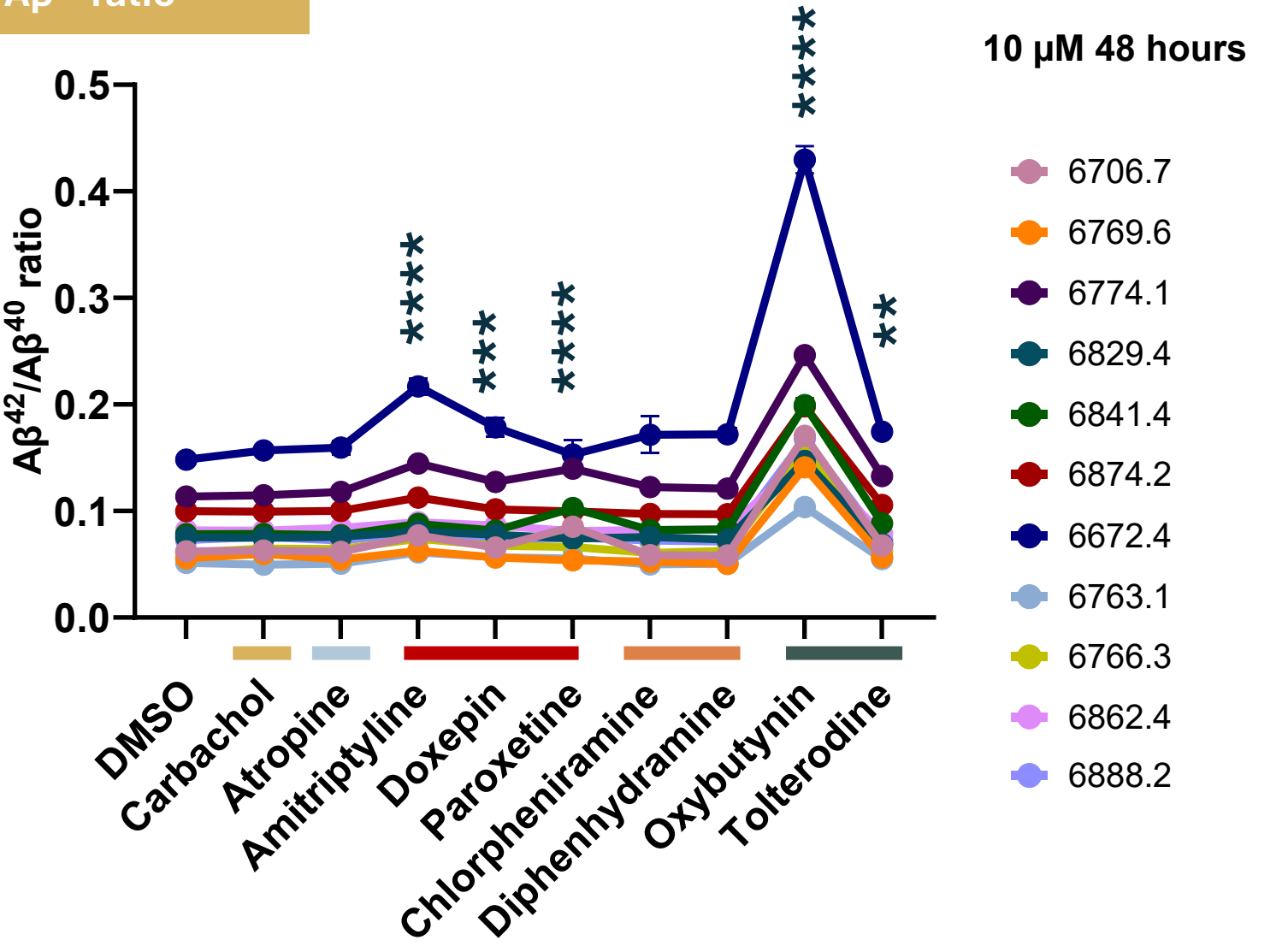
$A\beta^{42}/A\beta^{40}$ ratio ?



Amyloidogenic APP processing

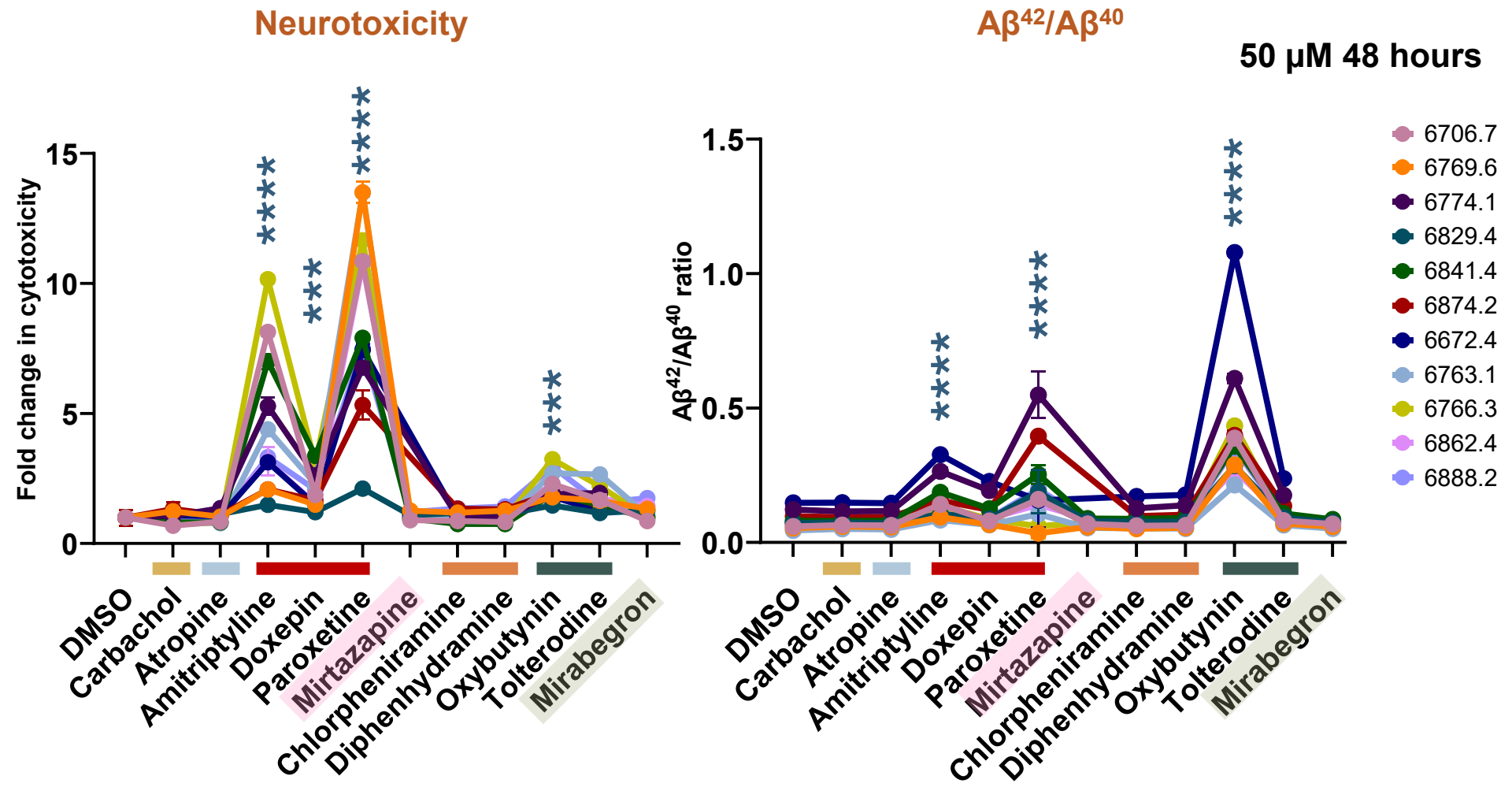
Antidepressants & bladder antimuscarinics increase $A\beta^{42}/A\beta^{40}$ ratio across donor cell lines

3 $A\beta^{42}/A\beta^{40}$ ratio



Cholinergic Agonist | Antispasmodic | Antidepressants | Antihistamines | Bladder antimuscarinics

Non-anticholinergic alternatives do not induce neurotoxicity nor increase $A\beta^{42}/A\beta^{40}$ ratio

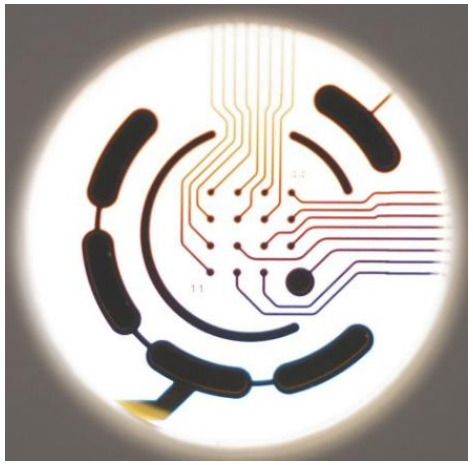


Mirtazapine: Non-anticholinergic antidepressant

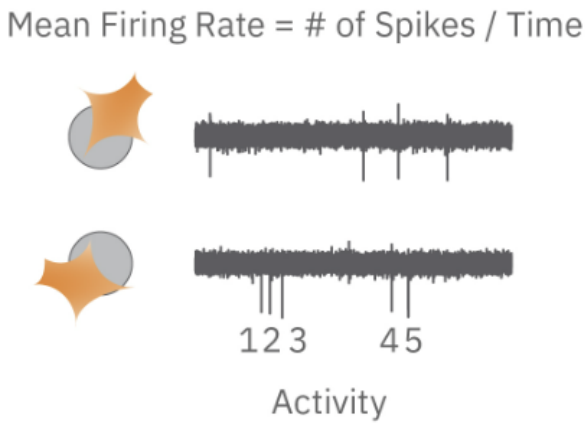
Mirabegron: Non-anticholinergic urologic

Cholinergic Agonist | Antispasmodic | Antidepressants | Antihistamines | Bladder antimuscarinics

Assessing synaptic firing activity of hiPSC-derived neurons using multi electrode arrays (MEAs)

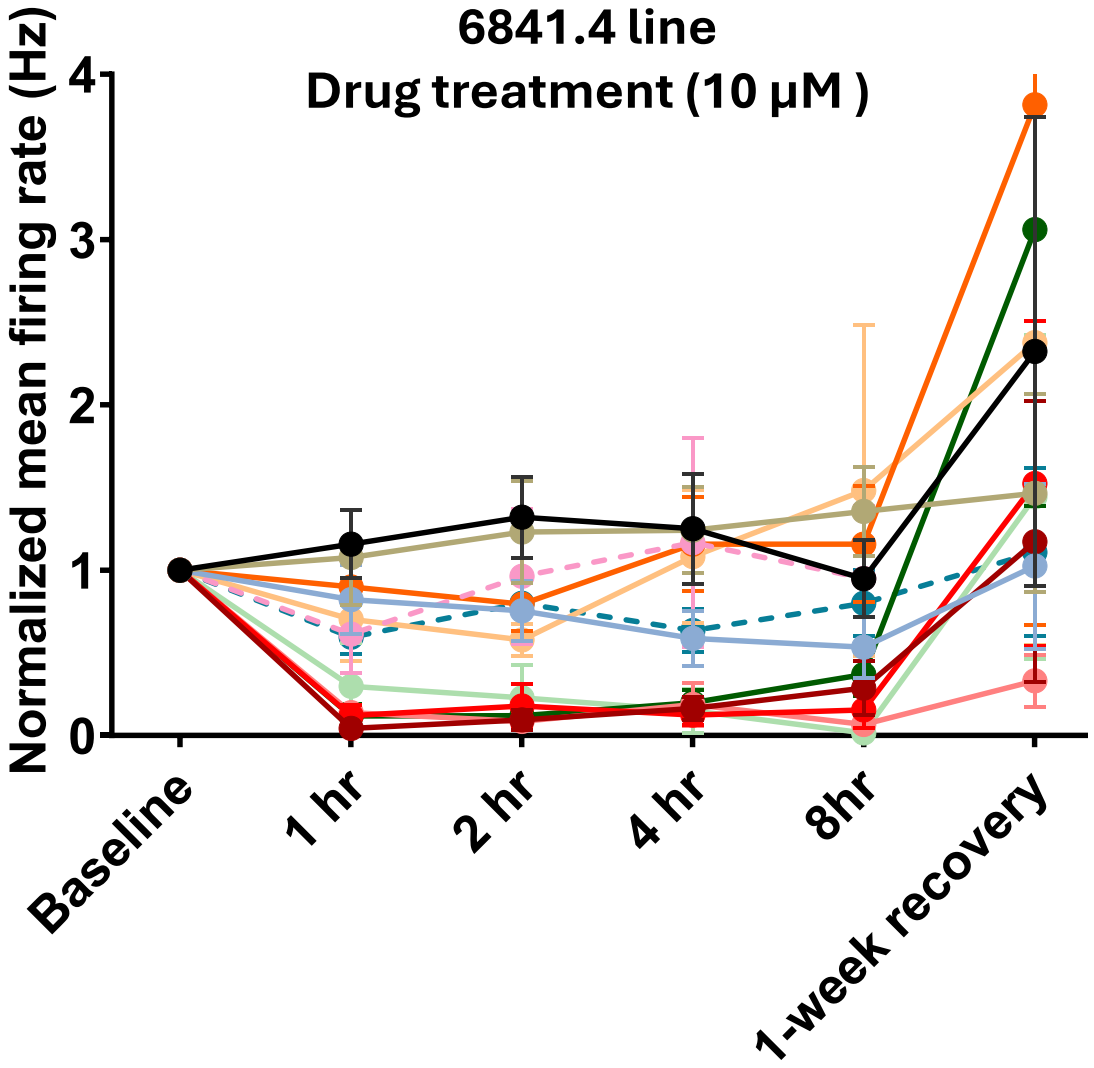


MEA recording:
High-throughput method to measure neuronal firing activity of the same culture over time



- Neuronal mean firing rate *(robustness)*
- Neuronal network burst frequency *(connectivity)*
- Network interburst interval *(regularity)*

Antidepressants & bladder antimuscarinics significantly reduce neuronal firing activity across donor cell lines



Non-dementia-linked ACMs:

- DMSO
- Carbachol
- Atropine
- Chlorpheniramine
- Diphenhydramine

Dementia-linked ACMs:

- Amitriptyline ****
- Doxepin ***
- Paroxetine **
- Oxybutynin ****
- Tolterodine ****

Non-ACM alternatives

- Mirtazapine
- Mirabegron

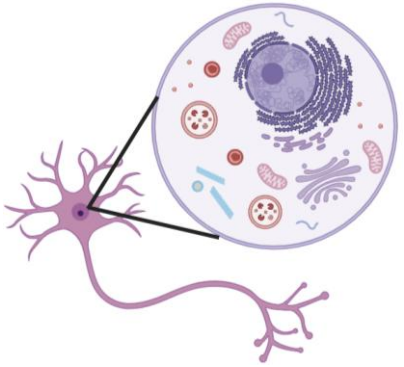
2-way ANOVA, p-value at 4-hour compared to baseline

Summary

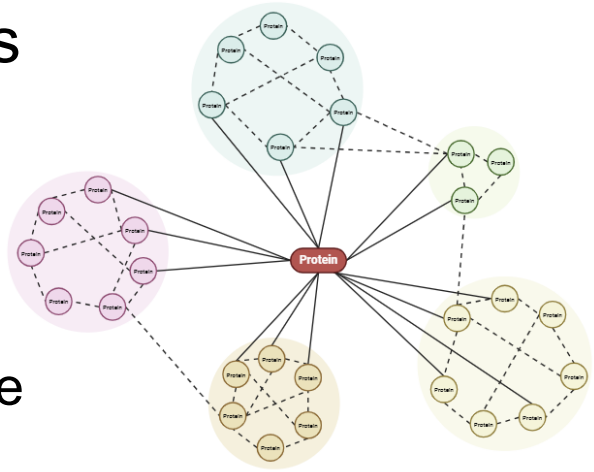
- Dementia-linked-ACMs – **antidepressants** & **bladder antimuscarinics** – **induce neurotoxicity, increase the $A\beta^{42}/A\beta^{40}$ ratio, and impair neuronal synaptic firing** without altering tau phosphorylation level, corroborating the links found in the pharmacoepidemiology studies
- Non-dementia-linked-ACMs – **antihistamines** & **antispasmodic** – **do not trigger these AD-related molecular neurotoxic phenotypes**
- **Non-ACM alternatives** for treating depression and overactive bladder **do not induce neurotoxicity,** suggesting that the anticholinergic property modulates specific downstream pathways to drive neurodegeneration

Future directions

- How do dementia-linked ACMs affect the integrity and function of neuronal organelles (mitochondria & lysosome)?

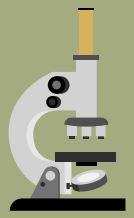


- What are the common signaling pathways that:
  1. dementia-linked ACMs share to elicit neurotoxic outcome?
  2. that distinguish dementia-linked ACMs to those that are not associated with dementia?



ACT U19 Project 3 Objectives

Aim 1: To directly test mechanisms of neurotoxicity from anticholinergics (ACMs) and address confounding by indication by deploying human stem cell-based molecular assays



Aim 2: To determine comparative associations of antihypertensives (AHTs) with neuropathology, dementia and AD, and neuroimaging outcomes. Test cellular mechanisms of neuroprotection.

Gray S, Yu O, Gatto NM, Marcum ZA, Latimer CS, Postupna N, Su Y, Barthold D, van Dalen JW, Richard E, Keene CD, Shaw PA, McEvoy LK, Larson EB, Crane PK. Angiotensin II stimulating antihypertensives and dementia-related neuropathology. *JAMA Network Open*. 9(2): e2559113. doi:10.1001/jamanetworkopen.2025.59113 (2026).

Angiotensin II–Stimulating Antihypertensives and Dementia

Background

Antihypertensives (AHT) can be categorized according to their activity at the type 2 and 4 angiotensin II receptors.

Ang II Stimulating AHT

- Angiotensin II receptor blockers (ARBs)
- Dihydropyridine calcium channel blockers
- Thiazide diuretics

Ang II Inhibiting AHT

- Angiotensin-converting enzyme inhibitors (ACE-Is)
- β-blockers
- Non-dihydropyridine calcium channel blockers

Background

- Observational studies support the angiotensin II hypothesis where Ang II stimulating AHTs are associated with lower dementia risk compared with inhibiting AHTs.
- Use of Ang II stimulating AHTs was associated with:
  - 45% lower incidence rate of dementia over 6.7 years of follow-up.
  - 24% lower incidence rate of probable dementia or amnestic mild cognitive impairment (MCI) over 4.8 years of follow-up in the Systolic Blood Pressure Intervention Trial (SPRINT).

JAMA Netw Open. 2022; 5(1):e2145319

Neurology. 2021;96(1):e67

JAMA Netw Open. 2023;6(1):e2249370

Lancet Reg Health Eur. 2024 May 15;42:100927

Study Sample (N=3,466)

Eligibility:

- ACT participants with ≥ 1 person-year (PY) of Ang II stimulating or inhibiting AHT exposure
- ≥ 1 biennial follow-up visit
- Completed chart review (collected AHT, blood pressure and some comorbidities)
- ≥ 80% of continuous KPWA enrollment between first record of Ang-II stimulating or inhibiting AHT use and ACT baseline visit
- Had blood pressure data in years of AHT use, and key covariates (education, self-rated health)

Antihypertensive Exposure

- Person-year (PY) of stimulating and inhibiting AHTs in two sources:

Pre-1977	Since 1977
Manual review and abstraction of paper-based medical records which captures the year and name of each AHT. **One PY** defined as one mention of AHT in a calendar year	Electronically in KPWA automated pharmacy dispensing data. **One PY** defined as two fills in a calendar year

- **Primary exposure (continuous):** Cumulative PY of stimulating and inhibiting AHTs
- **Secondary exposure (categorical):** Recent exposure in the past 2 calendar years. 3 groups: stimulating only, inhibiting only (referent), or mixed users.
- **Secondary analysis:** exposures (PY and any) to each of the 6 subclasses
- All AHT exposures are modeled as time-varying

Outcomes and Statistical Analysis

Outcomes: 1) All-cause dementia, 2) Alzheimer's disease

Model: Cox PH models with age as time axis

Study entry: age at the later of 1st Ang II stimulating or inhibiting AHT use, or ACT baseline visit

Follow-up ended: age at the earliest of dementia onset date, last ACT visit or first KPWA disenrollment

Covariates adjustment:

- Constant: demographics at ACT baseline, age at 1st AHT use
- Time-varying: average BP while on AHT, comorbidities (atrial fibrillation, myocardial infarction, diabetes, stroke, heart failure)

Characteristics (n=3,466)

At ACT baseline visit	No dementia (N=2512)	Dementia (N=954)
Age at ACT baseline visit, mean (SD)	73.4 (6.1)	76.1 (6.3)
Female, N (%)	1410 (56.1)	613 (64.3)
White, N (%)	2223 (88.5)	850 (89.1)
History of comorbidities, N (%)		
Atrial fibrillation	347 (13.8)	129 (13.5)
Coronary heart disease	650 (25.9)	265 (27.8)
Diabetes	443 (17.6)	170 (17.8)
Heart failure	328 (13.1)	136 (14.3)
Myocardial infarction	460 (18.3)	166 (17.4)
Stroke	301 (12.0)	122 (12.8)

AHT Exposure and Blood Pressure

At end of follow-up	No dementia (N=2512)	Dementia (N=954)
Ang II stimulating AHT medication		
Ever used, N (%)	1954 (77.8)	717 (75.2)
Total PY of use, mean (SD)	11.7 (9.1)	11.0 (8.8)
Ang II inhibiting AHT medication		
Ever used, N (%)	2268 (90.3)	840 (88.1)
Total PY of use, mean (SD)	11.7 (8.4)	10.9 (8.2)
Type of Ang II AHT medication ever used, N (%)		
Stimulating only	244 (9.7)	114 (11.9)
Inhibiting only	558 (22.2)	237 (24.8)
Both types	1710 (68.1)	603 (63.2)
Average annual systolic BP mmHg, mean (SD)	136.9 (12.7)	138.7 (12.4)

Primary Exposures – Cumulative PY

	All-cause dementia	Alzheimer's disease
	HR (95% CI)	**HR (95% CI)**
Stimulating vs Inhibiting	1.00 (0.98-1.01)	0.99 (0.98-1.01)
Subclass vs ACE-Is	**HR (99% CI)***	**HR (99% CI)***
β-blockers	1.02 (0.99-1.04)	1.02 (0.99-1.05)
Non-dihydropyridine CCB	1.01 (0.98-1.04)	1.01 (0.97-1.04)
ARB	0.99 (0.95-1.03)	0.99 (0.95-1.03)
Thiazide diuretics	1.02 (0.99-1.04)	1.02 (0.99-1.04)
Dihydropyridine CCB	0.99 (0.96-1.03)	1.00 (0.96-1.03)

Hazards ratio = Risk ratio comparing 1 additional PY of Ang II stimulating AHT to 1 additional PY of Ang II inhibiting AHT

* Bonferroni correction for 5 pairwise comparisons were applied (i.e. 99% CI).

Secondary Exposures – Recent Use

	All-cause dementia	Alzheimer's disease
Inhibiting only (referent)	**HR (95% CI)**	**HR (95% CI)**
Stimulating only	0.80 (0.65-0.99)	0.79 (0.63-1.00)
Both	0.89 (0.76-1.04)	0.89 (0.75-1.05)
Subclass vs ACE-Is	**HR (99% CI)***	**HR (99% CI)***
β-blockers	1.07 (0.83-1.39)	1.00 (0.75-1.32)
Non-dihydropyridine CCB	0.80 (0.58-1.09)	0.68 (0.47-0.97)
ARB	0.78 (0.57-1.06)	0.72 (0.51-1.02)
Thiazide diuretics	0.93 (0.72-1.20)	0.85 (0.63-1.13)
Dihydropyridine CCB	0.89 (0.67-1.20)	0.80 (0.57-1.10)

Hazards ratio = Risk ratio comparing use of each type of AHT in past 2 calendar years to the referent Ang II AHT

* Bonferroni correction for 5 pairwise comparisons were applied (i.e. 99% CI).

Summary

- First study that has examined PY of Ang II regimens with dementia outcomes, adjusting for longitudinal blood pressure.
- Key findings (Ang II inhibiting as reference):
  - No association between PY of Ang II-stimulating regimens and dementia risk.
  - Recent Ang II-stimulating exposure was associated with a lower risk dementia.
- Explanation is not clear for these findings:
  - For PY exposure: past exposures may have less effect on dementia risk.
  - Recent exposure findings align with prior research, although the biological mechanisms are unclear given the decades progression of dementia.
  - Recent Ang II stimulating exposure may prevent “last step” in this process.
- Additional analyses are planned.

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Emily Turschak
Maddie Valentine
Adrian Wang
Andy Williams, PhD
Jessica Young, PhD

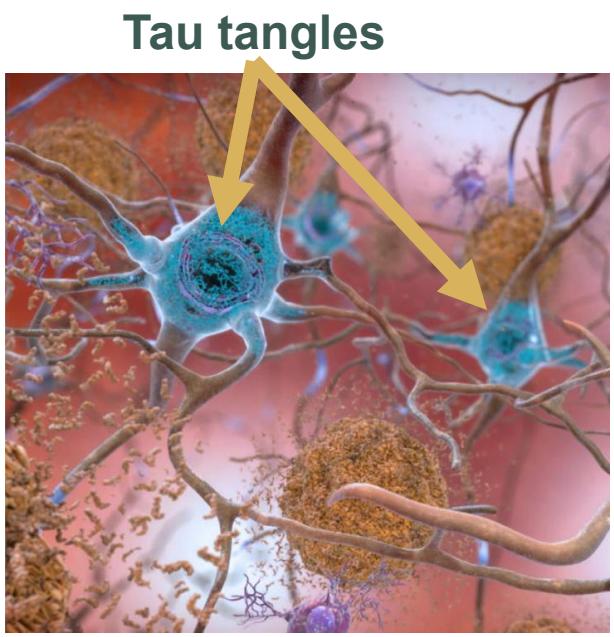
KPWHRI Study Team

Shelly Gray, PharmD, MS
Onchee Yu, MS
Nicole M. Gatto, MPH, PhD
Kelly Meyers, BA
Zachary A. Marcum, PharmD, PhD
Yu-Ru Su, PhD
Douglas Barthold, PhD
Jan Willem van Dalen, PhD
Edo Richard, MD, PhD
Linda McEvoy, PhD
Eric B. Larson, MD, MPH
Paul K. Crane, MD, MPH
Andrea LaCroix, PhD

ACT ADULT CHANGES IN THOUGHT STUDY
Kaiser Permanente Washington Health Research Institute
UW Medicine LABORATORY MEDICINE & PATHOLOGY
ISCRM Institute for Stem Cell and Regenerative Medicine

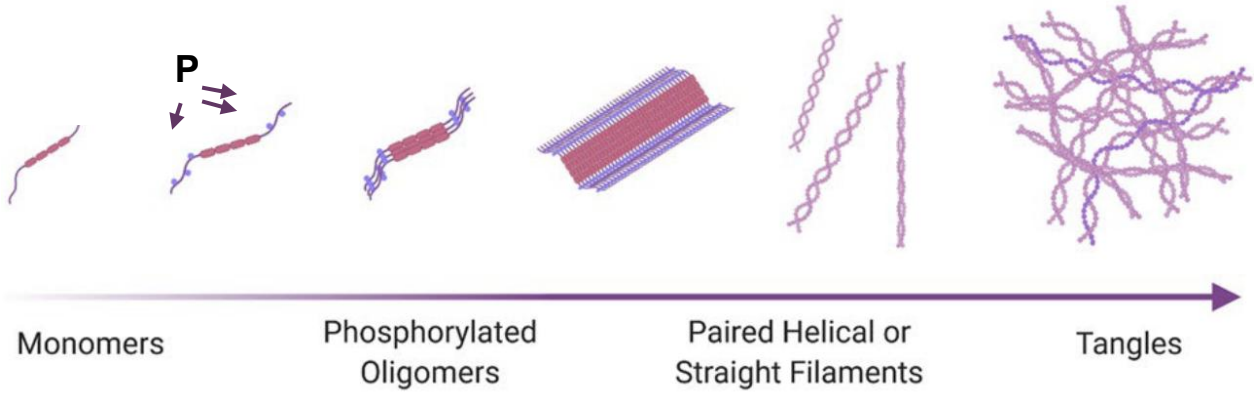
Supplemental slides

Tau hyperphosphorylation leads to intracellular tangles deposition, a pathological hallmark of AD

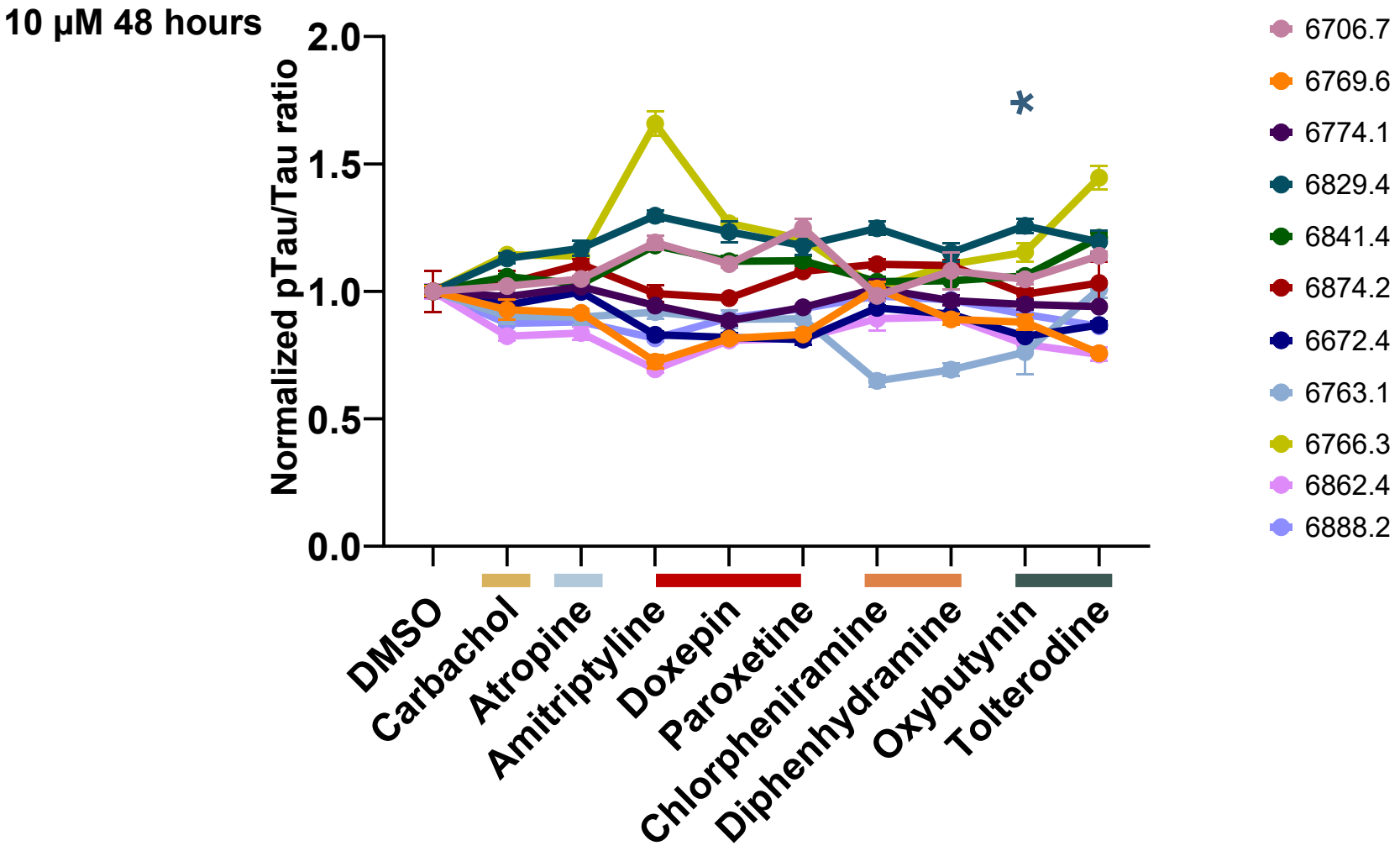


NIH

pTau/Total Tau ratio ?



Tested ACMs do not exhibit consistent alteration in pTau/ Tau ratio across ACT donor cell lines

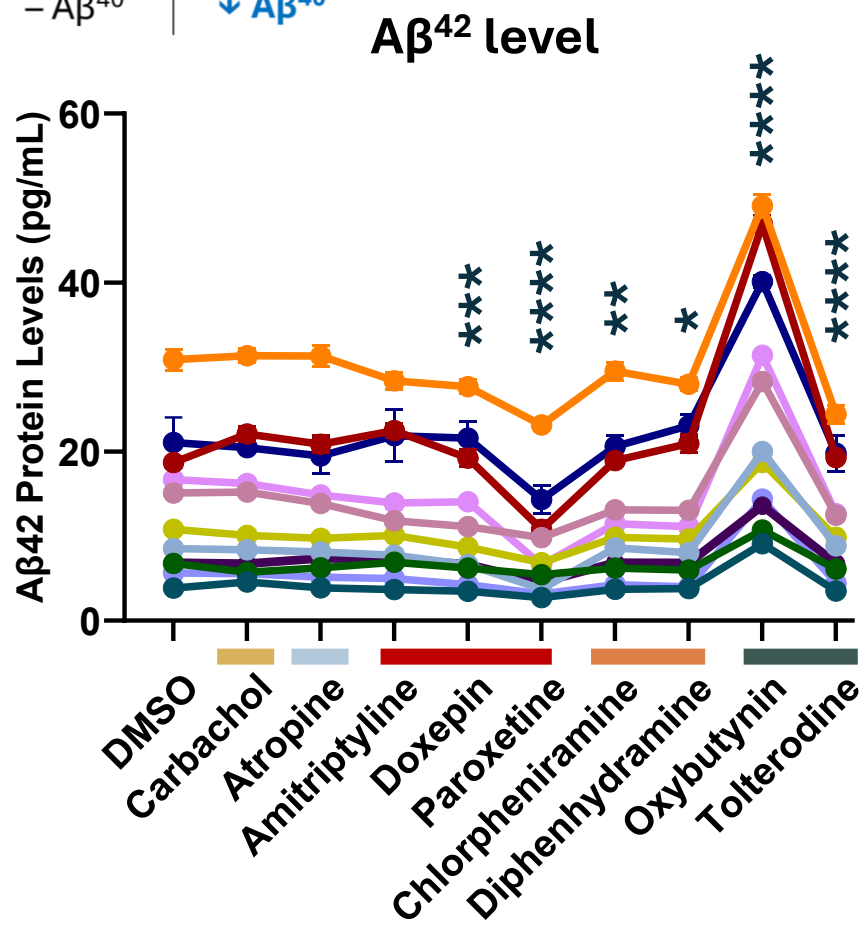


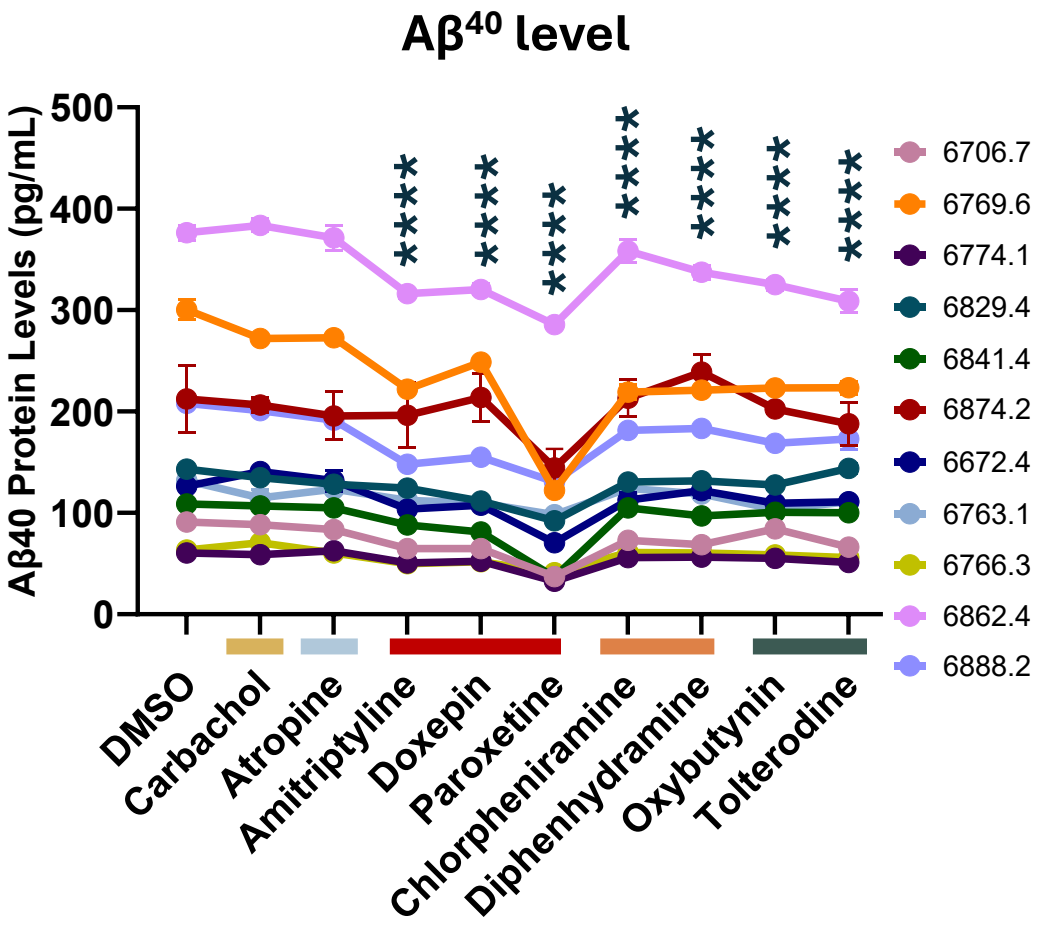
Antidepressants & bladder antimuscarinics increase $A\beta^{42}/A\beta^{40}$ ratio through distinct mechanisms

↑ $A\beta^{42}/A\beta^{40}$

↑ $A\beta^{42}$	– $A\beta^{42}$
– $A\beta^{40}$	↓ $A\beta^{40}$

10 µM 48 hours





Cholinergic Agonist | Antispasmodic | Antidepressants | Antihistamines | Bladder antimuscarinics

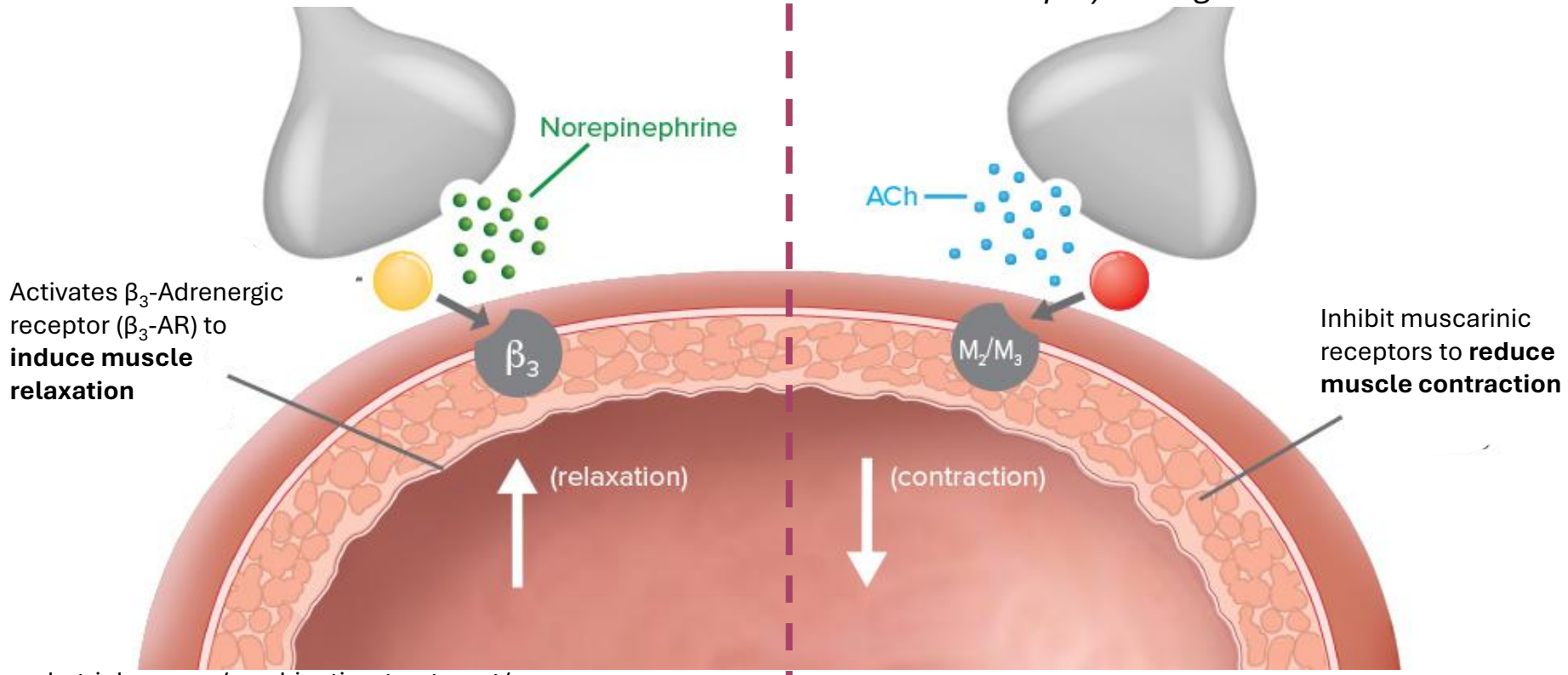
Alternative urologics without anticholinergic effects have recently become available

Mirabegron (2012) & Vibegron (2020)

Increasingly prescribed to individuals with MCI or prodromal AD

Bladder antimuscarinics (anticholinergics)

Remain widely used due to cost (~20-30x cheaper) among other reasons



myrbetriqhcp.com/combination-treatment/

Potential effect on dementia risk?

Established effect on dementia risk