Anticholinergic Burden- media hype or cause for concern?

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Are your over the counter medicines making you ill? As it's revealed some hay fever drugs and sleeping pills may raise the risk of dementia, what about the other medicines in your bathroom cabinet

- **New research links over-the-counter drugs to a higher risk of dementia**
- **Some products contain drugs that block a brain chemical linked to memory**
- **Expert: 'Just because a drug is sold in a pharmacy doesn't mean it's safe'**

By JO WATERS FOR THE DAILY MAIL
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NHS Evidence- Behind the Headlines

http://www.nhs.uk/news/2015/01january/pages/media-dementia-scare-about-common-drugs.aspx

Up to 50% of elderly people could be taking an anticholinergic-could mean half of them take them, or none take them

Having headlines that didn't make it clear the association was only seen in people **over the age of 65**

Failing to mention the study was based on **prescribed drugs**, rather than those bought over the counter

Failing to make it clear the antihistamines involved were only one, **older class** known to cause drowsiness

Naming a brand (Benadryl) focused on by researchers that has a completely **different drug in it in the UK**

A prospective cohort study cannot definitively prove this drug class causes Alzheimer's disease or dementia, but it can show they are linked in some way. Further research is needed to properly investigate and explain any links identified

Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study

JAMA Intern Med. Published online January 26, 2015.
doi:10.1001/jamainternmed.2014.7663

- 3,434 US people aged over 65 with no dementia at the start of the study
- Followed for an average of 7.3 years to see who developed dementia or Alzheimer's disease
- Looked for statistically significant links between these prescribed medications taken in the past 10 years and the likelihood of developing dementia or Alzheimer's disease
- Cumulative exposure was defined as cumulative total standardised daily doses (TSDDs)
- Statistical analysis adjusted for a range of potential confounders identified from past research, including:

  - demographic factors such as age, sex, and years of education
  - body mass index
  - whether or not they smoked
  - their exercise levels
  - self-rated health status
  - other medical problems, including hypertension, diabetes, stroke, and heart disease
  - whether they had a variant of the apolipoprotein E (APOE) gene
  - Parkinson's disease
  - high levels of depressive symptoms
  - cumulative use of benzodiazepine medicines – this could indicate a sleep or anxiety disorder

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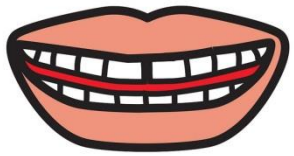
- The most common anticholinergic classes used over the long term were **antidepressants, antihistamines, and bladder control medicines**
- 797 participants (**23.2%**) developed dementia. Most (637 of the 797, 79.9%) had Alzheimer's disease
- The only statistically significant result was in the group with the highest long-term exposure level (TSDDs of more than 1,095 days):
  - **54%** more likely to develop dementia compared with those with no anticholinergic exposure over the previous 10-year period
- Main statistically significant finding was in a group taking the equivalent of any of the following medications daily for more than three years:

  - **oxybutynin chloride, 5mg**
  - **chlorpheniramine maleate, 4mg**
  - **olanzapine, 2.5mg**
  - **meclizine hydrochloride, 25mg**
  - **doxepin hydrochloride, 10mg**

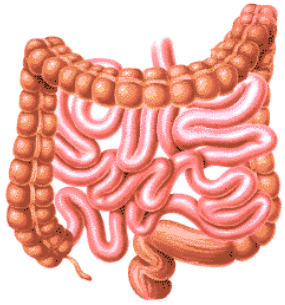
Why do anticholinergics cause side effects?

- Acetylcholine main transmitter in parasympathetic nervous system
- Works on nicotinic and muscarinic receptors
  - 5 subtypes (M1-M5)
  - Widespread in body -> potential for side effects

Detrusor muscle – urine retention (M2 & M3)

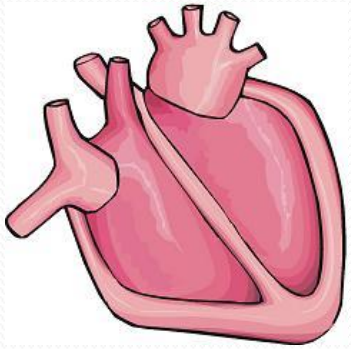


Saliva- dry mouth (M1,M3 & M4)



GI tract- constipation (M1,M2 & M3)

Eye- blurred vision (M3 & M5)



Vagus nerve- tachycardia (M2)

Muscarinic receptors in the brain

- All subtypes present (M1-M5)
- Important in cognition, memory, learning
- Cholinesterase inhibitors e.g. donepezil increase transmission hence role in treating dementia
- Blood brain barrier may be disrupted in dementia -> increased susceptibility to anticholinergic side effects

CFAS (Cognitive Function & Ageing Study) http://www.cfas.ac.uk/

- Started in late 1980s (CFAS I) and 2008 (CFAS II)
- 18,000 UK residents over 65
- Funded by MRC and DH, lead by Cambridge University
- Longitudinal multicentre study of health and cognition in older people

ACB (Anticholinergic Cognitive Burden Study)

- Scoring system for anticholinergic effect of commonly used medicines e.g. antihistamines, antidepressants
- Literature & consensus agreement
  - 0 = non activity
  - 1 = low activity
  - 2 = moderate activity
  - 3 = high activity

Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and
practical application. Aging Health. 2008;4(3):311-20

Drugs on the Anticholinergic Burden (ACB) scale

(A total ACB scale score of three or more is considered clinically relevant)

ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alverine	Belladonna alkaloids	Atropine
Atenolol	Carbamazepine	Benztropine
Beclometasone dipropionate	Cyclobenzapine	Chlorpheniramine
Bupropion hydrochloride	Cyproheptadine	Chlorpromazine
Captopril	Loxapine	Clemastine
Chlorthalidone	Meperidine	Clomipramine
Cimetidine hydrochloride	Methotrimeprazine	Clozapine
Clorazepate	Molindone	Darifenacin
Codeine	Oxcarbazepine	Desipramine
Cochicine	Pethidine hydrochloride	Dicyclomine
Dextropropoxyphene	Pimozide	Diphenhydramine
Diazepam		Doxepin
Digoxin		Flavoxate
Dipyridamole		Hydroxyzine
Disopyramide phosphate		Imipramine
Fentanyl		Meclizine
Fluvoxamine		Nortriptyline
Furosemide		Orphenadrine
Haloperidol		Oxybutynin
Hydralazine		Paroxetine
Hydrocortisone		Perphenazine
Isosorbide preparations		Procyclidine
Loperamide		Promazine
Metoprolol		Promethazine
Morphine		Propantheline
Nifedipine		Pyrilamine
Prednisone/Prednisolone		Scopolamine
Qunidine		Thiroidazine (withdrawn)
Ranitidine		Tolterodine
Theophylline		Trifluoperazine
Timolol maleate		Trihexyphenidyl
Trazodone		Trimipramine
Triamterene		
Warfarin		

CFAS- ACB findings 2011

- Use of anticholinergic meds high (48%)
- ACB score 5+ scored 4% lower on MMSE
- Increased mortality with increased ACB score:
  - End year 2: Score 0 = 7% vs Score 4+ = 20%
  - Every extra ACB point increased mortality risk by 26%
- Cumulative risk from number of anticholinergic drugs and dose used

The impact of anticholinergic burden in Alzheimer's dementia-the LASER-AD study

Fox, C et al Age Ageing (2011) 40 (6): 730-735.

- To examine the effect of medications with anticholinergic effects on cognitive impairment and deterioration in Alzheimer's Disease.
- 224 UK patients, moderate AD (MMSE 14.85)
- Mean ACB score 1.1
- No significant correlation ACB score and cognition using ADAS-COG, MMSE and SIB at baseline, 6 or 18 months – use of cholinesterase inhibitors taken into account
- No effect of use of anticholinergics on mortality

- Concluded anticholinergic burden may only be important in mild dementia

Anticholinergic drug use and risk for dementia: target for dementia prevention

Jessen, F et al Eur Arch Psychiatry Clin Neurosci (2010) 260 (Suppl 2):S111–S115

- Analysed results of a longitudinal epidemiology study (German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe)
- 2,065 patients aged over 75 without dementia in primary care followed over 54 months
- 37% (963) used anticholinergic drugs at some point during study
- Use of anticholinergics increased risk of dementia (HR 2.081; $p<0.001$)
- Classified level of anticholinergic activity from 1 (lowest) to 4 (highest)
- Risk doubled from level 1 to level 4 usage

Use of Anticholinergic Medications by Older Adults with Dementia

Roe et al Journal of the American Geriatrics Society
Volume 50, Issue 5, pages 836–842, May 2002

- Retrospective comparison study, 836 patients
- Those on donepezil sig more likely to take anticholinergics
  - 138/418 (33.0%) vs 98/418 (23.4%); p = 0.001
- Higher use for urinary incontinence in donepezil group
  - Oxybutynin – 3.6% vs 1.9%
- NICE guidance recommends not to use oxybutynin (immediate release) in frail older women[1]

1. Urinary incontinence: The management of urinary incontinence in women NICE CG 171 https://www.nice.org.uk/guidance/cg171 Sep 2013

What does the evidence show?

- Anticholinergics are widely used in the elderly including those with dementia
- Good evidence that they worsen cognitive function
  - Particularly in early dementia
- Associated with increased mortality in one study

What should we do?

- Reassure younger patients taking anticholinergics
  - Effects are with long term use and reversible
  - Don't stop taking medication without advise from their clinician
- Review patients at high risk from anticholinergic burden
  - Older people with confirmed dementia
  - Patients aged over 70

Review of patients on OAB meds

- Reviews undertaken in 14 practices across Fylde & Wyre CCG
- 1229 prescribed anticholinergics (1.3%)
- Assigned anticholinergic burden risk score as below:

Over 65	Over 85 & frail	Contraindication: myasthenia gravis, urinary/ gastro obstruction, retention, ulcerative colitis, toxic megacolon	Other anticholinergic medicines eg Amitriptyline Chlorpheniramine Clomipramine Dicyclomine Diphenhydramine Doxepin Hydroxyzine Imipramine Nortriptyline Paroxetine Procyclidine Promazine Promethazine Trifluoperazine Trimipramine Tiotropium	Current smoker (nicotine counteracts efficacy)	Caution in: Acute angle glaucoma, GORD, heart failure, CAD, hyperthyroidism, hypertension, BPH, AF, dementia (score one point for each condition)

Score: >4 = high risk 2 or 3 = moderate risk 0 or 1 = low risk

Review of patients on OAB meds

Risk score	0	1	2	3	4+	TOTAL
No of patients	136 (18%)	188 (25%)	261 (34%)	127 (17%)	52 (7%)	764

	RED	AMBER	GREEN	Total answering question
UPS[2] symptom control	60 (15%)	210 (54%)	119 (31%)	389
Adherence	39 (10%)	20 (5%)	326 (85%)	385
Side-effects	75 (20%)	9 (2%)	285 (77%)	369

Suggestion	Trial off treatment	Change treatment	Increase dose	Decrease dose	See GP	Refer	Other
No of patients	48	137	21	12	17	4	52

Managing anticholinergic burden

- Consider ACB score when initiating new meds in elderly patients especially if dementia
- Could ACB be cause of cognitive impairment?
  - Consider before considering new dementia diagnosis
- Review elderly patients on anticholinergics for OAB
  - Symptom control- is drug still needed?
  - Alternative medication
    - Trospium less likely to cross blood brain barrier
    - Mirabegron- alternative mode of action to anticholinergics