Anticholinergic Burden-media hype or cause for concern?

Diane McGinn
Dmac Medicines Management
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
PUBLISHED: 01:15, 31 January 2015 | UPDATED: 11:55, 31 January 2015
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
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

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

- Detrusor muscle – urine retention (M2 & M3)
- Saliva - dry mouth (M1, M3 & M4)
- GI tract - constipation (M1, M2 & M3)
- Vagus nerve - tachycardia (M2)
- Eye - blurred vision (M3 & M5)
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

Drugs on the Anticholinergic Burden (ACB) scale
(A total ACB scale score of three or more is considered clinically relevant)

<table>
<thead>
<tr>
<th>ACB Score 1 (mild)</th>
<th>ACB Score 2 (moderate)</th>
<th>ACB Score 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimemazine</td>
<td>Amantadine</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Alverine</td>
<td>Belladonna alkaloids</td>
<td>Atropine</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Carbamazepine</td>
<td>Benztrapine</td>
</tr>
<tr>
<td>Beclometasone dipropionate</td>
<td>Cyclobenzapine</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Bupropion hydrochloride</td>
<td>Cyproheptadine</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Captopril</td>
<td>Loxapine</td>
<td>Clemastine</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>Meperidine</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Cimetidine hydrochloride</td>
<td>Methotrimeprazine</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Molindone</td>
<td>Darifenacin</td>
</tr>
<tr>
<td>Cocticine</td>
<td>Oxcarbazepine</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>Pimozide</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Doxepin</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Flavoxate</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Hydroxyzine</td>
<td></td>
</tr>
<tr>
<td>Disopyramide phosphate</td>
<td>Imipramine</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Meclizine</td>
<td></td>
</tr>
<tr>
<td>Fluoxaxime</td>
<td>Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>Orphenadrine</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Oxybutynin</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Perphenazine</td>
<td></td>
</tr>
<tr>
<td>Isosorbide preparations</td>
<td>Procyclidine</td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>Promazine</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Promethazine</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Propantheline</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Pyrilamine</td>
<td></td>
</tr>
<tr>
<td>Prednisone/Prednisolone</td>
<td>Scopolamine</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>Thioridazine (withdrawn)</td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Tolterodine</td>
<td></td>
</tr>
<tr>
<td>Theophyline</td>
<td>Trifluoperazine</td>
<td></td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>Trihexyphenidyl</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>Trimipramine</td>
<td></td>
</tr>
<tr>
<td>Triamterene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

- 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

- 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

- 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. 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

<table>
<thead>
<tr>
<th>Risk score</th>
<th>0 (18%)</th>
<th>1 (25%)</th>
<th>2 (34%)</th>
<th>3 (17%)</th>
<th>4+ (7%)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>136</td>
<td>188</td>
<td>261</td>
<td>127</td>
<td>52</td>
<td>764</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RED</th>
<th>AMBER</th>
<th>GREEN</th>
<th>Total answering question</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPS² symptom control</td>
<td>60 (15%)</td>
<td>210 (54%)</td>
<td>119 (31%)</td>
</tr>
<tr>
<td>Adherence</td>
<td>39 (10%)</td>
<td>20 (5%)</td>
<td>326 (85%)</td>
</tr>
<tr>
<td>Side-effects</td>
<td>75 (20%)</td>
<td>9 (2%)</td>
<td>285 (77%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggestion</th>
<th>Trial off treatment</th>
<th>Change treatment</th>
<th>Increase dose</th>
<th>Decrease dose</th>
<th>See GP</th>
<th>Refer</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>48</td>
<td>137</td>
<td>21</td>
<td>12</td>
<td>17</td>
<td>4</td>
<td>52</td>
</tr>
</tbody>
</table>
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