# Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

**Reviewers**

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**Cardiovascular disease**
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## Mental health

# Long-term anticholinergic use associated with raised risk of dementia in older people

Elderly patients who take anticholinergic drugs for prolonged periods have an increased risk of developing dementia, an American study has found.

Data were obtained from the Adult Changes in Thought study, a population-based prospective cohort study of brain ageing and incident dementia which was commenced in 1994. Cohort members were randomly selected from members of the Seattle Group Health (GH) Cooperative who were aged 65 or over and did not have dementia. In order to have sufficient prescribing data, only those who had been enrolled with the cooperative for more than ten years were included in the present study.

A total of 3,434 participants were followed up at two yearly intervals. Incident cases of dementia were identified by using a screening instrument followed by a standardised diagnostic evaluation.

Anticholinergic drugs were defined as those deemed to have strong anticholinergic activity by an expert panel from the American Geriatrics Society. The most commonly prescribed drugs were first-generation antihistamines e.g. chlorpheniramine, tricyclic antidepressants e.g. amitriptyline and bladder antimuscarinics e.g. oxybutynin.

Anticholinergic use was determined from the GH electronic pharmacy dispensing records. Cumulative anticholinergic exposure was defined as the total number of standardised daily doses (SDD) dispensed over the previous ten years. An SDD was defined as the minimum effective daily dose e.g. 5 mg of oxybutynin.

During a mean follow-up time of 7.3 years, 797 participants (23.2%) were diagnosed with dementia, of whom 637 had Alzheimer's disease. A significant dose-response relationship was observed between the level of anticholinergic exposure and the incidence of Alzheimer's disease ($P < 0.001$). At the highest level of anticholinergic use (equivalent to 5 mg oxybutynin for three years or more), there was a significantly increased risk of dementia; adjusted hazard ratio 1.54 (95% CI:1.21-1.96).

This is an observational study and cannot demonstrate cause and effect. The results were adjusted for a number of social, lifestyle and clinical factors but the possibility of residual confounding cannot be ruled out.

The authors recognised the possibility that anticholinergic medication could have been prescribed to alleviate prodromal symptoms of dementia, but attempted to eliminate this by excluding the most recent 12 months of drug use (exposure was measured from 1 to 11 years before the current assessment).

It is well known that anticholinergic drugs can cause acute reversible cognitive impairment in elderly patients. This study suggests that prolonged use is also associated with a risk of irreversible cognitive deterioration.

A small autopsy study found that amyloid plaque densities were more than 2.5 times higher in patients treated with long-term anticholinergic medication[1] but these findings have yet to be replicated.

A causal link is far from proven but I think that we should be cautious when prescribing anticholinergic drugs to elderly patients and advise them of the possible risks.

We should avoid the use of first-generation antihistamines and, where possible, select tricyclic antidepressants with low anticholinergic activity i.e. trazodone or lofepramine.

For patients with urge incontinence, NICE recommends a trial of conservative measures before considering pharmacological treatment. It also advises that we should consider the total anticholinergic load and risk of side effects before offering an antimuscarinic drug.[2]

If we or our patients are concerned about cognitive side effects, we could choose an antimuscarinic with low brain penetration (trospium or darifenacin)[3] or an alternative drug (mirabegron, desmopressin or topical oestrogens).[2]

**DR PHILLIP BLAND**

● **Gray SL, Anderson ML, Dublin S et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015;doi:10.1001**

**REFERENCES**

**1** Perry EK, Kilford L, Lees AJ et al. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. *Ann Neurol* 2003;54:235-8
**2** National Institute for Health and Care Excellence. CG171. Urinary incontinence: the management of urinary incontinence in women. NICE. London. 2013
**3** Callegari E, Malhotra B, Bungay PJ et al. A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. *Br J Clin Pharmacol* 2011;72:235-46

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