



Drugs with anticholinergic effects and risk of cognitive impairment, falls and all-cause mortality

A systematic review and meta-analysis reported that drugs with anticholinergic effects were associated with an increased risk of cognitive impairment and all-cause mortality in older people, and some drugs were linked to an increased risk of falls.

Overview: Drugs with anticholinergic effects block the neurotransmitter acetylcholine to inhibit smooth muscle function, such as in the lungs, gastrointestinal tract and urinary tract. These drugs are prescribed for a wide range of conditions, including Parkinson's disease, overactive bladder, chronic obstructive pulmonary disease, nausea and vomiting, depression and psychosis.

Drugs with anticholinergic effects can cause a broad range of adverse events, including constipation, dry mouth, dry eyes, urinary retention, confusion, falls and agitation. A recent prospective cohort study suggested an increased risk of dementia with long-term exposure to drugs with anticholinergic effects, most commonly tricyclic antidepressants, sedating antihistamines and anticholinergic drugs used to treat bladder conditions ([Gray et al. 2015](#)).



Current advice: NICE guidance on [falls in older people](#) recommends that people who have had a fall or are at increased risk of falling should have their medication reviewed as part of a multifactorial risk assessment. The guidance recommends that older people on psychotropic medications (including neuroleptics, sedatives, hypnotics and antidepressants) should have their medication reviewed and if possible discontinued to reduce their risk of falling.

The NICE guidance on [dementia](#) (currently [being updated](#)) recommends that a diagnosis of dementia should be made only after a comprehensive assessment, including a medication review to identify and minimise use of drugs that may adversely affect cognitive functioning.

New evidence: A systematic review and meta-analysis assessed the effect of drugs with anticholinergic effects on cognitive impairment, falls and all-cause mortality in older people ([Ruxton et al. 2015](#)). The investigators examined drugs with anticholinergic effects as a class, compared individual drugs, and assessed different scoring systems that measure exposure to drugs with anticholinergic effects.

The authors included 18 studies (total n=124,286) in the systematic review, with the results of 11 studies included in the meta-analysis. The majority of the studies were of people aged 65 years and over and were conducted in Europe (n=12), the USA (n=4), Canada (n=1) and Australia (n=1). Follow-up ranged from 1 month to 6 years.

The systematic review found that the individual studies had conflicting results on the effects of drugs with anticholinergic effects as a class.

Meta-analysis of 3 studies showed that exposure to drugs with anticholinergic effects as a class was associated with a significant increase in cognitive impairment (odds ratio [OR]=1.45, 95% confidence interval [CI] 1.16 to 1.73). Details of risks associated with specific drugs were not reported.

Four studies that assessed risk of falls were included in the meta-analysis, which examined the effects of 5 drugs – amitriptyline, olanzapine, paroxetine, risperidone and trazodone. The risk of falling was significantly increased with olanzapine (OR=2.16, 95% CI 1.05 to 4.44) and trazodone (relative risk [RR]=1.79, 95% CI 1.60 to 1.97), with some heterogeneity present in the trazodone analysis ($I^2=28.2\%$). Exposure to amitriptyline, paroxetine and risperidone was not associated with an increased risk of falls.

The authors did not report the effect on all-cause mortality of drugs with anticholinergic effects as a class or of individual drugs. They did report on all-cause mortality relative to score on the Anticholinergic Cognitive Burden (ACB) scale, a system that scores drugs with anticholinergic effects from 1 (possible anticholinergic effects based on in vitro data) to 3 (known anticholinergic effects that may cause delirium). This analysis showed a significant association between ACB scale and all-cause mortality, with an increase of 1 point on the scale approximately doubling risk (OR=2.06, 95% CI 1.82 to 2.33).

This study has a number of limitations. The majority of studies included were observational, with only 2 randomised controlled trials included, 1 of which was available only as an abstract. Significant heterogeneity was observed in the meta-analysis of some drugs or scoring systems. Limited data were available on the relative risks associated with specific drugs, with results available for only 5 named drugs.

Commentary by Dr Martin Duerden, GP and Clinical Senior Lecturer, Centre for Health Economics and Medicines Evaluation, Bangor University, North Wales:

“The growing problem of multimorbidity and its associated polypharmacy is creating a major challenge for modern healthcare. Most of the evidence for medicines comes from trials of individual drugs in the context of highly selected individuals who may not be representative of the ‘real world’ patients we treat. Furthermore, the guidelines we use tend to be focused on individual conditions, when the reality is that people may have several conditions.

“Of late there has been a lot of interest in the potential harm caused by drugs that have anticholinergic effects. Concerns exist that several treatments with some anticholinergic activity might have cumulative harmful effects when given to a person with more than one clinical condition. This potential for harm increases with frailty and age. Various anticholinergic burden or risk scales have been devised to aid medication reviews so that certain drugs can either be stopped, or the medication regimen altered to reduce this burden.

“This systematic review and meta-analysis by Ruxton and colleagues examines the evidence of cognitive impairment, falls and mortality from drugs with anticholinergic effects. The evidence is not very strong, but there does appear to be an association between some individual drugs and these harms. There also seems to be a correlation between overall anticholinergic burden and mortality.

“Taken alongside the other known adverse effects of these drugs, it seems sensible to be cautious when prescribing any medication with anticholinergic effects. The catch is that there is surprisingly little evidence to show that using measures of anticholinergic burden to reduce exposure reduces the

harm from these drugs. Researching this area is very difficult, and it may be that we have to continue hoping that this process, which sounds worthy, may be beneficial.

“Anticholinergic risk scales are currently contained in various toolkits for polypharmacy, such as those by [NHS Scotland](#) and the [All Wales Medicines Strategy Group](#). The findings of the Ruxton et al. study provide reasonable support to continue using these tools when deciding on and reviewing treatments for older or frail people, or people with complex multimorbidities.”

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