Anticholinergic medicines and the risk of dementia

A large, nested, case-control study in UK general practices found that some classes of anticholinergic medicines were significantly associated with an increase in incidence of dementia. Medicines with less anticholinergic burden should be chosen, where possible, and patients made aware of the risk and benefits. The NICE guidance on multimorbidity and also on medicines optimisation recommends that a screening tool, such as the STOPP/START tool in older people, can be used to identify medicines-related safety concerns.

Overview and current advice

It is well documented in the literature that medicines with anticholinergic effects can impair cognitive functioning, particularly in older people. The NICE guideline on dementia recommends considering minimising the use of medicines that may adversely affect cognitive functioning and, if possible, look for alternatives, when assessing whether to refer a person with suspected dementia for diagnosis and during medication reviews with people living with dementia. NICE also recommends that healthcare professionals should be aware that there are validated tools for assessing anticholinergic burden, for example, the Anticholinergic Cognitive Burden Scale (Boustani et al., 2008), but there is insufficient evidence to recommend one over the others. NICE guidance on multimorbidity and also on medicines optimisation recommends that a screening tool, such as the STOPP/START tool in older people, can be used to identify medicines-related safety concerns. In the NICE guideline for the management of incontinence in women, it is recommended that use of other existing medication affecting the total anticholinergic load should be considered when offering antimuscarinic medicines, such as oxybutynin, to treat overactive bladder. The risks associated with anticholinergic medicines have also been highlighted in polypharmacy resources such as the NHS Scotland guidance (2018) and the All Wales Medicines Strategy Group guidance (2014).

New evidence

A large, nested, case-control study including 40,770 people diagnosed with dementia and 283,933 controls investigated the association between daily doses of anticholinergic medicines and incidence of dementia (Richardson et al., 2018). The study was performed using UK general practice data from the Clinical Practice Research Datalink (CPRD). Patient records were selected for people who were aged between 65 and 99 years and who had at least 6 years of data before the diagnosis was made. The median age of patients at diagnosis was 83 years (interquartile range [IQR] 78 to 87 years) and the median drug exposure period was 7.1 years (IQR 4.0 to 11.3).

The authors defined anticholinergic medicine exposure using an anticholinergic cognitive burden (ACB) scale (Campbell et al., 2013). Medicines were assigned a score of 0 to 3, where 0 was assigned
to medicines with no expected anticholinergic activity and 3 was assigned to medicines that have
definite anticholinergic activity. For the medicines available in the UK in the last 30 years without an
ACB score, the investigators made some assumptions. For example thiazide diuretics, loop diuretics
and antihistamines were allocated an ACB score of 1 and tricyclic antidepressants have an ACB score
of 3. The authors also carried out pre-specified sensitivity analysis including recoding medicines by
using the Anticholinergic Drug Scale (ADS) instead of the ACB scale.

After categorisation, 35.5% (14,453) of people diagnosed with dementia had prescriptions for
medicines with an ACB score of 3 compared to 30.4% (86,403) of controls, and exposure to these
medicines was significantly associated with incident dementia (adjusted odds ratio [OR] 1.11, 95%
confidence interval [CI] 1.08 to 1.14). The authors also reported significant associations with
medicines with an ACB score of 1 and 2 (OR 1.10, 95% CI 1.06 to 1.15; OR 1.10, 95% CI 1.03 to
1.16, respectively) although there was little evidence of a dose-response relationship.

Subgroup analyses were performed for medicines with an ACB score of 3 which are used to treat a
number of different conditions. The authors reported a significant association between antidepressant,
urological and antiparkinsonian medicines with an ACB score of 3, and dementia incidence (OR 1.11,
95% CI 1.08 to 1.14; OR 1.18, 95% CI 1.13 to 1.23; OR 1.29, 95% CI 1.11 to 1.50, respectively), after
adjustment for potential confounders at the end of the drug exposure period. The medicines most
consistently associated with dementia were amitriptyline, dosulepin and paroxetine from
antidepressants, and predominantly oxybutynin and tolterodine from urological medicines.
Antipsychotic, gastrointestinal and respiratory anticholinergic medicines were not significantly
associated with incident dementia.

This study supports previously reported findings of the association between some anticholinergic
medicines and long-term cognitive impairment and, although the study design does not preclude the
possibility of reverse causality, where early symptoms of dementia could lead to an increased
likelihood of being prescribed anticholinergic medicines, the authors reported that associations were
observed even when the exposure to the medicine was 15 to 20 years prior to the diagnosis being
made. This means reverse causality, although possible, is less likely to explain the associations
observed.

Although the authors adjusted for potential confounders at both the start and end of the drug exposure
period, many causes of dementia are still unknown therefore residual confounding is a possibility. In
addition, known risk factors for dementia, such as lifestyle and demographics, could not be adjusted
for fully due to the incompleteness of the general practice data. The study design may have also
overestimated drug exposure as adherence could not be measured; adherence may also be a
confounder as it could differ between those with and without a diagnosis of dementia.

Commentary
Commentary provided by Professor Louise Allan, Professor of Geriatric Medicine, University of
Exeter
This study is useful for prescribers and patients because, for the first time, we have evidence that
suggests an association between the long-term use of anticholinergic medicines and the incidence of
dementia, whereas previous studies have mostly looked at short-term use. The authors were able to
look at exposure periods of up to 20 years. In addition, the authors were able to compare different
classes of anticholinergics. This gives clarity that the effects on dementia incidence seem to be mainly
due to antidepressant, urological or antiparkinsonian medicines rather than antipsychotic,
gastroenterological or respiratory medicines.

This paper cannot comment on whether withdrawal of these medicines at the onset of symptoms of
dementia would make a difference to the person’s symptoms, but it does nevertheless seem sensible
to avoid these medicines in people with cognitive symptoms. What it does suggest is that anticholinergic antidepressants, antiparkinsonian and urological medicines should be avoided as part of midlife and late life approaches to prevention of dementia.

This study supports the practice that, where there is a clear alternative agent with less anticholinergic activity, then this should be considered in preference, all other things being equal. Where the use of an anticholinergic is deemed likely to be of benefit then patients or their carers should be made aware of the associations of these medicines with dementia so they can make an informed choice about whether any perceived benefits outweigh the potential increased risk of dementia, to inform shared decision making where this is possible.

Declaration of interests:
Professor Louise Allan declared no interests.

Study sponsorship
The study was supported by the Alzheimer’s Society.

References
Boustani N, Campbell N, Munger S et al. (2008) Impact of anticholinergics on the aging brain: a review and practical application Aging Health 4:3, 311-320
Campbell N L, Maidment I, Fox C et al. (2013) The 2012 update to the anticholinergic cognitive burden scale Journal of the American Geriatrics Society 61 (S1), S142-S143

About this Medicines Evidence Commentary
Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.