EDITORIAL

Anticholinergic drugs and risk of dementia

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ANTIDEPRESSANT, UROLOGICAL AND ANTI-PARKINSONIAN DRUGS WITH DEFINITE anticholinergic effects are associated with an increased risk of incident dementia up to 20 years after exposure, a UK nested case-control study has found.[1]

Data were obtained from the Clinical Practice Research Datalink, a UK primary care database derived from more than 11.3 million anonymised patient records. A total of 40,770 patients aged 65-99 years with dementia diagnosed between April 2006 and July 2015 were selected as cases. There were 283,933 matched controls (usually seven for each case) who did not have dementia when the case subject was diagnosed.

Drugs were categorised using the Anticholinergic Cognitive Burden (ACB) scale as either: no anticholinergic activity (score = 0), possible activity (score = 1), definite activity (score = 2) or definite activity with reported delirium (score = 3).

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Anticholinergic drug exposure was measured by the number of defined daily doses (the average maintenance daily dose) prescribed during the drug exposure period (DEP). The DEP had a mean duration of 7.1 years (range 1-16 years) and ended four years prior to the date of dementia diagnosis.

Approximately one third of the study population (35% of cases and 30% of controls) were prescribed at least one ACB 3 anticholinergic during the exposure period. Compared with those who were not prescribed any anticholinergics, the ACB 3 patients had an adjusted odds ratio of dementia of 1.11 (95% CI: 1.08-1.14). A dose-response effect was observed for both ACB 2 and 3 anticholinergic drugs but not for ACB 1 drugs.

The large sample size allowed for separate analysis of specific drug classes. Of those drugs with an ACB score of 3, antidepressant, urological and anti-parkinsonian drugs were significantly linked to dementia incidence, whereas antihistamines, antispasmodic and antipsychotic drugs were not. For ACB 3 antidepressants (predominantly amitriptyline, dosulepin and paroxetine) and urological drugs (predominantly oxybutynin and tolterodine), a significant association with incident dementia was seen throughout the DEP, even for exposure 15-20 years before diagnosis.

Antidepressants with an ACB score of 1 (predominantly SSRIs) were also significantly associated with incident dementia but this association was greatest for the period 4-10 years prior to dementia diagnosis and was not significant for the period 15-20 years prior to diagnosis.

These findings are consistent with reverse causation: there is evidence to suggest that depression is a prodromal feature of dementia, with symptoms apparent from 11 years prior to diagnosis.[2] Conversely, the significant association between incident dementia and ACB 3 antidepressants across all time periods (4-10, 10-15, and 15-20 years prior to diagnosis) is consistent with a causal link. There is limited evidence linking anticholinergics to amyloid deposition, neurodegeneration and Alzheimer's disease.[3]

Expert panels have produced several anticholinergic rating scales but unfortunately there is poor agreement between them.[4] The study findings are consistent with those of a US prospective cohort study which reported a dose-response relationship between anticholinergic exposure and incident Alzheimer's disease.[5] However, the much larger number of participants and longer time scale of the current study have allowed the researchers to narrow down the focus of concern to just three drug classes.

Although a causal link is not established and rating scales are confusingly inconsistent with one another, it would appear sensible wherever possible to avoid prescribing strongly anticholinergic antidepressant, urological and anti-parkinsonian drugs to older patients. In any case, before commencing or continuing to prescribe these drugs, it is important to advise patients of the possible long-term risk.

The study authors conclude: 'Clinicians should continue to be vigilant with respect to the use of anticholinergic drugs, and should consider the risk of long-term cognitive effects, as well as short-term effects, associated with specific drug classes when performing their risk-benefit analysis.'

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