

## EDITORIALS

## Anticholinergic drugs and dementia in older adults

Should we be concerned?

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Drugs with anticholinergic activity (also known as anticholinergics) prevent acetylcholine from binding to muscarinic and nicotinic receptors, which might result in numerous adverse drug events, especially in older adults. Anticholinergics, used by 10-27% of older adults,<sup>1-3</sup> manage diverse health conditions such as overactive bladder, seasonal allergies, and depression. It is well established that these drugs can cause temporary short term impairment in cognition, including attention and reaction time.<sup>4</sup> Over the past decade, however, mounting evidence suggests that overall use of anticholinergics might be associated with an increased risk of dementia.<sup>5-7</sup>

In a linked paper, Richardson and colleagues (doi:10.1136/bmj.k1315) examine the association between anticholinergics (as defined by the 2012 version of the Anticholinergic Cognitive Burden (ACB) scale) and dementia risk by performing a rigorous nested case-control study using data from within the UK Clinical Practice Research Datalink.<sup>8</sup> Their main findings were that people prescribed greater dosage quantities over time of probable (ACB category 2) and definite (ACB category 3) anticholinergics had a higher risk of dementia. Use consistent with the highest dose category (>1460 defined daily doses) was associated with an adjusted odds ratio for dementia of 1.57 (95% confidence interval 1.18 to 2.09) for probable and 1.31 (1.22 to 1.41) for definite anticholinergics. A cumulative dose-response relation was not found for possible (ACB category 1) anticholinergics.

The researchers also performed secondary analyses to examine the association between specific classes of anticholinergics as well as cumulative dose within class. The most consistent evidence for increased dementia risk was found for definite anticholinergic antidepressants, antiparkinsonian drugs, and drugs to treat urinary incontinence. However, no increased risk was found for anticholinergics used to treat gastrointestinal conditions or respiratory agents; the latter category included over-the-counter antihistamines. Similar findings were observed when applying the same strategy to one of the other major weighted three category anticholinergic scales, the Anticholinergic Drug Scale.<sup>9</sup>

This study of a large representative sample of older adults has several strengths. The authors carefully dealt with reverse causation bias that can occur because anticholinergics are used for early symptoms (prodromal) of dementia before the diagnosis, by excluding anticholinergics in the four years prior to the index date. Another important aspect of this study is the long exposure window that was examined before the index date; anticholinergic use was available for 10 to 15 years for 59% of participants and for 15 to 20 years for 26% of participants. Lastly, the authors used a specific replicable method for defining dementia using diagnosis codes from administrative files and they controlled for several important covariates, including indications for anticholinergic drugs. Taken together, these strengths have extended research in this area.<sup>5-7</sup>

Other aspects of the study deserve further comment however. One is that identifying dementia cases from administrative files might underestimate the true rates of the disease diagnosed compared with using a consistent prospective population based ascertainment approach.<sup>6</sup> Another concern in this and other pharmacoepidemiological studies is unmeasured or residual confounding. In particular, although the authors carefully addressed the problem of depression, information on severity of depression measured by a standardised instrument was not available in administrative data as it would be in a prospective cohort study.<sup>6</sup>

This research raises important issues about the best way to summarise anticholinergic burden for future research. Numerous anticholinergic risk scales have been developed to quantify anticholinergic burden, with considerable differences in included drugs and whether or not to consider dosage.<sup>1-10</sup> One wonders as the specialty moves forward whether a standardised international list of probable or definite anticholinergics could be agreed on so future studies could consistently define anticholinergic dosage burden over time. The study by Naples and colleagues suggests that this approach might be feasible.<sup>1</sup> Among five common scales defining drugs with anticholinergic activity, agreement was found for 20 with probable or definite anticholinergic activity.<sup>1</sup>

In the meantime, what should clinicians do until studies are conducted to further elucidate the underlying biological

mechanisms and determine the risk of dementia with specific classes, including over-the-counter anticholinergic antihistamine use not captured by this or previous studies? As suggested by guidelines, anticholinergics in general should be avoided in older adults.<sup>11 12</sup> Specifically, for most highly anticholinergic drugs, non-pharmacological and pharmacological alternatives are available and should be considered.<sup>13 14</sup>

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare: none.

Provenance and peer review: Commissioned; not peer reviewed.

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