

## 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>

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- 1 Naples JG, Marcum ZA, Perera S, et al. Health, Aging and Body Composition Study. Concordance between anticholinergic burden scales. *J Am Geriatr Soc* 2015;63:2120-4. 10.1111/jgs.13647 26480974
- 2 Kachru N, Carnahan RM, Johnson ML, Aparasu RR. Potentially inappropriate anticholinergic medication use in community-dwelling older adults: a national cross-sectional study. *Drugs Aging* 2015;32:379-89. 10.1007/s40266-015-0257-x 25832970
- 3 Marcum ZA, Wirtz HS, Pettinger M, et al. Anticholinergic medication use and falls in postmenopausal women: findings from the women's health initiative cohort study. *BMC Geriatr* 2016;16:76. 10.1186/s12877-016-0251-0 27038789
- 4 Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. A systematic review of amnesic and non-amnesic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging* 2012;29:639-58. 22812538
- 5 Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch Intern Med* 2009;169:1317-24. 10.1001/archinternmed.2009.229 19636034

- 6 Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015;175:401-7. 10.1001/jamainternmed.2014.7663 25621434
- 7 Gray SL, Hanlon JT. Anticholinergic medication use and dementia: latest evidence and clinical implications. *Ther Adv Drug Saf* 2016;7:217-24. 10.1177/2042098616658399 27695623
- 8 Richardson K, Fox CM, Maidment I. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315.
- 9 Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol* 2006;46:1481-6. 10.1177/0091270006292126 17101747
- 10 Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. *J Am Geriatr Soc* 2015;63:85-90. 10.1111/jgs.13206 25597560
- 11 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227-46. 26446832
- 12 O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8. 10.1093/ageing/afu145 25324330
- 13 Hanlon JT, Semla TP, Schmadre KE. Alternative medications for medications in the use of high-risk medications in the elderly and potentially harmful drug-disease interactions in the elderly quality measures. *J Am Geriatr Soc* 2015;63:e8-18. 10.1111/jgs.13807 26447889
- 14 Development and clinical trials of a new Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons. <https://www.senator-project.eu/> Assessed April 17<sup>th</sup>, 2018

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