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Anticholinergic drug usage and cognitive impairment: findings from three large European cohort studies

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Introduction

Neurologists are familiar with the use of anticholinergic drugs for a variety of conditions including nausea and vomiting, vertigo and bladder dysfunction, a range of indications that reflects the wide distribution of acetylcholine receptors—muscarinic and nicotinic—in the central and peripheral nervous system. The side effect profile of this group of drugs is well recognised, particularly in the frail and the elderly in whom drowsiness, glaucoma, retention of urine, confusion, constipation and hallucinations are common.

What may be less familiar to prescribers is the range of drugs that are not traditionally thought of as "anticholinergic" but which have anticholinergic effects which may be of clinical relevance, particularly when these drugs are used in combination. Examples include antihistamines, antidepressants and antipsychotics, and less likely candidates such as warfarin and antiarrythmics.

The Anticholinergic Cognitive Burden (ACB) scale has been developed to stratify the effect different drugs could have on cognitive function as a result of their anticholinergic properties. Possible anticholinergics (e.g., aripiprazole, haloperidol, venlafaxine) are given a score of 1 and definites anticholinergics a score of 2 (e.g., carbamazepine, pimozide) or 3 (e.g., amitriptyline, doxepin).

Using the ACB scale, three large European population-based studies have examined the association of prescribed anticholinergic drugs with cognitive impairment in real-world populations, and the results are of clinical relevance to all prescribers.

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Anticholinergic drugs and risk of dementia: case–control study

This was a large-scale British cross-sectional study using data from General Practices in the UK contributing to the Clinical Practice Research Datalink. The aim of the study was to estimate the association between duration and level of exposure of different anticholinergic drugs and subsequent incident dementia. A nested case–control design was used to compare the use of anticholinergic drugs in individuals with an established diagnosis of dementia to controls without dementia.

The study compared 40,770 patients aged 65–99 years with a newly established diagnosis of dementia between April 2006 and July 2015 with 283,933 controls. Anticholinergic drugs were classified according to the ACB scale, and total exposure was estimated. In addition, the drugs were further characterised according to indication—analgesic, antidepressant, antipsychotic, cardiovascular, gastrointestinal, anti-Parkinson, respiratory, urological, or other.

The median age of patients at index date was 83 (78–87), and 63% were female. The median drug exposure period was 7.1 years (interquartile range 4.0–11.3, range 1–16). During the exposure period, 89% of cases and 87% of controls received at least one prescription for a drug with an ACB score of 1. 1429 (3.5%) cases and 7909 (2.8%) controls were prescribed a drug with an ACB score of 2. Significantly, 14,453 (35%) cases and 86,403 (30%) controls were prescribed at least one anticholinergic drug with an ACB score of 3.

The authors found that there was a positive and significant association between the prescription of any drug with an ACB score of 1, 2, or 3 and dementia, with corresponding odds ratios of 1.10 (95% confidence interval 1.06–1.15), 1.10 (1.03–1.16), and 1.11 (1.08–1.14), respectively. A dose–response effect seemed to be evident for prescribed doses of drugs with an ACB score of 2 or 3, but not for drugs with an ACB score of 1.

Although there was a significant association between the incidence of dementia and the prescription of antidepressant,

anti-Parkinsonian, or urological drugs with an ACB score of 3, there was no association with antispasmodic, antipsychotic, antihistamine, or other drugs with the same ACB score. The authors suggest the results show a significant association between certain classes of anticholinergics and future dementia incidence.

Comment

This is a very large-scale UK population-based study which controlled for a variety of confounders using a robust database. A retrospective drug exposure history of up to 15–20 years before the dementia diagnosis was taken, making reverse causality less likely. Using a subgroup analysis of different drug groups, the authors were able to more clearly pinpoint the risks associated with exposure to certain anticholinergic groups.

Despite the retrospective drug exposure, we need to be aware that this study reports an association rather than proving causality. In addition, despite the large numbers, the odds ratios are relatively small in this study. The dementia diagnosis is taken from GP records, without note of who made the diagnosis. Additionally, we are not given neuropsychological, neuropathological or neuroimaging correlates of dementia, and the dementias are not divided according to subtypes. Further longitudinal data in future studies, such as serial cognitive or neuroimaging may also help us delineate the speed and pattern of cognitive impairment.

Richardson K et al. (2018) BMJ 361:k1315.

Anticholinergic burden and cognitive function in a large German cohort of hospitalised geriatric patients

In this large German retrospective cohort study, the authors investigated the association of anticholinergic drugs and cognitive impairment in a cohort of hospitalised geriatric patients. Using the national Geriatrics in Bavaria Database (GiB-DAT), 797,440 prescriptions to 89,579 hospitalised patients treated in geriatric units were analysed between January 2013 and June 2015.

The authors used the ACB scale to classify anticholinergic drug use, whilst cognitive function was determined using Mini-Mental State Examination (MMSE) and the standardised scale for dementia (4D + S). In addition, the authors were able to incorporate a number of sociodemographic, functional and neurological characteristics.

The mean age was 82 years, and 66.3% of patients were female. 46.3% of patients received at least one anticholinergic drug. Of these, 30,828 (74.4%) received only one anticholinergic, 8778 (21.2%) received two, 1604 (3.9%) received three and 246 (0.6%) received more than three. The mean ACB score was 1.9 (1–12).

A higher ACB score was associated with worsening MMSE score and dementia incidence on the 4D + S scale, with odds ratios of 1.1 and 1.15, respectively. Increasing age, female sex, increasing age and increasing number of drugs were also associated with cognitive impairment on both scales. The anticholinergic burden was significantly higher in patients with severe cognitive impairment than in patients without cognitive impairment [mean ACB total score 2.0 vs. 1.8, determined with the MMSE ($p < 0.0001$)]. Mean ACB score was highest in the group of patients with severe dementia, followed by lower ACB scores in the group of patients with moderate, mild or no dementia ($p < 0.0001$).

There was a significant association between a lower MMSE and the use of mild as well as definite anticholinergic drugs, but the odds ratio was higher for definite anticholinergic drug use. There was no difference in MMSE between those patients who were on anti-dementia drugs and anticholinergics as well compared to those on anti-dementia drugs alone. The authors conclude that anticholinergic usage is associated with cognitive impairment (MMSE and dementia diagnosis), and that both ACB score 1 and ACB score 3 drugs can significantly contribute to overall anticholinergic burden.

Comment

This is a very large European retrospective study using a well-established database. A measure of cognitive impairment was used alongside a diagnosis of dementia, unlike the other trials. The authors took pains to control for comorbidities, and used robust measurements.

An issue the authors raise is that the MMSE was taken on admission, whilst the drug history was taken on discharge. We also are not given detailed information about the medical history surrounding the patients' admission (which may have affected cognitive performance and drug prescribing). Whilst both the MMSE and 4D + S scale are quick and reliable tests of cognitive impairment, they cannot replicate complex neuropsychological assessment, or the validity of a diagnosis made in a dementia clinic. Like the previous study, dementia diagnoses were not subdivided and there were no imaging or pathological correlates.

Pfistermeister B et al. (2017) PLoS One 12(2):e0171353.

Anticholinergic drug use and cognitive performances in middle age: findings from the CONSTANCES cohort

This was a large French population cross-sectional study looking at the relationship between anticholinergics and cognitive performance in middle-aged adults. The authors

used baseline data of a number of participants aged 45–70 years from the Consultants des centres d'examen de santé de la sécurité sociale (CONSTANCES) cohort, a randomly selected population of participants in France.

Between February 2012 and June 2016, data were collected through baseline questionnaires, medical examination and cognitive tests. Four different Neuropsychological batteries assessed episodic verbal memory, language and verbal fluency, psychomotor speed as well as attention and visuospatial perception, respectively. Cumulative anticholinergic drug use was extracted from the French insurance database over the study period. The authors described anticholinergic burden according to the ACB scale, as well as estimated total exposure to the drug.

34,267 participants with a mean age of 57.8 were included in the study. During the 3 year period preceding inclusion, anticholinergics were dispensed at least once to 16,172 (47.2%) participants. 12,220 (76%) received at least one ACB-1 drug, 822 (5%) at least one ACB-2/3 drug, and 3130 (19%) at least one drug in both ACB categories. Exposure to two or more different anticholinergics was recorded for 52.4% of anticholinergic drug users.

Importantly, being exposed to anticholinergics was negatively associated with all cognitive test z scores for most of the exposure levels in univariate analyses. The effect size increased with cumulative anticholinergic exposure (p trend < 0.001). After adjustment for confounders this association was medium for executive function tests but less pronounced for episodic memory tests (immediate and delayed free recall). The effect size was medium for antipsychotics and small for drugs targeting the gastrointestinal tract or metabolism, opioids and anxiolytics. The authors conclude that these results point to a negative association between cumulative anticholinergic exposure and cognitive performance in middle-aged adults, but that a significant proportion of this association may be attributable to antipsychotic drugs.

Comment

This study uses a large cohort of patients from a randomly selected population in France. Neuropsychometric assessments used were well-established tests administered by trained Neuropsychologists. Antipsychotics were subdivided into drug classes, which helped elucidate the large contribution of antipsychotic use. What helped set this study apart is its young demographic (mean age 57.8), suggesting that it is not only the elderly who are subject to the detrimental effects of anticholinergics.

The authors have noted that it is difficult to capture medication usage frequency accurately, and that there may be classes of anticholinergics missing. The use of a one-off (albeit well validated) set of assessments means it is difficult to extrapolate longitudinal data. We also cannot be sure if there is any possibility of reversibility of the cognitive impairment upon discontinuation of anticholinergics in this cohort. Overall, using a validated clinical diagnosis of dementia in studies like this may make it more clinically valuable for clinicians.

Ziad A et al. (2018) J Neurol Neurosurg Psychiatry 89:1107–1115.

Discussion

These three large-scale European population-based studies consistently suggest an association between anticholinergic use and cognitive impairment (both on clinical diagnosis and cognitive testing performance). It seems that the problem is not purely a geriatric one, as those in their middle age may as well be affected. There is evidence of heterogeneity between cognitive impairment and different drug classes, although the findings from these studies seem mixed.

The three studies also highlight the significant use of antipsychotics in modern European populations. As these groups age, the burden of cognitive impairment is likely to increase. As a response to the Richardson et al. paper in the BMJ, in 2018 the National Institute for Health and Care Excellence (NICE) in the UK has suggested to GPs that anticholinergic drugs should be 'avoided' in mid- and later-life patients.

Although all three studies are large and robust, we must note that they all show an association, rather than proving causality. In addition, the studies have measured drug prescription, rather than actual drug adherence. We are lacking randomised controlled, prospective studies which might allow us to measure drug usage and cognitive impairment longitudinally. Given some of the differences in findings between different drug classes, we do need to additionally further stratify individual anticholinergic drugs individually according to their cognitive profile.

Neurologists must acknowledge the significance of both the current, and also potential future problem of the cognitive impairment associated with anticholinergic use. Given the effectiveness of some of these medications, it is important we do not simply urge patients to stop taking anticholinergics altogether. We must, however, promptly review our own prescribing practices in light of this new evidence, and counsel patients more openly about these possible significant adverse effects.