

Use of drugs with anticholinergic effects and cognitive impairment in community-living older persons
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Many drugs with anticholinergic effects are often prescribed for the elderly for various therapeutic reasons such as Parkinson's disease, urge incontinence and mood disturbances. Various reports estimated that drugs with anticholinergic effects are used by between 13.7% and 27% of the community-living elderly [1–3] and as much as 60% in nursing homes residents [4].

The unwanted peripheral and central side-effects are well known and common and include cognitive impairment [5] but are often attributed to normal consequences of ageing or the disease process. Acetylcholine levels decrease with advancing age and reduced cholinergic activity is a characteristic feature of dementia including Alzheimer's disease [6]. The use of drugs with anticholinergic effects is clearly an important exogenous source of anticholinergic load in the body and older people are more vulnerable. Because M1 receptor density is reduced by half in the elderly subjects, additional muscarinic antagonism could increase the risk of precipitating an accelerated decline in memory [7].

The use of drugs with anticholinergic activity is a biologically plausible and potentially modifiable risk factor for cognitive impairment. A number of clinical studies have provided empirical evidence of cognitive impairment associated specifically with benzodiazepines, amantadine, trihexphenidyl, oxybutynin, diphenhydramine [8–12]. Recent studies have measured serum levels of anticholinergic activities (SAA) in community-dwelling seniors and showed that high levels of SAA were significantly more likely to perform poorly on the MMSE [13].

Despite the importance of anticholinergic load in the elderly and cognitive impairment, only one population-based epidemiological study (PAQUID cohort) has shown that the current use of drugs with anticholinergic properties was significantly associated with low cognitive performance among community-dwelling elderly people [1].

The aim of this population-based study was to assess the association between the overall use of drugs with anticholinergic effects and cognitive performance among community-dwelling elderly persons, and assess its relative contribution to cognitive impairment in the presence of other recognized risk factors such as gender, age, ethnicity, education, depression, stroke and cardiometabolic factors.

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Method and measurements

The present study used data collected in a large sample of community-dwelling older adults in the Singapore Longitudinal Aging Study (SLAS), a prospective study of ageing and health [14]. The participants were older adults aged 55 and above resident in five districts in South East Singapore. A total of 2,804 residents (response rate 78%) gave signed informed consent for participation.

Cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) [15], which measures global cognitive functioning on domains that included memory, attention, language, praxis and visuo-spatial ability. The MMSE has been validated for use in the local population in Singapore and poor cognitive performance as defined by the MMSE total score of 23 or less was shown to have 97.5% sensitivity and 75.6% specificity in predicting dementia [16].

All prescription and non-prescription medications taken by the participant within the year were ascertained from self-reports and physical inspection of pill bottles, boxes, packets, diaries and other materials to assist recall. For patients who were unable to recall, the appropriate caregiver most familiar with the patient was consulted and provided the information. Recent use of drugs known to possess moderate or strong anticholinergic activity was identified from published lists of anticholinergic drugs commonly prescribed

[5, 6], and ordered in seven therapeutic classes: H1-antihistamines, antiemetics, gastrointestinal and urinary antispasmodics, bronchodilators, antiparkinsonian drugs, tricyclic antidepressants and antipsychotics.

We collected baseline information on potential confounding or mediating variables, including age (in years), gender, education (in years), cigarette smoking (current smokers versus past-smokers or non-smokers), alcohol drinking (at least one alcoholic drink daily or less) and depression.

The presence of depressive symptoms was determined by the 15-item Geriatric Depression Scale (GDS-15) [17]. This scale has been validated locally for identifying late-life depression in Chinese, Malay and Indian subjects [18, 19]. The internal reliability coefficient (Cronbach's α) was 0.84. Scores range from 0 to 15, and scores of 5 or more are indicative of depression.

Chronic medical illnesses

The presence of cardiometabolic diseases and risk factors, stroke, CNS neurodegenerative and other specified chronic disorders was determined by corroborating information from respondent's self-reports of a physician diagnosis and treatment in the past 12 months, identification of medications produced by the respondents, investigative and operative procedures for coronary heart and other diseases, blood pressure, lipids and glucose measurements.

Relative risks were estimated by odds ratio (OR) and their 95% confidence intervals (CI). We calculated the population attributable risk (PAR)% as $PAR\% = (Prevalence \times (Adj\ OR - 1)) / Adj\ OR$. All analyses were performed using SAS software.

Results

Cognitive impairment was present in 360 (14.8%) of community-living older person. Drugs with anticholinergic effects were identified in 33 (1.2%) of the participants. Tricyclic antidepressants were the most commonly prescribed drugs with in this age group followed by hydroxyzine, chlorpheniramine, tolteridone and chlorpromazine (Table 1).

Table 1. Anticholinergic drugs (N = 34) used by study participants (n = 33)
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More participants currently using drugs with anticholinergic effects were found in those with cognitive impairment (N = 11, 3.1%) compared to those with no cognitive impairment (N = 22, 0.9%). The association between the use of drugs with anticholinergic effects and cognitive impairment was statistically significant (OR = 2.66; 95% CI 1.06–6.68, P = 0.038), after adjusting for confounding factors (Table 2). In contrast, the adjusted OR (95% CI) of association for antihypertensive drugs was 0.91 (0.69–1.21), and for antidiabetic drugs was 0.96 (0.65–1.40).

Table 2. Multivariate odds ratio of association of anticholinergic drug use and other risk factors for cognitive impairment, and their population attributable risks (PAR)
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Other risk factors found to be significantly associated with cognitive impairment included female gender (OR = 2.08; P < 0.001), age over 75 years old (OR = 2.64; P < 0.001), Malay and Indian ethnicity (OR = 3.56; P < 0.001), education <6 years (OR = 10.97; P < 0.001), depressive symptoms (OR = 2.00; P < 0.005) and stroke and other CNS disorders (OR = 3.39; P < 0.001).

Given that only 1.3% (33/2,795) of the study participants used drugs with anticholinergic effects, the estimated PAR was 0.8%. In comparison, the estimated PAR for other modifiable risk factors like stroke (3.9% prevalence) was 2.7%, and depression (13.1% prevalence) was 6.6%.

Discussion

Our study confirms a significant association between current use of drugs with anticholinergic effects and cognitive impairment, and quantifies its measurable contribution to the observed prevalence of cognitive impairment, alongside the contributions attributable to other established risk factors.

The strength of this study is the population perspectives of the results that were pertinent to the community-living elderly. The results from multivariate analyses were shown to be robust in demonstrating concurrent associations with other risk factors. This allowed the relative contribution of drugs with anticholinergic effects on cognitive impairment to be assessed alongside established modifiable factors such as stroke or depression.

Many other drugs such as digoxin, frusemide and cimetidine have been shown to demonstrate in vivo anticholinergic like activity [20] but their clinical significances are uncertain. Because they could potentially increase the overall anticholinergic load, we have also examined this group of drugs in the present study, but found no significant association with cognitive impairment.

The prevalence of anticholinergic drug use was reported in other population studies to be between 13.7% [1] and 27% [3], and their PAR could be estimated at between 8.0% and 14.3%. It is noteworthy that the prevalence of use and PAR in this population was lower. This could possibly be due to the younger age and community-dwelling sample of older adults in this population, or the under-ascertainment of the use of such drugs, or greater awareness and caution of use by medical practitioners. It is not uncommon for physicians to prescribe both an anticholinergic drug with an acetylcholinesterase inhibitor drug, but in this population, we found only one patient who was prescribed donepezil, but not together with an anticholinergic drug.

However, in this study, the extent to which the OR provided an unbiased estimate of the actual causal association of anticholinergic drugs with cognitive impairment should be discussed. It was likely that the majority of identified use of cholinergic drug pertained to current and recent use. To the extent that a few instances may have been previous drug use that had ceased for unknown periods of time, the OR may be underestimated. On the other hand, the plausibility of reverse causation should also be considered. As some of these drugs may be prescribed for behavioural, psychological and urinary symptoms of diseases that cause cognitive impairment and dementia, the estimates of association and PAR could be overestimated. Finally, the criteria we used to select drugs of interest with anticholinergic effects were arbitrary, and it was difficult to differentiate strong and weak central and peripheral anticholinergic activity of these drugs, as well as the central effects from non-cholinergic mechanisms for some drugs.

Another limitation is that although the MMSE was shown in this population to be highly valid and reliable in assessing cognitive impairment [16], it was not independent of education in this population; hence, it was necessary that the analysis should carefully control for this possible measurement artefact.

Conclusion

This study demonstrates a measurable contribution of the use of drugs with anticholinergic effects as a

modifiable risk factor for cognitive impairment in older persons. Drug prescriptions in the elderly should always consider the adverse effect of drugs with anticholinergic properties on cognitive function.

Key points

- Various drugs with unwanted anti-cholinergic actions are often used in elderly patients but may aggravate cognitive decline.
- The use of drugs with anticholinergic actions is associated with more than 2-fold significant increase in the prevalence of cognitive impairment among community-dwelling older persons.
- Drug prescriptions in the elderly should consider the adverse cognitive effect of drugs with anticholinergic actions.

Conflicts of interest

None. No commercial company sponsored or played any role in the design, methods, subject recruitment, data collections, analysis and preparation of paper.

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