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**SYSTEMATIC REVIEW**

# Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review

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## Abstract

**Objectives**: to determine the effect of drugs with anti-cholinergic properties on relevant health outcomes.
**Design**: electronic published and unpublished literature/trial registries were systematically reviewed. Studies evaluating medications with anti-cholinergic activity on cognitive function, delirium, physical function or mortality were eligible.
**Results**: forty-six studies including 60,944 participants were included. Seventy-seven percent of included studies evaluating cognitive function ($n = 33$) reported a significant decline in cognitive ability with increasing anti-cholinergic load ($P < 0.05$). Four of five included studies reported no association with delirium and increasing anti-cholinergic drug load ($P > 0.05$). Five of the eight included studies reported a decline in physical function in users of anti-cholinergics ($P < 0.05$). Three of nine studies evaluating mortality reported that the use of drugs with anti-cholinergic properties was associated with a trend towards increased mortality, but this was not statistically significant. The methodological quality of the evidence-base ranged from poor to very good.
**Conclusion**: medicines with anti-cholinergic properties have a significant adverse effect on cognitive and physical function, but limited evidence exists for delirium or mortality outcomes.

**Keywords:** *anti-cholinergic, anti-muscarinic, cholinergic antagonist, adverse effect, cognition, function, mortality, older people, systematic review*

## Introduction

Drugs with anti-cholinergic properties are commonly prescribed for a variety of medical illnesses [1]. With a globally ageing population, much of this drug burden falls on the elderly. Ninety percent of older adults report taking at least one prescription medication [2]. It has been estimated that 20–50% of older people have been prescribed at least one medication with anti-cholinergic activity [3]. Younger adults may also be prescribed long-term anti-cholinergic treatment for conditions such as asthma or to manage the side-effects of medicines used to treat psychiatric disorders [3]. It has been recommended that increased care should be taken to avoid the inappropriate prescribing of anti-cholinergic drugs

due to the wide spectrum of central effects such as the onset of dizziness, sedation, confusion, in addition to increasing delirium, causing a decline in cognitive and physical function [1]. Peripheral adverse effects are also commonly reported and include dry mouth, dry eyes, constipation, blurred vision and increased heart rate [1].

Much of the previous evidence has focused on a link between medications with anti-cholinergic properties and cognitive function [3, 4]. Medications with anti-cholinergic properties recognized by the anti-cholinergic cognitive burden (ACB) scale have been recently correlated with an additional 0.33 point decline in Mini-Mental State Examination (MMSE) score over 2 years [5], a 2-fold increase in cognitive impairment with as little as 60–90 days of use [6], and ∼50–80% increase in the risk of incident cognitive impairment over 6 years [7].

A decline in cognitive function and the diagnosis of mild cognitive impairment is associated with a progression to dementia within 5 years [8], making primary prevention and avoidance of anti-cholinergic medications wherever possible, of significant importance as a strategy to protect against persistent cognitive decline [9]. Similarly, it is well known that functional impairment in older adults limits independent living and impacts on their quality of life [10]. Mild cognitive impairment has also been attributed to an increased risk of falls, further increasing morbidity and reduced physical function in older people [11].

This systematic review assesses the empirical research surrounding the effect of increasing anti-cholinergic load on cognitive function, delirium, physical function and mortality. To the author's knowledge, this is the first systematic review to evaluate the association between medications with anti-cholinergic properties and delirium or physical function. This paper will also provide an important update required to review the current literature on a possible association with cognitive function and mortality.

## Search strategy and selection criteria

### Search methods

A PRISMA compliant systematic review was undertaken [12]. The primary search was conducted of the published literature using the electronic databases EMBASE (2002–2013) and Ovid MEDLINE (2002–2013) to Week 3 October 2013. The search terms adopted are presented in Table 1. This was adapted for the different search databases.

A secondary search was conducted of the unpublished grey literature and trial registries. The following databases were accessed from January 2002 to Week 3 October 2013: open Grey, the WHO International Clinical Trials Registry Platform, Current Controlled Trials and the UK National Research Register Archive. An additional search of reference lists from all potentially eligible papers and review articles was also undertaken for completeness.

Table 1. Search terms used for the electronic database searches

| |
|---|
| (1) (Anticholinergic* or Anticholinergic agent* or Cholinergic antagonist* or Anti-cholinergic* or Antimuscarinic* or Antimuscarinic agent* or Muscarinic antagonist* or Anti-muscarinic*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui] (mortality or death or survival).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui] |
| (2) (Cognitive function or Cognitive disorder* or Cognitive impairment or Dementia or Delirium).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui] |
| (3) (Physical function or Physical activity or Function* or Activity*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui] |
| (4) OR/2–4 |
| (5) 1 and 5 |
| (6) Limit 6 to English language |
| (7) Limit 6 to year = '2002 –Current' |

### Eligibility criteria

Studies were deemed eligible if they satisfied each of the following criteria:

(a) Studies investigating anti-cholinergic effects on adults. This was confirmed by cross-checking of the mentioned drugs against the 2012 updated ACB scale [13]; http://www.agingbraincare.org/tools/abc-anticholinergic-cognitive-burden-scale/). All studies included were required to indicate the dosage and duration at which medicines were used or how the anti-cholinergic load was calculated.
(b) Studies investigating the effect of medicines with anti-cholinergic properties on one of the following outcomes: mortality, cognitive function, delirium or physical function.
(c) Either randomised controlled trial (RCT), prospective cohort, cross-sectional or prospective case-controlled studies.

Studies were excluded if:

(a) The primary exposure was not clearly stated or the drug used did not have anti-cholinergic properties.
(b) The anti-cholinergic load was based on serum sample analysis alone.
(c) Studies that reported the right exposure but did not report the effect of stated anti-cholinergic medicines against the selected outcomes.
(d) Retrospective studies, case reports, journal editorials, literature reviews, clinical audits or studies that were not published in the English language.
(e) Animal studies.

We selected to review only those studies published after 1 January 2002 to capture the results of studies evaluating systematic recognition of anti-cholinergic medications through various scales. Other systematic reviews have described the relationship between anti-cholinergics and cognitive outcomes [3, 4, 14] and included results prior to 2002. This review therefore updates these previous studies.

### Identification of studies

Two reviewers (N.B., W.Y.C.) independently reviewed the study titles and/or abstracts to identify potentially eligible studies against the review eligibility criteria. Any disagreements were resolved through discussion and adjudicated by a third investigator (C.S.K.).

The full text for all potentially eligible studies were gathered and independently re-reviewed by two reviewers (N.B., W.Y.C.) against the eligibility criteria to determine final eligibility. Any disagreements were resolved through discussion and adjudicated by three senior reviewers (C.S.K., C.F. and I.M.).

### Data extraction

Data extraction were independently conducted by five reviewers (N.B., W.Y.C., M.G., I.K., C.S.K.) and verified by two senior reviewers (I.M., C.F.). Data extraction were undertaken using a pre-defined data table. Data extracted included: study design, number of participants, year of the study undertaken, selection criteria, results of each study with regards to the effect of anti-cholinergic medications on the outcomes of interest, significance of the associations were based on the statistical results reported in each study.

### Risk of bias assessment

Two critical appraisal tools were used to assess methodological quality and risk of bias. The Newcastle-Ottawa scale [15] was used to assess the quality of non-randomised studies. The Cochrane Risk of Bias tool [16] was used to assess methodological quality for all RCTs.

Risk of bias assessments were conducted by two independent reviewers (N.B., W.Y.C.). In the event of disagreement on critical appraisal score, agreement was met through discussion, adjudicated by a third reviewer (C.S.K.).

### Data analysis

The data extraction table were reviewed to determine the most appropriate analysis technique to answer the research question. There appeared considerable study heterogeneity in relation to population diagnosis and characteristics, medication and dose, follow-up period, outcome measurement and reporting of data. This therefore precluded the adoption of a meta-analysis to pool data. Accordingly, a qualitative narrative review of the literature, answering the research questions, was the most appropriate analysis strategy for synthesising trends in findings.

## Results

### Search results

The results of the search strategy are summarised in Figure 1. From a total of 7078 identified citations, 133 were deemed potentially eligible. From these 46 studies met the eligibility criteria and were included in the final review.

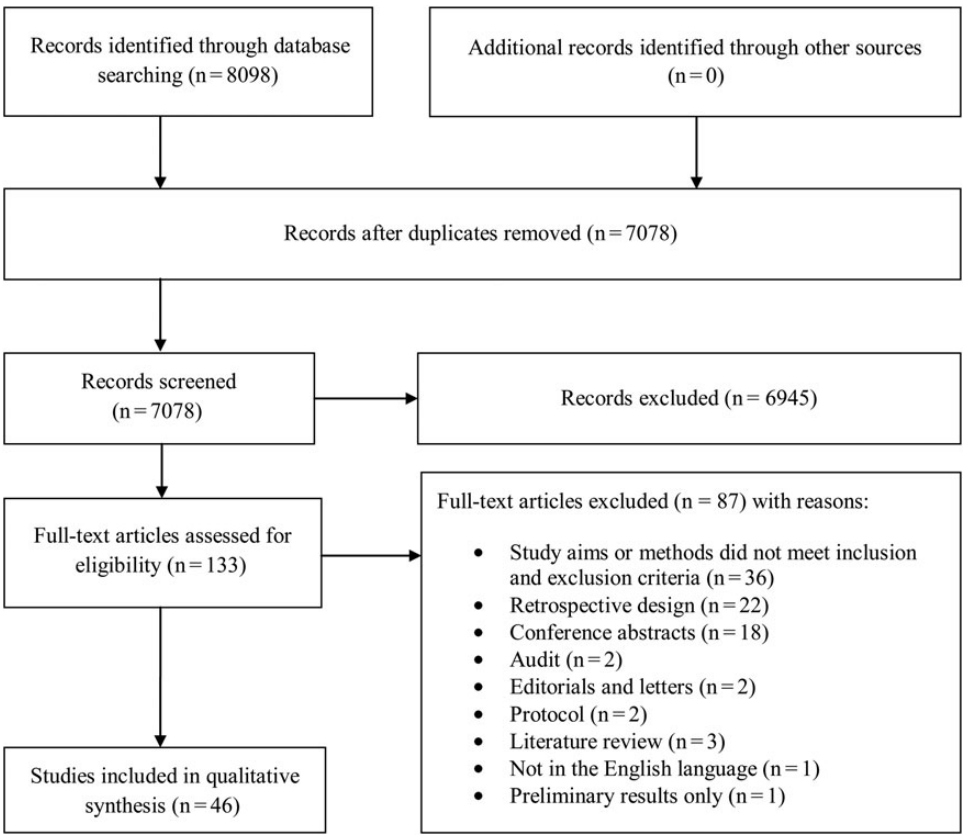


**Figure 1.** PRISMA flow diagram of search strategy results.

### Characteristics of included studies

The characteristics of included studies are summarised in Table 2. The studies consisted of 38 cohort studies, six RCTs and two case–control study.

In total, 60,944 participants, with mean age range of 39.9–87.5 years were included. This consisted of 25,225 males and 32,543 females; cohort gender proportions were not stated in two studies [18, 46]. Thirty-three studies were conducted in community dwellings and 14 studies in hospital settings, one study was conducted across both settings [44]. Participants in the hospital settings were admitted for a variety of medical reasons including cancer [29], general frailty/long-term care [41] and acute bladder symptoms [25, 30]. Supplementary data available in *Age and Ageing* online, Table S1 illustrate the estimates of anti-cholinergic load or burden to estimate the ACB in each included study.

### Results of risk of bias assessment

The results of the critical appraisal and risk of bias assessments are presented in Supplementary data available in *Age and Ageing* online, Tables S2–S4. The findings indicate that the evidence-base was largely moderate in methodological quality.

Supplementary data available in *Age and Ageing* online, Table S3 present the appraisal results of the single case–control study. The results indicated that whilst demonstrating a number of key strengths, the evidence-base was unclear on the validity of the comparison between cases and control participants, with unacceptable non-response rates demonstrated for the study cohort.

The Cochrane Risk of Bias tool for RCTs demonstrated the evidence presented with a moderate risk of bias. Several studies poorly demonstrated the randomisation procedures, and were limited by incomplete analysis of the dataset through intention-to-treat principles, and rarely adjusted analyses for missing data, thereby reducing the strength of these statistical analyses.

### Data synthesis

A summary of the results of each included study is presented in Table 3 with a more comprehensive summary as Supplementary data available in *Age and Ageing* online, Table S5.

### Anti-cholinergic effect on cognitive function

Thirty-three studies reported the impact of medications with anti-cholinergic properties on cognitive function [5–7, 18, 19, 22–25, 27, 28, 30, 31, 33, 34, 36–40, 42, 43, 46, 48–50, 52–58]. This was evaluated with a number of tools, most commonly the MMSE.

There was a repeated finding of an association between anti-cholinergic medications and a significant decline in cognitive ability, as demonstrated by 23 studies [5–7, 18, 19, 22–25, 28, 30, 31, 33, 40, 42, 43, 46, 48, 52–55, 58].

Ten studies reported no significant association between medicines with anti-cholinergic properties and cognitive function [27, 28, 34, 36–39, 49, 50, 57]. A number of differences in study design and variable definitions may have accounted for the study results, such as differences in medications evaluated (single versus scale-based identification of anti-cholinergics), characteristics of the control group, duration of study and measurement of dose–effect.

### Anti-cholinergic effect on delirium

Five studies assessed the impact of anti-cholinergic burden on delirium [20, 21, 29, 44, 47]. Only one study demonstrated a significant association between drugs with anti-cholinergic properties and delirium [20]. Delirium, as assessed by the Delirium Rating Scale, was more likely in people prescribed medicines with anti-cholinergic properties prior to a stroke (OR: 11.3; 95% CI: 1.19–108.2) or during hospitalisation (OR: 5.82; 95% CI: 1.96–17.2), compared with those not prescribed anti-cholinergics [20].

Luukkanen *et al.* [44], Pandharipande *et al.* [47], Campbell *et al.* [21] and Gaudeau *et al.* [29] reported contrary findings, reporting no association between the use of medicines with anti-cholinergic properties and delirium.

### Anti-cholinergic effect on physical function

Eight studies assessed the impact of medications with anti-cholinergic properties on physical function [32, 33, 35, 38, 40, 42, 56, 57]. Of five studies reported that anti-cholinergic drugs were associated with reduced physical function [32, 33, 35, 40, 42].

Three studies reported no association between ACB and physical function [38, 56, 57]. Wilson *et al.* [56] assessed the level of mobility. They reported that participants could walk without the use of a walking aid in 46% of the Drug Burden Index (DBI) category 0, 37.7% of those in the DBI category <1 and 34% of those in the DBI category > 1. Whilst this is only one aspect of function, this does provide some conflicting evidence against the evidence-base.

### Anti-cholinergic effect on mortality

Nine studies investigated the effect of anti-cholinergic medications on mortality [5, 11, 17, 26, 41, 44, 45, 51, 56]. Six studies reported that the use of drugs with anti-cholinergic properties was not statistically associated with increased mortality [11, 17, 41, 44, 51, 56].

Three studies reported contrary findings [5, 26, 48]. Fox *et al.* [5] reported that after adjusting for key variables including baseline MMSE score and number of non-anti-cholinergic medications, every additional point on the ACB scale increased the odds of death by 26% (OR: 1.26, 95% CI: 1.20–1.32) [5]. De Luise *et al.* [26] reported a risk ratio of tiotropium use and total mortality of 0.77 (95% CI: 0.56–0.78). However, the population considered in this study is notably different from other assessments of anti-cholinergic use with a focus on respiratory disease (Table 2).

**Table 2.** Study design and characteristics of the included studies

| Study | Design; setting | Country | Number of participants | Mean age (years) | % Male | Participant characteristics |
|---|---|---|---|---|---|---|
| Agar [17] | *Post hoc* analysis of RCT; Hospital and community | Australia | 461 | 72 | 48 | Patients included in Palliative Care Trial with diagnosis of cancer, known date of death, Australia—modified Karnofsky Performance Scale (AKPS) score of >60 at baseline and AKPS score falls <60 at any time during follow-up |
| Ancelin [18] | Cohort study; Community | France | 372 | 66.2 | NS | Patients with age >60 years and without dementia at recruitment |
| Boustani [19] | Cohort study; Community | USA | 1558 | 77.6 | 33.6 | Patients with age ≥65 years and were African American |
| Caeiro [20] | Case–control study; Hospital | Portugal | 74 | 62 | 55 | Patients included with admission diagnosis of cerebral infarct or intracerebral haemorrhage/ intraventricular haemorrhage, assessment delirium performed within 4 days after stroke onset, a Glasgow Coma Scale score ≥5 on the day of the delirium examination |
| Cai [5] | Cohort study; Community | USA | 3690 | 72 | 30 | Patients aged 65 and older who were living independently or with family in a community setting. Medication dispensing data defined the exposure, and a two-stage screening and diagnosis design provided the outcome assessment of cognitive impairment |
| Campbell [7] | Cohort study; Community | USA | 1652 | 81.8 | 30.9 | Patients with age ≥70 years who were African American, community dwelling, had normal cognitive function at baseline and enrolled in Indianapolis-Ibadan Dementia Project between 2001 and 2007 |
| Campbell [21] | Cohort study; Hospital | USA | 147 | 76.5 | 37 | Patients with age ≥65 years who were screened to have cognitive impairment, admitted to general medical ward, English speaking and delirium-free at admission |
| Cancelli [22] | Cohort study; Community | Italy | 750 | 75 | 38.7 | Patients with age ≥65 years who were living independently or at an institution |
| Cao [23] | Cross-sectional; Community | USA | 932 | 78 | 0 | Patients included were aged ≥65 years, female Medicare beneficiaries from 1 September 1992, residents in Baltimore area, self-reported difficulty in two or more functional domain which included: (i) mobility and exercise tolerance, (ii) upper extremity function, (iii) complex activity heavily involving cognition and sensory input and (iv) basic self-care |
| Carriere [24] | Cohort study; Community | France | 6912 | 73.7 | 40.3 | Patients were recruited from electoral roll and were community dwelling, aged ≥65 years and from three French cities |
| Cruce [25] | Cross-sectional; Hospital | Canada | 88 | 50.7 | 31.8 | Patients with diagnosis of multiple sclerosis, aged 18–65 years, EDSS score <7.5, on stable dosage of classical anti-cholinergic drugs (oxybutynin or tolterodine) for bladder dysfunction for at least 6 months prior to assessment and had stable multiple sclerosis with no recent relapse or treatment with steroids within the past 3 months |
| De Luise [26] | Cohort study; Hospital | USA | 10,603 | NS | 47.8 | Patients admitted between January 1977 and December 2003 |
| Drag [27] | Cross-sectional study; Hospital | USA | 450 | 67.95 | 95.3 | Patients admitted to Extended Care Centre and had completed the cognitive screen, had premorbid IQ ≥70 and did not have delirium or dementia |
| Fox [5] | Cohort study; Community | UK | 12,423 | 75.2 | 40 | Patients were a random sample of ≥65 years old, living at home and institutions |
| Fox [28] | Cohort study; Community | UK | 244 | 81 | 28.6 | Patients included standardised diagnosis of dementia, fulfilment of criteria for possible or probably Alzheimer's disease with age ≥55 years, had lived in North London or Essex (UK) and in contact with family or statutory carer for ≥4 h a week |
| Gaudreau [29] | Cohort study; Hospital | Canada | 261 | 59.6 | 56 | Patients included if they had histological diagnosis of cancer in consecutive admissions to the unit |
| Geller [30] | Cohort study; Hospital | USA | 35 | 70.4 | 0 | Patients were postmenopausal women, age ≥55 years, seeking treatment for overactive bladder and opting for anti-cholinergic therapy |
| Gnijidic [31] | Cohort study; Community | Australia | 1705 | 77.2 | 100 | Patients had to be born in English-speaking countries or learned English before the age of 12 years, community-dwelling men, age ≥70 years, living within the defined region of the New South Wales Electoral role whose cognition was intact or had mild cognitive impairment or dementia |
| Gnjidic [32] | Cross-sectional study; Community | Australia | 1705 | 76.9 | 100 | Patients included were male, aged ≥70 years and resident of South Wales |
| Han [33] | Cohort study; Community | USA | 544 | 74.4 | 100 | Patients included were male, aged ≥65 years and part of Connecticut Veterans Longitudinal Cohort with a diagnosis of hypertension. |

*Continued*

Table 2. Continued

| Study | Design; setting | Country | Number of participants | Mean age (years) | % Male | Participant characteristics |
|---|---|---|---|---|---|---|
| Harvey [34] | Randomised, double-blinded controlled trial; Community | USA | 377 | 39.9 | 73 | Patients had to have a diagnosis of Schizophrenia, baseline positive and negative syndrome scale (PANSS score) of 60–120 and were aged 18–64 years and outpatients or inpatients hospitalised for <4 weeks |
| Hilmer [35] | Cohort Study; Community | USA | 2172 | 73 | 47 | Patients were community dwellers with age 70–79 years who had participated in the Health ABC study |
| Kay [36] | Randomised, double-blinded controlled trial; Commercial trial centre | USA | 150 | 67.3 | 38 | Patients were healthy subjects aged ≥60 years, English as first language and were able to follow instructions and complete computerised cognitive tests. Excluded if anti-cholinergic use was contraindicated or they suffered from dementia, depression or had MMSE ≤27 |
| Kersten [37] | RCT; Community | Norway | 87 | 85 | 61 | Patients were long-term nursing home residents from 22 nursing homes. Have a total anti-cholinergic drug scale (ADS) of ≥3. Patients were not blind, deaf, aphasic, delirious or with severe dementia (Clinical Dementia Rating scale of 3) |
| Kersten [38] | RCT; Community | Norway | 87 | 85 | 61 | Patients were long-term nursing home residents from 22 nursing homes. Have a total ADS of ≥3. Patients were not blind, deaf, aphasic, delirious or with severe dementia (Clinical Dementia Rating scale of 3) |
| Kolanowski [39] | Longitudinal study; Community | USA | 87 | 85.7 | 23 | Patients were included if English speakers, with age ≥65 years, diagnosis of dementia using DSM-IV criteria, MMSE score ≥8 but <24, no new psychoactive drugs prescribed and presence of behavioural symptoms as reported by staff and documented in the latest minimum dataset |
| Koyama [40] | Cohort study; Community | USA | 1484 | 87.5 | 0 | Patients were community-dwelling women who had previously been enrolled on the Study of Osteoporotic Fractures from 1986 to 1988. A cohort of African-American women were later recruited from 1997 to 1998 |
| Kumpula [41] | Cohort study; Hospital | Finland | 1004 | 81.3 | 25 | Patients included were living in 1 of 53 long-term care wards in seven hospitals in Helsinki. Exclusion due to incomplete medication data and unavailable mortality data |
| Lampela [42] | Cohort study; Community | Finland | 621 | 81.7 | 29.8 | Patients were randomly selected ≥75 years from previous cross-sectional data of Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study with consent to participate |
| Lipton [43] | Randomised, double-blinded crossover controlled trial; Community | USA | 129 | 71.2 | 41.8 | Patients were age >65 years, and had to score 10 or less than on the short orientation memory and concentration test on enrolment |
| Low [31] | Cohort study; Community | Australia | 2058 | 62.5 | 51.7 | Patients were randomly selected from electoral roll |
| Luukkanen [44] | Cohort study; Hospital and Community | Finland | 425 | 86.1 | 18.4 | Patients were from geriatric wards, residential or nursing home residents aged over 70 years. Diagnosis of dementia using DSM-IV criteria, MMSE score |
| Mangoni [45] | Cohort study; Hospital | Netherlands | 71 | 85 | 29.6 | Patients were ≥65 admitted with hip fractures and scheduled for surgery |
| Merchant [46] | Cross-sectional study; Community | Singapore | 2804 | NS | NS | Patients were enrolled in the Singapore Longitudinal Aging Study, community dwellers and aged ≥55 years |
| Pandharipande [47] | Cohort study; Hospital | USA | 198 | 55.5 | 52 | Patients who were admitted onto medical/coronary ICU and were mechanically ventilated, without a baseline neurological disease to confound the assessment of delirium |
| Pasina [48] | Cross-sectional study; Hospital | Italy | 1232 | 78.6 | 49.4 | Patients were ≥65 years and admitted into internal medicine and geriatric wards participating in the Registry of Polytherapies SIMI (REPOSI study) in 2010 |
| Shah [49] | Cohort study; Community | USA | 896 | 74.8 | 30.7 | Patients were community-dwelling older clergy without dementia who were participating in the Religious Orders Study—a longitudinal epidemiologic study of aging where participants have been assessed annually for a mean of 10 years |

| | | | | | | |
|---|---|---|---|---|---|---|
| Shakakibara [50] | Cohort study; Community | Japan | 62 | 70 | 40.3 | Patients were consecutive subjects in neurology outpatients. All had diagnosis of overactive bladder. Exclusion criteria were anti-cholinergic agents within 2 weeks of entry into study, indwelling foley catheters, intermittent catheterisation, postvoid residual urine volume >100 ml, high prostate-specific antigen, acute urinary tract infection, closed angle glaucoma, diseases of anti-cholinergic contraindication |
| Uusvaara [51] | Cohort study; community | Finland | 400 | 80 | 35 | Patients were community dwelling, aged 75–90 years, had a diagnosis of cardiovascular disease and were a part of the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study cohort |
| Uusvaara [52] | Cohort study; community | Finland | 400 | 80 | 35 | Patients were community dwelling, aged 75–90 years, had a diagnosis of cardiovascular disease and were a part of the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study cohort |
| Wagg [53] | Randomised, double-blinded, triple-crossover trial; Commercial trial centre | UK | 26 | 79 | 54 | Patients with age ≥75 years with mild cognitive impairment and body mass index of 18–30 kg/$m^2$. Excluded patients had short-form Geriatric Depression Scale score ≥5, and history of urinary retention or current medications to treat overactive bladder |
| Wesnes [54] | Randomised, double-blinded, triple-crossover trial; Commercial trial centre | UK | 12 | 69.1 | 50 | Patients with aged ≥65 years, willing and able to complete study test battery, had body mass index 18.0–30.0 kg/$m^2$, 60–100 kg for males, 55–90 kg for females and a total score of ≥27 in the MMSE at first visit |
| Whalley [55] | Cohort study; Community | UK | 281 | 77.1 | 57.6 | Patients who took part in 1932 Scottish Mental Survey and not known to be in treatment for a major illness, had major sensory impairment, were not recently bereaved and born in 1921 |
| Wilson [56] | Cross-sectional study for RCT data; Community | Australia | 602 | 85.7 | 29.1 | Patients were residents of residential aged care facilities with aged ≥70 years and likely to survive for the next 12 months |
| Wilson [11] | Cross-sectional study for RCT data; Community | Australia | 602 | 85.7 | 29.1 | Patients were residents of residential aged care facilities with aged ≥70 years and likely to survive for the next 12 months |
| Yeh [57] | Case–control study; Community | Taiwan | 71 | 83.4 | 100 | Patients had diagnosis of dementia as per the DSM-IV in a veteran (residential) home. Residents with primary diagnosis of major psychotic disorder, mental retardation, recent aggravation of behaviour and psychological symptoms of dementia, recent deterioration in health status or short-life expectancy were excluded |

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; EDSS, Extended Disability Status Scale; ICU, intensity care unit; IQ, intelligence quotients; kg, kilograms; kg/$m^2$, kilograms per square meter; MMSE, Mini-Mental State Examination; NS, not stated; PANSS, Positive and Negative Syndrome Scale; RCT, Randomised Controlled Trial; UK, United Kingdom; USA, United States of America; yrs, years.

**Table 3.** Executive summary of the results of the included studies by outcome of interest

| Study | Result interpretation |
|---|---|
| Outcome 1: cognitive function | |
| Ancelin [18] | Use of anti-cholinergic drugs is associated with mild cognitive impairment but not increased risk of dementia |
| Boustani [19] | Use of anti-cholinergic drugs was associated with a higher risk of incident cognitive impairment |
| Cai [6] | Use of at least three medications with ACB score of 1 for 90 days, or use of at least one medication with ACB score of 3 for 60 days, increases the risk of mild cognitive impairment |
| Campbell [21] | Use of anti-cholinergic drugs is associated with a significant increase in incident cognitive impairment |
| Cancelli [22] | Use of anti-cholinergic drugs is associated with a significant increase in cognitive impairment |
| Cao [23] | Use of anti-cholinergic drugs is associated with a significant risk of cognitive impairment |
| Carriere [24] | Use of anti-cholinergic drugs increases risk for cognitive impairment |
| Cruce [25] | Use of anti-cholinergic drugs for bladder symptoms in patients with MS has a negative impact on cognitive function |
| Drag [27] | Use of anti-cholinergic drugs is not associated with lower performance on cognitive measures |
| Fox [5] | Use of anti-cholinergic drugs is associated with increased risk of cognitive impairment |
| Fox [28] | Use of anti-cholinergic drugs in patients with Alzheimer's disease is not associated with deterioration in cognition |
| Geller [30] | Trospium chloride use is associated with significant difference in cognition |
| Gnijidic [31] | Use of anti-cholinergic drugs is not associated with increased risk of limitations in cognitive performance, mild cognitive impairment or dementia |
| Han [33] | Use of anti-cholinergic medications is associated with reduction in cognitive function |
| Harvey [34] | Use of atypical antipsychotics is not associated with significant risk of cognitive impairment |
| Kay [36] | Use of darifenacin is not associated with cognitive impairment but oxybutynin leads to cognitive impairment |
| Kersten [37] | Reduction of anti-cholinergic medications has no significant effects on cognitive function improvement |
| Kersten [38] | Increasing ADS scores is not associated with decrease in cognitive function |
| Kolanowski [39] | Use of anti-cholinergic medication is not associated with cognitive impairment |
| Koyama [40] | Higher anti-cholinergic load was significantly associated with poorer cognitive function at 10-year follow-up |
| Lampela [42] | Use of anti-cholinergic medications is associated with cognitive impairment |
| Lipton [43] | Use of darifenacin is not associated with significant difference in cognitive function |
| Low [58] | Use of anti-cholinergic medication is associated with lower level of complex attention in the young-old but not with greater cognitive decline |
| Merchant [46] | Use of anti-cholinergic drugs is associated with increased risk of cognitive impairment |
| Pasina [48] | Cumulative effects of anticholinergic drugs as assessed by ACB scale and ARS is associated with cognitive impairment |
| Shah [49] | There is a gradation in annual rate of cognitive function decline amongst incident users compared with never users. However, there was no significant difference between prevalent users and never users |
| Shakakibara [50] | Imidafenacin has no effect on cognitive function |
| Uusvaara [52] | DAPs may be associated with specific impairments in cognitive functioning. |
| Wagg [53] | Use of solifenacin is not associated with increased risk of cognitive impairment but significant differences are observed for oxybutynin |
| Wesnes [54] | Use of solifenacin is not associated with increased risk of cognitive impairment but significant differences are observed for oxybutynin |
| Whalley [55] | Use of anti-cholinergic drugs is associated with increased risk of cognitive impairment but not dementia |
| Wilson [56] | Use of anti-cholinergic drugs is not associated with increased risk of cognitive impairment |
| Yeh [57] | Reduction in anti-cholinergic drugs did not show in cognitive function improvement |
| Outcome 2: delirium | |
| Caeiro [20] | Use of anti-cholinergic drugs is associated with increased risk of delirium |
| Campbell [7] | Use of anti-cholinergic drugs is not associated with a significant difference in delirium |
| Gaudreau [29] | Use of anti-cholinergic drugs is not associated with significant difference in delirium |
| Luukkanen [44] | Use of anti-cholinergic drugs is not associated with a risk of development of delirium |
| Pandharipande [47] | Use of anti-cholinergic drugs is not associated with the development of delirium |
| Outcome 3: physical function | |
| Gnjidic [32] | No significant difference in chair stands, walking speed, narrow walk, balance and instrument activities of daily living |
| Han [33] | Use of anti-cholinergic drugs is associated with poorer performance on the instrument activities of daily living |
| Hilmer [35] | Use of anti-cholinergic drugs is associated with poorer performance on the instrument activities of daily living |
| Kersten [38] | Higher ADS scores are associated with higher ADL scores with no significant differences |
| Lampela [42] | Higher anti-cholinergic scores are associated with reduced ADL and IADL scores |
| Pasina [40] | Cumulative effects of anti-cholinergic drugs assessed by ACB and ARS scale is associated with functional impairment |

*Continued*

Table 3. Continued

| Study | Result interpretation |
|---|---|
| Wilson [56] | Use of anti-cholinergic drugs is associated with greater use of mobility aids |
| Yeh [57] | Reduction in anti-cholinergic burden did not show benefits in functional outcome improvements |
| Outcome 4: mortality | |
| Agar [17] | Use of drugs with anti-cholinergic properties is not associated with any difference in mortality |
| De Luise [26] | Tiotropium use is associated with lower mortality |
| Fox [5] | There was a dose–response effect of ACB score associated with mortality at 2 years |
| Kumpula [41] | Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality |
| Luukkanen [44] | Use of anti-cholinergic drugs is not associated with an increased risk of mortality |
| Mangoni [45] | Use of anti-cholinergic drug is associated with increased mortality |
| Uusvaara [51] | Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality |
| Wilson [11] | Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality |
| Wilson [56] | Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality |

ABS, anti-cholinergic burden score; ACB, anti-cholinergic burden; ADL, activities of daily living; ADS, anti-cholinergic drug scale; ARS, anti-cholinergic risk scale; IADL, instrumental activities of daily living; MS, multiple sclerosis.

## Discussion

This is the first systematic review to assess the effects of medications with anti-cholinergic properties on delirium and physical function, and an important update on cognitive function and mortality. The findings indicate that medicines with anti-cholinergic properties have a negative effect on cognitive function. The results also indicated no significant association between anti-cholinergic load and either mortality or delirium. Single- or limited-drug studies in the past have supported the relationship between these medicines and delirium. Using anti-cholinergic drug scales to identify all medications with anti-cholinergic properties did not appear to confirm such an association. Finally, this review identified that the use of medications with anti-cholinergic properties may be associated with a deterioration in physical function.

The negative effect of increased anti-cholinergic load on adverse cognitive outcomes revealed the strongest association throughout the evidence-base. This is in keeping with previous literature reviews which have examined the effect of anti-cholinergic burden on cognition [3, 4]. A previous review [3] noted that the effect of anti-cholinergic drugs on cognition is not always due to one anti-cholinergic drug alone, but instead an accumulation of a number of drugs with anti-cholinergic properties is an important consideration. Therefore, in this systematic review, it was decided to only include studies which quantified this load; either through dosage of the drug used in an RCT, or through using scales to quantify ACB.

Of those studies which did not report a negative effect of increased anti-cholinergic load on cognitive function, three of the five studies had relatively shorter follow-up periods (<2 years) or were cross-sectional studies. As studies included in the review had a highly variable follow-up period, ranging from a few weeks to 12 years, it was difficult to interpret whether the studies with short follow-ups would have progressed to report a significant association with cognitive decline should they have included a longer follow-up period.

There is little support that anti-cholinergic medications increase the risk of mild cognitive impairment, which then presents a risk of developing dementia. In addition, there is little, if any, evidence for a non-reversible impact of anti-cholinergics on cognition. Consequently, the findings of this review on cognition should be interpreted with caution until the evidence-base develops in this area.

In contrast to the continued evidence supporting anti-cholinergic burden and its effect on cognitive function, its effect on developing the more acute form of cognitive impairment, delirium, was less coherent. Once again these studies were heterogeneous in their quantification of anti-cholinergic load and reporting the outcome. Not all studies used the Confusion Assessment Method which is thought to be the most accurate and currently recommended diagnostic tool for delirium by the National Institute of Clinical Excellence guidance in the UK. This review did not find an association between anti-cholinergic load with delirium as reported in previous reviews [14], although this review was based on a larger, more contemporary literature dataset. One reason for this may be the improvement in characterising delirium not used in more historic studies. In addition what may have been seen in previous studies is the miscoding of delirium for cognitive impairment, therefore the diagnosis of delirium may not have been made, rather the term 'dementia' used to categorise all participants with cognitive impairment.

The majority of studies which reported the effect of anti-cholinergic medications on physical function reported a significant inverse relationship; the higher the anti-cholinergic burden the lower the physical functioning [33, 35, 56]. Yet again there were different methods of quantifying anti-cholinergic load used and different methods of measuring

physical function. Avoiding anti-cholinergic medications may therefore preserve and maximise function and prevent acute adverse events such as falls.

The effect of anti-cholinergic burden on mortality present inconclusive findings. The majority of studies reported no statistical association between these variables. However, in a large prospective cohort study undertaken by Fox *et al.* [5], an adjusted statistically significant negative effect of increased anti-cholinergic load with increased mortality was reported [59]. Whilst this difference in results may be due to the heterogenic nature of studies available, further research should be conducted in this area. Furthermore, these mortality figures should be viewed with caution given that the follow-up periods for these studies were insufficient, ranging from 8.9 weeks [17] to 3.3 years [51].

This paper is the first systematic review to examine the effect of anti-cholinergic medication load (excluding those measured by serum anti-cholinergic alone) on cognitive function, physical function, delirium and mortality over a large time frame spanning decades of research from published and unpublished sources. However, the included articles contained a number of limitations. First, due to the data available, the analysis focused on estimating the presence or absence of significant associations in drug response rather than estimating effect size which was not possible in this instance. Secondly, the MMSE was the major measure of cognitive change. This could be argued as an inappropriate tool for this means in its sensitivity and scope, whilst mortality, given the multi-factorial cause of this end-point, may have been insensitive to evaluation specifically against anti-cholinergeric agents. The approach in accounting for covariates, both confounders and effect modifiers, varied considerably across the included studies. There was variability in age and seriousness of medical morbidity for which the various drugs were prescribed; these factors are critical. Studies did not consider sub-clinical disease, which may have confounded any associations, but medication use was associated with health status, so despite adjusting for many health-related factors, the possibility of residual confounders between health status and outcome could not be excluded. Indication bias may have limited this review in those participants with, for example, cognitive impairment may have been more likely to be exposed to anti-cholinergic medications because of the presence of cognitive impairment. The ratings of anti-cholinergic exposure varied considerably across the included studies. In some studies, this was presented on a standard scale, in others as a dichotomous (yes/no) scale. Additionally, the reliability of these ratings across studies was difficult to establish. Managing these confounders should be considered when designing future studies in this area. Finally, the principle limitation to this review is the variability in study designs. This may be a contributing factor to the different effects being reported on physical function, delirium and mortality. However, by managing these studies separately during the analysis, and considering the appraisal of study quality, the distinction between higher and lower quality evidence was made during the interpretation of findings.

## Conclusions

This systematic review provides strong evidence for the adverse effect of increased anti-cholinergic load on cognition. The results also show consistent evidence that medicines with anti-cholinergic properties may be associated with reduced physical function. The effect on delirium and mortality appear less well-defined across the literature. Further evidence is required to truly establish their association with increasing anti-cholinergic burden.

## Key points

- Medicines with anti-cholinergic properties have a significant adverse effect on cognitive and physical function.
- Medicines with anti-cholinergic properties appear to have limited effect on delirium or mortality outcomes.
- The assessment of medicines with anti-cholinergic properties should be further evaluated with people at risk of poor outcome.

## Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

## Ethical considerations

No ethical approvals were required for this study design.

## Conflicts of interest

None declared.

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