Age and Ageing

Title Page

Title: 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Design: Electronic published and unpublished literature/trial registries were systematically reviewed.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

Declarations of Interest: None to declare.

Ethical Considerations: No ethical approvals were required for this study design.

Conflicts of Interest: The authors have no conflicts of interests to declare in relation to this paper.

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% to 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 anticholinergic 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 two years [5], a two-fold increase in cognitive impairment with as little as 60 to 90 days of use [6], and approximately 50 to 80% increase in the risk of incident cognitive impairment over six years [7].

A decline in cognitive function and the diagnosis of mild cognitive impairment is associated with a progression to dementia within five 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 to 2013) and Ovid MEDLINE (2002 to 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.

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. Physical function was defined as the ability to perform various activities which require physical capability, ranging from self-care (basic activities of daily living (ADL)) to more vigorous tasks which require increasing degrees of mobility, strength or endurance such as as walking, ascending stairs, carrying shopping or moving from a chair (BRUCE et al, 2009).

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 1st 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 (NB, WYC) 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 (CSK).

The full text for all potentially eligible studies were gathered and independently re-reviewed by two reviewers (NB, WYC) against the eligibility criteria to determine final eligibility. Any disagreements were resolved through discussion and adjudicated by three senior reviewers (CSK, CF and IM).

Data Extraction

Data extraction was independently conducted by five reviewers (NB, WYC, MG, IK, CSK) and verified by two senior reviewers (IM, CF). Data extraction was 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 (NB, WYC). In the event of disagreement on critical appraisal score, agreement was met through discussion, adjudicated by a third reviewer (CSK).

Data Analysis

The data extraction table was 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 7,078 identified citations, 133 were deemed potentially eligible. From these 46 studies met the eligibility criteria and were included in the final review.

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 to 87.5 years were included. This consisted of 25,225 males and 32,543 females; cohort gender proportions were not stated in two studies [17,18]. Thirty-three studies were conducted in community dwellings and 14 studies in hospital settings, one study was conducted across both settings [20]. Participants in the hospital settings were admitted for a variety of medical reasons including cancer [21], general frailty/long-term care [22] and acute bladder symptoms [23,24]. **Supplementary Table 1** illustrates 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 Table 2** to **4**. The findings indicate that the evidence-base was largely moderate in methodological quality.

Supplementary Table 3 presents 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 Table 5**.

Anti-cholinergic effect on cognitive function

Thirty-three studies reported the impact of medications with anti-cholinergic properties on cognitive function [5-7,17-19,23-32,37,38,41-45,48,49-52,54-58]. 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 [5-7,17-19,23-28,37,38,42-45,48,51,52,54,57].

Ten studies reported no significant association between medicines with anti-cholinergic properties and cognitive function [29-32,44,49,50,55,56,58]. A number of differences in study design and variable definitions may have accounted for the study results, such as differences in medications evaluated (single vs. 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 [20,21,33,36,47]. Only one study demonstrated a significant association between drugs with anti-cholinergic properties and delirium [47]. Delirium, as assessed by the Delirium Rating Scale (DRS), was more likely in people prescribed medicines with anti-cholinergic properties prior to a stroke (OR: 11.3; 95% CI: 1.19 to 108.2) or during hospitalisation (OR: 5.82; 95% CI: 1.96 to 17.2), compared to those not prescribed anti-cholinergics [47].

Luukkanen et al [20], Pandharipande et al [36], Campbell et al [33] and Gaudeau et al [21] 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 [27,34,39,41,50-52,58]. Of five studies reported that anti-cholinergic drugs were associated with reduced physical function [27,34,39,51,52].

Three studies reported no association between ACB and physical function [41,50,58]. Wilson et al [41] 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 [5,11,20,22,35,40,41,46,53]. Six studies reported that the use of drugs with anti-cholinergic properties was not statistically associated with increased mortality [11,20,22,40,41,46].

Three studies reported contrary findings [5,35,54]. 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%: 1.20 to 1.32) [5]. De Luise et al [35] reported a risk ratio of tiotropium use and total mortality of 0.77 (95% CI: 0.56 to 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**).

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. Lastly, 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 a 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 (less than two 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. This is considered as the most accurate diagnostic tool for delirium, advocated by the UK's National Institute of Clinical Excellence (NICE). No association between anti-cholinergic load and delirium was identified within the review, in agreement with previous reviews [14]. However, the majority of studies which reported the effect of anti-cholinergic medications on physical function reported a significant inverse relationship i.e. the higher the anti-cholinergic burden, the lower the physical functioning [27,34,41]. 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 was inconclusive. The majority of studies reported no statistical association between these variables. However, in a large prospective cohort study, Fox et al [5] reported a significant negative effect of increased anti-cholinergic load with increased mortality. Whilst this difference may be attributed to heterogeneous included studies, 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 [40] to 3.3 years [46].

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 from both published and unpublished sources. However the included articles contained a number of limitations. Firstly, 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 principle measure of cognitive change. This may be considered an inappropriate tool for this means in its sensitivity and scope given the multi-factorial causes of cognitive impairment, may have been insensitive to evaluate the effects of anti-cholinergeric agents.

A third limitation in this review relates to 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. Studies did not consider sub-clinical disease, which may have confounded any associations. Therefore despite adjusting for many health-related factors, the possibility of residual confounders between health status and outcome could not be excluded. Another limitation can been seen with the rating 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. 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 effects of the incidence of delirium and mortality appear less well-defined across the literature. Further evidence is required to truly establish their association with increasing anti-cholinergic burden.

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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"

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

Study	Design; Setting	Country	Number of participants	Mean age (yrs)	% Male	Participant Characteristics
Agar [40]	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 [17]	Cohort study; Community	France	372	66.2	NS	Patients with age >60 years and without dementia at recruitment.
Boustani [25]	Cohort study; Community	USA	1558	77.6	33.6	Patients with age ≥65 years and were African-American.
Caeiro [47]	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 to 2007.
Campbell [33]	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 [48]	Cohort study; Community	Italy	750	75	38.7	Patients with age ≥ 65 years who were living independently or at an institution
Cao [26]	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 2 or more functional domain which included 1) mobility and exercise tolerance 2) upper extremity function 3) complex activity heavily involving cognition and sensory input 4) basic self care.
Carriere [45]	Cohort study; Community	France	6912	73.7	40.3	Patients were recruited from electoral roll and were community-dwelling, aged ≥65 years and from 3 French cities.
Cruce [24]	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 [35]	Cohort study; Hospital	USA	10,603	NS	47.8	Patients admitted between January 1977 to December 2003.
Drag [30]	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 [44]	Cohort study; Community	UK	244	81	28.6	Patients included standardised diagnosis of dementia, fulfillment 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 hours a week.
Gaudreau [21]	Cohort study; Hospital	Canada	261	59.6	56	Patients included if they had histological diagnosis of cancer in consecutive admissions to the unit.
Geller [23]	Cohort study; Hospital	USA	35	70.4	0	Patients were post-menopausal women, age ≥55 years, seeking treatment for overactive bladder and opting for anticholinergic therapy
Gnijidic [37]	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 [39]	Cross-sectional study; Community	Australia	1705	76.9	100	Patients included were male, aged ≥70 years and resident of South Wales
Han [27]	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.
Harvey [31]	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 less than 4 weeks.
Hilmer [34]	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 [29]	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 anticholinergic use was contraindicated or they suffered from dementia, depression or had MMSE ≤27.
Kersten [49]	Randomised Controlled Trial; Community	Norway	87	85	61	Patients were long-term nursing home residents from 22 nursing homes. Have a total anticholinergic drug scale (ADS) of greater than or equal 3. Patients were not blind, deaf, aphasic, delirious or with severe dementia (Clinical Dementia Rating scale of 3)
Kersten [50]	Randomised Controlled Trial; Community	Norway	87	85	61	Patients were long-term nursing home residents from 22 nursing homes. Have a total anticholinergic drug scale (ADS) of greater than or equal 3. Patients were not blind, deaf, aphasic, delirious or with severe dementia (Clinical Dementia Rating scale of 3)
Kolanowski [32]	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 Data Set.
Koyama [51]	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 [22]	Cohort study; Hospital	Finland	1004	81.3	25	Patients included were living in 1 of 53 long-term care wards in 7 hospitals in Helsinki. Exclusion due to incomplete medication data and unavailable mortality data.
Lampela [52]	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 [28]	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 [37]	Cohort study; Community	Australia	2058	62.5	51.7	Patients were randomly selected from electoral roll.
Luukkanen [20]	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 [53]	Cohort study; Hospital	Netherlands	71	85	29.6	Patients were ≥65 admitted with hip fractures and scheduled for surgery.
Merchant [18]	Cross-sectional study; Community	Singapore	2804	NS	NS	Patients were enrolled in the Singapore Longitudinal Aging Study, community dwellers and aged ≥55 years.
Pandharipande [36]	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 [54]	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 [56]	Cohort study; Community	USA	896	74.8	30.7	Patients were community-dwelling older clergy without dementia who were partiipating in the Religious Orders Study - a longitudinal epidemiologic study of aging where participants have been assessed annually for a mean of 10 years.
Shakakibara [55]	Cohort study; Community	Japan	62	70	40.3	Patients were consecutive subjects in neurology outpatients. All had diagnosis of overactive bladder. Exclusion criteria were anticholinergic agents within 2 weeks of entry into study, indwelling foley catheters, intermittent catheterisation, post-void residual urine volume >100 mL, high prostate-specific antigen, acute urinary tract infection, closed angle glaucoma, diseases of anti-cholinergic contraindication.
Uusvaara [46]	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 [57]	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 [42]	Randomised, double blind, triple-crossover trial; Commercial trial	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

	centre					overactive bladder.
Wesnes [19]	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 [43]	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 [41]	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 [58]	Case-control study; Community	Taiwan	71	83.4	100	Patients had diagnosis of dementia as per the DSM-IV in a veteran (residental) home. Residents with primary diagnosis of major psychotic disorder, mental retardation, recent aggravation of behaviour and psychological symptoms of dementia, recent deteriation in helth 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.

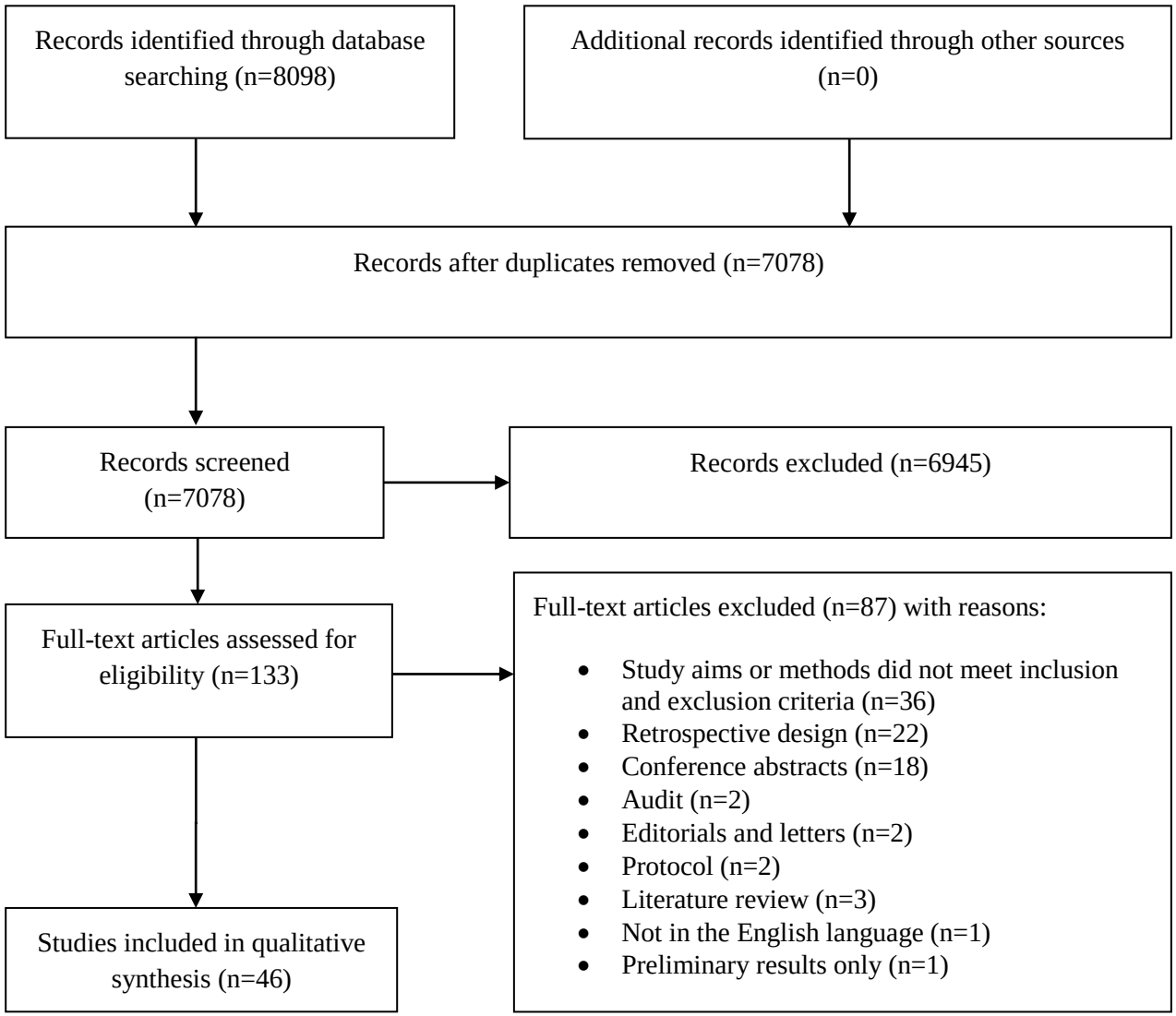
Table 3: Executive summary of the results of the included studies by outcome of interest.

Study	Result Interpretation
Outcome 1: Cognitive Function	
Ancelin [17]	Use of anti-cholinergic drugs is associated with mild cognitive impairment but not increased risk of dementia.
Boustani [25]	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 [33]	Use of anti-cholinergic drugs is associated with a significant increase in incident cognitive impairment.
Cancelli [48]	Use of anti-cholinergic drugs is associated with a significant increase in cognitive impairment.
Cao [26]	Use of anti-cholinergic drugs is associated with a significant risk of cognitive impairment.
Carriere [45]	Use of anti-cholinergic drugs increases risk for cognitive impairment.
Cruce [24]	Use of anti-cholinergic drugs for bladder symptoms in patients with MS has a negative impact on cognitive function.
Drag [30]	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 [44]	Use of anti-cholinergic drugs in patients with Alzheimer's disease is not associated with deterioration in cognition.
Geller [23]	Trospium chloride use is associated with significant difference in cognition.
Gnijidic [37]	Use of anti-cholinergic drugs is not associated with increased risk of limitations in cognitive performance, mild cognitive impairment or dementia.
Han [27]	Use of anti-cholinergic medications is associated with reduction in cognitive function.
Harvey [31]	Use of atypical antipsychotics is not associated with significant risk of cognitive impairment.
Kay [29]	Use of darifenacin is not associated with cognitive impairment but oxybutynin leads to cognitive impairment.
Kersten [49]	Reduction of anti-cholinergic medications has no significant effects on cognitive function improvement.
Kersten [50]	Increasing ADS scores is not associated with decrease in cognitive function.
Kolanowski [32]	Use of anti-cholinergic medication is not associated with cognitive impairment.
Koyama [51]	Higher anticholinergic load was significantly associated with poorer cognitive function at 10-year follow-up.
Lampela [52]	Use of anticholinergic medications is associated with cognitive impairment.
Lipton [28]	Use of darifenacin is not associated with significant difference in cognitive function.
Low [38]	Use of anti-cholinergic medication is associated with lower level of complex attention in the young-old but not with greater cognitive decline.
Merchant [18]	Use of anti-cholinergic drugs is associated with increased risk of cognitive impairment.
Pasina [54]	Cumulative effects of anticholinergic drugs as assessed by ACB scale and ARS is associated with cognitive impairment.
Shah [56]	There is a gradation in annual rate of cognitive function decline amongst incident users compared to never users. However there was no significant difference between prevalent users and never users.
Shakakibara [55]	Imidafenacin has no effect on cognitive function.
Uusvaara [57]	DAPs may be associated with specific impairments in cognitive functioning.
Wagg [42]	Use of solifenacin is not associated with increased risk of cognitive impairment but significant differences are observed for oxybutynin.
Wesnes [19]	Use of solifenacin is not associated with increased risk of cognitive impairment but significant differences are observed for oxybutynin.
Whalley [43]	Use of anticholinergic drugs is associated with increased risk of cognitive impairment but not dementia.
Wilson [41]	Use of anti-cholinergic drugs is not associated with increased risk of cognitive impairment.
Yeh [58]	Reduction in anticholinergic drugs did not show in cognitive function improvement.
Outcome 2: Delirium	

Caeiro [47]	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 [21]	Use of anti-cholinergic drugs is not associated with significant difference in delirium.
Luukkanen [20]	Use of anti-cholinergic drugs is not associated with a risk of development of delirium.
Pandharipande [36]	Use of anti-cholinergic drugs is not associated with the development of delirium.
Outcome 3: Physical Function	
Gnjidic [39]	No significant difference in chair stands, walking speed, narrow walk, balance and instrument activities of daily living.
Han [27]	Use of anti-cholinergic drugs is associated with poorer performance on the instrument activities of daily living.
Hilmer [34]	Use of anti-cholinergic drugs is associated with poorer performance on the instrument activities of daily living.
Kersten [50]	Higher ADS scores are associated with higher ADL scores with no significant differences.
Lampela [52]	Higher anticholinergic scores are associated with reduced ADL and IADL scores.
Pasina [51]	Cumulative effects of anticholinergic drugs assessed by ACB and ARS scale is associated with functional impairment.
Wilson [41]	Use of anti-cholinergic drugs is associated with greater use of mobility aids.
Yeh [58]	Reduction in anticholinergic burden did not show benefits in functional outcome improvements.
Outcome 4: Mortality	
Agar [40]	Use of drugs with anti-cholinergic properties is not associated with any difference in mortality.
De Luise [35]	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 [22]	Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality.
Luukkanen [20]	Use of anti-cholinergic drugs is not associated with an increased risk of mortality.
Mangoni [53]	Use of anti-cholinergic drug is associated with increased mortality.
Uusvaara [46]	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 [41]	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

Figure 1: PRISMA flow diagram of search strategy results.



Supplementary Tables 1-5

Supplementary Table 1: The assessment of anti-cholinergic medications and their drug burden for include studies.

Study	Duration of study.	Anticholinergic rating
Agar [40]	Mean survival time for the 112 patients was 8.9 weeks	Clinician Rated Anti-cholinergic Scale. Each medicine rated from 0 (no effect) to 3 (marked effect). Total score was sum individual medicine received. Total burden was stratified by 0-2, 3-5 and 6-9.
Ancelin [17]	8 years	Drugs were categorised having anti-cholinergic burden of 0-3: 0 = no anti-cholinergic drugs 1 = no likely effect of anti-cholinergic drugs 2 = low effect of anti-cholinergic drugs 3=high effect of anti-cholinergic drugs
Boustani [25]	5 years	Use of any drug with anti-cholinergic activity. Definition not specified.
Caeiro [47]	NS	Anticholinergic drug use (i) before stroke, (ii) during hospitalization but before the assessment were recorded.
Cai [6]	12 months	Medication exposure defined by ACB scale. Exposure was categorized into duration of use of multiple medications with low anticholinergic burden or single agent use using cutoff ACB scores of less than or greater than 3.
Campbell [7]	Duration of hospital admission	Drugs were classified into ACB scale. This was previously developed from systematic review of literature to identify drugs with documented anticholinergic activity. 0=no effect, 1=mild effect, 2=moderate effect, 3=severe effect.
Campbell [33]	6 years	Anti-cholinergic Cognitive Burden scale (ACB) used to identify drugs with possible or definitive anti-cholinergic properties. Drugs with no known clinically relevant negative cognitive effects score = 1; score = 2 or 3 for clinically definite anti-cholinergic.
Cancelli [48]	NS	Drug burden = patients drug were classed as level 1= no likely Anti-cholinergic (ACH) effect, level 2= moderate, level 3= high ACH effect. Then level 2 or 3 = considered ACH users, level 1 = non-ACH users.
Cao [26]	2 years	Drug burden was quantified using an index of drug-mediated modification of specific pharmacological effects. Drugs were identified in 2004 edition of Mosby's Drug Consult as having anti-cholinergic effect. Hyperbolic dose-response model to normalise pharamcodynamic contribution of a specific drug was used. Drugs can be calculated with an equation.
Carriere [45]	4 years	Inventory of all drugs taken. Reported medicines coded according to World Health Organisation's Anatomical Therapeutic Chemical Classification. Those drugs with anti-cholinergic properties were established from the Theriaque, the Banque de Deonnees Automatisee sur les Medicaments and VIDAL classifications
Cruce [24]	0	Oxybutynin ACB score = 3 Tolterodine ACB score = 3
De Luise [35]	NS	Anatomical therapeutic chemical (ATC) classification system to identify prescriptions for long-acting anti-cholinergic.
Drag [30]	0	All drugs rated as 0=no known anti-cholinergic properties, 1=potentially anti-cholinergic as evidenced by receptor binding studies, 2=anti-cholinergic adverse effect sometimes noted, usually at excessive doses, 3=markedly anti-cholinergic. Burden score calculated by summing ratings.

Fox [5]	2 years	ACB Scale. This was previously developed from systematic review of literature to identify drugs with documented anti-cholinergic activity. 0=no effect, 1=mild effect, 2=moderate effect, 3=severe effect.
Fox [44]	1.5 years	ACB Scale. This was previously developed from systematic review of literature to identify drugs with documented anti-cholinergic activity. 0=no effect, 1=mild effect, 2=moderate effect, 3=severe effect.
Gaudreau [21]	4 weeks	23 individual agents with primary or secondary antimuscarinic properties identified. Chosen based on available literature.
Geller [23]	12 weeks	Trospium Chloride ACB Score 3
Gnijidic [37]	NS	Drug burden index defined by sum of burden of drugs with sedative effects or anticholinergic effects (Drug dose was used in the calculation of drug load where drug burden index = daily dose / (daily dose + minimum recommended dose).
Gnjidic [39]	NS	Drug burden index defined by sum of burden of drugs with sedative effects or anticholinergic effects (Drug dose was used in the calculation of drug load where drug burden index = daily dose / (daily dose + minimum recommended dose).
Han [27]	2 years	Clinician rated anti-cholinergic score applied to list of medications used in the cohort by two authors of the paper. 0 (no effect) to 3 (strong effect). Drugs with no anti-cholinergic effect as a whole were assigned a 0 score.
Harvey [31]	5 years	Drug burden index defined by sum of burden of drugs with sedative effects or anti-cholinergic effects (Drug dose was used in the calculation of drug load where drug burden index = daily dose / (daily dose + minimum recommended dose).
Hilmer [34]	8 weeks	Olanzapine ACB score = 3, Risperidone ACB score = 1
Kay [29]	3 weeks of treatment for each arm. Increasing dose strength per week.	Oxybutynin ACB score = 3 Darifenacin ACB score = 3 Placebo ACB score = 0
Kersten-1 [50]	11 months	Authors reviewed drug regimen and use anticholinergic drug scale (ADS) to assess burden. 0 = no known anticholinergic activity (AA), 3 = markedly anticholinergic activity.
Kersten-2 [51]	11 months	Authors reviewed drug regimen and use anticholinergic drug scale (ADS) to assess burden. 0 = no known anticholinergic activity (AA), 3 = markedly anticholinergic activity.
Kolanowski [32]	0	Drugs were classified into ACB Scale. This was previously developed from systematic review of literature to identify drugs with documented anti-cholinergic activity. 0=no effect, 1=mild effect, 2=moderate effect, 3=severe effect.
Koyama [52]	10 years	Authors assigned a computed sum of ACB score (0 = no anticholinergic activity; 1 = possible anticholinergic activity; 2 or 3 = clinically relevant anticholinergic activity) for all potentially inappropriate medications which met the 2003 Beers Criteria.
Kumpula [22]	1 year	All drugs rated as 0=no known anti-cholinergic properties, 1=potentially anti-cholinergic as evidenced by receptor binding studies, 2=anti-cholinergic adverse effect sometimes noted, usually at excessive doses, 3=markedly ACB score calculated by summing ratings.

Lampela [53]	NS	Authors reviewed drug regimens and classified them into both ARS (1 = drugs with moderate anticholinergic potential, 2=strong potential, 3= very strong potential) and ADS (drugs ranked from 0 – no known anticholinergic activity to 3 – significant anticholinergic activity).
Lipton [28]	2 weeks	Darifenacin ACB score 3
Low [37]	4 years	Anti-cholinergic drug scale (ADS): 0 = no known anti-cholinergic properties 1 = potential anti-cholinergic activity to 3 = marked anti-cholinergic activity.
Luukkanen [20]	2 years	Drugs with documented anti-cholinergic properties from the medical literature, and used daily were recorded. Subjects receiving 2 or more drugs with anti-cholinergic properties were analysed separately to those with less than 2.
Mangoni [54]	1 year	Authors reviewed drug regimen and assessed ADSS for each patient including ARS (1 = drugs with moderate anticholinergic potential, 2=strong potential, 3= very strong potential); ADS (drugs ranked from 0 – no known anticholinergic activity to 3 – significant anticholinergic activity); ACB (0=no effect, 1=mild effect, 2=moderate effect, 3=severe effect.) and DBI (Drug burden index calculated = sum of [dose of the drug in question taken in 24 hours/(dose of the drug taken in 24 hours + the 24 hour dose needed to achieve 50% of the maximum effect)], the sum after considering all the medication the patient is on was categorised as none = 0, low = <1, high >1)
Merchant [18]	0	The use of drugs known to possess moderate or strong anti-cholinergic activity was identified from published lists of anti-cholinergic drugs commonly prescribed.
Pandharipande [36]	24 hours	Prescription of anti-cholinergic medications (i.e. atropine, diphenhydramine, bupropion, hydrochloride, metoclopramide, prochloperazine, promethazine) to 32%.
Pasina [55]	3 months	Drug-related anticholinergic burden was calculated using the sum of points for each anticholinergic medication dispensed during hospital admission according to the anticholinergic burden (ACB) scale (0= no drugs used, 1 = drugs used but with no likely effect, 2 = drugs used with low effect, 3 = drugs used with high effect) and anticholinergic risk scale (ARS) (1 = drugs with moderate anticholinergic potential, 2=strong potential, 3= very strong potential).
Shah [57]	10 years.	Drugs were classified into ACB Scale. This was previously developed from systematic review of literature to identify drugs with documented anti-cholinergic activity. 0=no effect, 1=mild effect, 2=moderate effect, 3=severe effect.
Shakakibara [56]	3 months	Not yet given anticholinergic rating.
Uusvaara [46]	3.3 years	Drugs used on regular daily basis considered. Drugs with anti-cholinergic properties identified according to previous scientific literature. Classified into those using ≥1 drug with anti-cholinergic property (users) and those not using anti-cholinergics (non-users).
Uusvaara [58]	0 years	Drugs used on regular daily basis considered. Drugs with anti-cholinergic properties identified according to previous scientific literature. Classified into those using ≥1 drug with anti-cholinergic property (users) and those not using anti-

		cholinergics (non-users).
Wagg [42]	21 days of treatment and 21 days of washout and crossover so patients receive all 3 treatments. Assessment was performed at end of each treatment period.	Solifenacin ACB score=3. Oxybutynin ACB score=3.
Wesnes [19]	31 days. 1 day of treatment and 14 days washout period and crossover so all patients receive all 3 treatments.	Solifenacin ACB score=3. Oxybutynin ACB score=3
Whalley [43]	12 years	Authors reviewed patient self-reported drugs using current literature for anti-cholinergic activity and classified the ACB from 0 to 3. (0= no drugs used, 1 = drugs used but with no likely effect, 2 = drugs used with low effect, 3 = drugs used with high effect)
Wilson [41]	NS	Drug burden index calculated = sum of [dose of the drug in question taken in 24 hours/(dose of the drug taken in 24 hours + the 24 hour dose needed to achieve 50% of the maximum effect)], the sum after considering all the medication the patient is on was categorised as none = 0, low = <1, high >1.
Wilson [11]	1 year	Drug burden index calculated = sum of [dose of the drug in question taken in 24 hours/(dose of the drug taken in 24 hours + the 24 hour dose needed to achieve 50% of the maximum effect)], the sum after considering all the medication the patient is on was categorised as none = 0, low = <1, high >1.
Yeh [59]	12 weeks	Authors used the CR-ACHS (also known as the ADS). Anticholinergic medications were rated from 0 (no effect) to 3 (strong effect)

ACB – Anti-cholinergic burden; Anti-cholinergic activity (ACH); Anti-cholinergic drug scale (ADS), Anti-cholinergic drug scoring system (ADSS), Anticholinergic risk scale (ARS), Clinician-rated Anti-cholinergic Score (CR-ACHS); NS – not stated

Supplementary Table 2: The Newcastle-Ottawa scale risk of bias assessment for non- randomised included studies.

Study	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
Agar [40]	X	X	✓	✓	✓	✓	✓	✓
Ancelin [17]	✓	✓	✓	✓	?	X	✓	X
Boustani [25]	X	X	?	?	X	X	✓	X
Cai [6]	✓	X	✓	X	✓	✓	✓	✓
Campbell [7]	X	X	✓	✓	X	?	✓	✓
Campbell [33]	X	X	✓	✓	X	✓	✓	✓
Cancelli [48]	✓	✓	✓	X	X	✓	?	?
Cao [26]	X	X	?	X	X	✓	✓	X
Carriere [45]	✓	X	✓	?	X	?	✓	✓
Cruce [24]	X	X	✓	?	X	?	✓	X
De Luise [35]	X	X	?	✓	X	?	?	?
Drag [30]	X	X	?	✓	X	✓	✓	✓
Fox [5]	✓	X	✓	?	?	?	?	?
Fox [44]	✓	X	✓	?	X	?	?	?
Gaudreau [21]	X	X	✓	X	X	✓	?	✓
Geller [23]	X	X	X	?	X	?	?	X
Gnijidic [37]	X	X	✓	?	X	?	?	?
Gnjidic [39]	X	X	?	?	X	?	?	?
Han [27]	X	X	✓	X	✓	✓	✓	✓
Hilmer [34]	✓	✓	✓	✓	X	✓	✓	✓
Lampela [52]	✓	✓	✓	✓	✓	✓	?	?
Kersten [50]	✓	✓	✓	✓	X	✓	X	✓
Kolanowski [32]	✓	X	✓	X	X	✓	?	?
Koyama [51]	✓	✓	✓	✓	?	✓	✓	✓
Kumpula [22]	✓	X	X	✓	X	✓	✓	?
Low [38]	✓	X	X	✓	X	✓	✓	?
Luukkanen [20]	✓	X	✓	X	X	✓	✓	✓
Merchant [18]	✓	X	?	?	X	?	?	?
Mangoni [53]	X	✓	✓	✓	✓	✓	✓	✓
Pandharipande [36]	✓	X	✓	?	X	✓	X	X

Pasina [54]	✓	✓	?	✓	✓	✓	✓	X
Shah [56]	✓	✓	✓	✓	✓	✓	✓	✓
Shakakibara [55]	X	✓	✓	X	X	?	✓	✓
Uusvaara [46]	X	X	?	?	X	✓	X	X
Uusvaara [46]	X	X	?	?	X	✓	NA	X
Whalley [43]	✓	X	✓	?	?	✓	✓	X
Wilson [41]	✓	X	✓	✓	X	✓	✓	✓
Wilson [11]	✓	X	✓	✓	X	✓	✓	✓

X = inadequate; ✓ = adequate; ? = unclear; NA = not applicable

Supplementary Table 3: The Newcastle-Ottawa scale risk of bias assessment for included Case-Control study.

Study	Case definition adequate	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Caeiro [47]	✓	✓	✓	?	✓	✓	X
Yeh [58]	X	✓	X	✓	✓	✓	X

X = inadequate; ✓ = adequate; ? = unclear

Supplementary Table 4: The Cochrane Risk of Bias tool results for included RCTs.

Study	Randomisation sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding outcome assessors	Loss to follow up (incomplete data)	Selective reporting
Harvey [31]	X	✓	✓	✓	X	✓
Kay [29]	X	✓	✓	✓	X	✓
Kersten [49]	✓	X	X	X	X	✓
Lipton [28]	X	✓	✓	✓	X	✓
Wagg [42]	?	✓	✓	✓	X	✓
Wesnes [19]	?	?	?	?	?	✓

X = inadequate; ✓ = adequate; ? = unclear

Supplementary Table 5: Comprehensive summary of the results of the included studies by outcome of interest.

Study	Outcome assessed	Results	Interpretation
Outcome 1: Cognitive Function			
Ancelin [17]	Cognitive Function	Cognitive tests in users vs non-users of anticholinergic drugs: Simple reaction time mean (SD) 13.4 (5.9) vs 19.4 (7.0) p= <0.001 Logical reasoning mean 1.26 (1.0) vs 0.8 (0.8) p = 0.35 Attention mean 21.6 (5.6) vs 27.5 (10.2) <0.001 Primary verbal memory mean 5.6 (1.6) vs 4.3 (1.9) p=0.13 Total number of correct name-face association 2.8 (2.0) vs 1.5 (2.5) p=0.12 Narrative Recall mean 24.3 (8.6) vs 16.8 (8.9) p<0.01 Implicit memory mean 2.2 (3.4) vs 1.8 (2.9) p=0.51 Visuospatial span 4.1 (1.9) vs 3.1 (1.3) p<0.01 Visuospatial construction 23.4 (2.4) vs 21.4 (4.4) p=0.01 Naming total correct 9.3 (1.1) vs 8.3 (1.7) p<0.01 Fluency Total 33.5 (11.4) vs 23.2 (11.6) p<0.01	Use of anti-cholinergic drugs is associated with mild cognitive impairment but not increased risk of dementia.
Boustani [25]	Cognitive Function	Use of medication with anticholinergic activity: consistent use of antihistamines increased the risk of incident cognitive impairment (odds ratio 2.42, 95% CI: 1.17-5.04)	Use of anti-cholinergic drugs was associated with a higher risk of incident cognitive impairment.
Cai [6]	Cognitive Function	Use of medications with total ACB score of 3 or higher for at least 60 days increased the risk of screening positive on the Community Screening Instrument for Dementia (OR 2.13; 95% CI: 1.22-3.71); diagnosis of mild cognitive impairment by expert panel diagnosis was higher in those using at least 3 medications with ACB = 1 (OR 2.63, 95% CI 1.22-5.69)	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 [33]	Cognitive Function	Risk of cognitive impairment among patients receiving definite anti-cholinergics OR 1.46 (95% CI: 1.07-1.99) p=0.0181.	Use of anti-cholinergic drugs is associated with a significant increase in incident cognitive impairment.
Cancelli [48]	Cognitive Function	ACH users were more likely to have a MMSE score below the 10th percentile than non-ACH users (20.5% vs 7.5%; OR 3.18 (1.93-5.23, p<0.001)). ACH users were more likely to have Global Deterioration Scale (GDS) score above the 90th percentile (21.2% vs 6.70%; OR 3.75 (2.26-6.22)).	Use of anti-cholinergic drugs is associated with a significant increase in cognitive impairment.
Cao [26]	Cognitive Function	Odds ratio adjusted for identified confounders (full model) of association of increasing burden of anti-cholinergics with: Mini-mental state examination OR 2.4 (95% CI: 1.1-5.1) Activities of daily living OR 3.4 (95% CI: 1.7-6.9) Chair stands OR 4.2 (95% CI: 2.0-8.7) Balance OR 4.9 (95% CI: 2.0-12) Walking speed OR 3.6 (95% CI: 1.6-8.0) Mobility OR 3.2 (95% CI: 1.5-6.9)	Use of anti-cholinergic drugs is associated with a significant risk of cognitive impairment.

		Upper extremity function OR 2.7 (95% CI: 1.3-5.4) Grip OR 2.4 (95% CI: 1.1-5.3)	
Carriere [45]	Cognitive Function	Women adjusted OR: Difference from baseline in Isaac Set Test total ≤-6 OR 1.47 (95% CI: 1.16-1.86, p=0.002) Difference in Benton Visual Retention Test ≤2 OR=1.13 (95% CI: 0.89 to 1.43, p=0.33) Difference in Trail Making Test A ≥16 OR 1.05 (95% CI: 0.78-1.42) Trail Making Test B ≥35 OR 0.98 (95% CI: 0.73-1.31) Mini-mental state examination ≤-2 OR 1.26 (95% CI: 1.00-1.60, p=0.05). Men adjusted OR: Difference in Isaac Set Test total ≤-6 OR 1.03 (95% CI: 0.67-1.59, p=0.89) Difference in Benton Visual Retention Test ≤2 OR 1.70 (95% CI: 1.13-2.56, p=0.01) Difference in Trail Making Test A ≥16 OR 0.84 (95% CI: 0.48-1.46) Trail Making Test B ≥35 OR 1.61 (95% CI: 0.98-2.64) Mini-mental state examination ≤-2 OR 1.39 (95% CI: 0.92-2.09, p=0.12).	Use of anti-cholinergic drugs increases risk for cognitive impairment.
Cruce [24]	Cognitive Function	Symbol digital modality test (SDMT) mean in MS patients taking anti-cholinergic drugs (ACD) = 36.55 vs MS patients not taking ACD = 49.05 p<0.0001. Selective Reminding Test-long-term storage (SRT-LTS) mean in MS patients taking ACD = 37.43 vs. MS patients not taking ACD = 45.48 p<0.0019. Selective Reminding Test-consistent long-term retrieval mean in MS patients taking anticholinergic drugs (ACD) = 26.43 vs. MS patients not taking ACD = 37.17 p<0.0002. Selective Reminding Test-delayed recall mean in MS patients taking anticholinergic drugs (ACD) = 7.81 vs. MS patients not taking ACD = 9.65 p<0.0001.	Use of anti-cholinergic drugs for bladder symptoms in patients with MS has a negative impact on cognitive function.
Drag [30]	Cognitive Function	Correlations between anti-cholinergic drug scale burden scores and cognitive scores after controlling for premorbid IQ and geriatric depression scale score: MMSE 0.01 Frontal Assessment Battery -0.003 Judgement 0.10 Hopkins Verbal Learning Test-Revised immediate -0.02 Hopkins Verbal Learning Test-Revised delayed 0.03.	Use of anti-cholinergic drugs is not associated with lower performance on cognitive measures.
Fox [5]	Cognitive Function	Odds ratio of changes in MMSE scores compared to people with ACB score of 0 (reference ACB of 0): ACB of 1 OR 0.03 (95% CI: -0.11 – 0.17) ACB of 2 OR 0.01 (95% CI: -0.20 – 0.21) ACB of 3 OR -0.15 (95% CI: -0.42 – 0.12) ACB of 4 OR -0.34 (95% CI: -0.67 - -0.01) Definite use of anti-cholinergic drugs and MMSE decline: OR -0.33 (95% CI: -0.64 - -0.03)	Use of anti-cholinergic drugs is associated with increased risk of cognitive impairment.
Fox [44]	Cognitive Function	Month 18 mean differences for cognitive measures categorised by ABS Score 0 or ≥1:	Use of anti-cholinergic drugs in patients with Alzheimer's disease is not associated with

		Alzheimer's Disease Assessment Battery-Cognitive subsection OR -1.49 (-1.96 – 1.06, p=0.42) MMSE: OR 0.69 (-0.84 – 2.21, p=0.37) Severe Impairment Battery (SIB) 6.23 (-0.26 to 12.73, p=0.06).	deterioration in cognition.
Geller [23]	Cognitive Function	Change in Hopkins Verbal Learning Test-Revised Form (HVLT-R) score at 4 weeks after trospium initiation from baseline: mean value 60.0 +/-11.9 p<0.05 vs baseline	Trospium chloride use is associated with significant difference in cognition.
Gnijidic [37]	Cognitive Function	DBI 0 Addenbrookes Cognitive Examination (ACE) <83 1.41 (95% CI: 0.99-2.02) Trail Making Task (TMT) not completed 1.05 (95% CI: 0.64-1.75) Cognitive Impairment 1.80 (95% CI: 1.17-2.77) DBI >0 and <1 ACE 1.20 (95% CI: 0.8-1.78) TMT 1.13 (95% CI: 0.66-1.93) Cognitive impairment 1.45 (95% CI: 0.89-2.36) DBI≥1 ACE 2.48 (95% CI: 1.35-4.58) TMT 0.73 (95% CI: 0.22-2.41) Cognitive impairment 3.52 (95% CI: 1.78-6.93).	Use of anti-cholinergic drugs is not associated with increased risk of limitations in cognitive performance, mild cognitive impairment or dementia.
Han [27]	Cognitive Function	Cognitive function measured using Hopkins Verbal Recall Test. Adjusted association between cumulative anti-cholinergic exposure and cognitive function (memory): mean effect estimate 0.42 (95% CI: 0.17-0.67, p=0.001).	Use of anti-cholinergic medications is associated with reduction in cognitive function.
Harvey [31]	Cognitive Function	Performance on cognitive measures: Continuous performance Test (CPT): Risperidone – mean effect size = 0.30; olanzapine mean effect size = 0.46. California Verbal Learning Test (CVLT): Learning Trial 1: Risperidone – mean effect size = 0.60; Olanzapine = 0.61. Learning Trial 15 Risperidone – mean effect size = 0.30; Olanzapine = 0.36. Long-delay free recall Risperidone = 0.28; Olanzapine = 0.38. Recognition discriminability: Risperidone = 0.08; Olanzapine = 0.22. Spatial Working Memory Test (SWMT): Total correct at 15s: Risperidone = 0.26; Olanzapine = 0.26. Total Correct at 5s: Risperidone = 0.0; Olanzapine 0.05. Trail making test: Part A: Risperidone 0.07; Olanzapine 0.29. Part B: Risperidone 0.08; Olanzapine 0.15. Verbal fluency Examination (VFE): Category fluency: Risperidone 0.11; olanzapine 0.10. Letter fluency: Risperidone 0.07; Olanzapine 0.20. Wisconsin Card Sorting Test (WCST) Categories: Risperidone 0.17; Olanzapine 0.09. Preservative errors: Risperidone 0.08; Olanzapine 0.10. Total errors: Risperidone 0.13; Olanzapine 0.05.	Use of atypical antipsychotics is not associated with significant risk of cognitive impairment.
Kay [29]	Cognitive	Accuracy of delayed recall on the Name-Face Association Test at 3 weeks	Use of darifenacin is not associated with

	Function	compared to placebo (least square mean): Darifenacin 15 mg: OR -0.06 (95% CI: -1.08 – 0.96), p=0.022 Oxybutynin ER 20 mg: OR -1.30 (95% CI: -2.28 - -0.31), p=0.011 Immediate memory recall (least square mean): Name-face association: Darifenacin 15 mg (-0.30) Oxybutynin ER 20 mg (-0.74) First-last name association: Darifenacin 15 mg (-0.00) Oxybutynin ER 20 mg (-0.32) Facial recognition: Darifenacin 15 mg (0.29) Oxybutynin EF 20 mg (-1.37) Delayed memory recall (least square mean): First-last name association: Darifenacin 15 mg (0.18) Oxybutynin EF 20 mg (-0.39) Misplaced objects: Darifenacin 15 mg (-0.73) Oxybutynin EF 20 mg (-1.03) Visual attention (least square mean): Matching to sample: Darifenacin 15 mg (-1.94) Oxybutynin EF 20 mg (-0.11) Visual sequence comparison: Darifenacin 15 mg (-2.33) Oxybutynin EF 20 mg (-1.09) Information-processing speed (least square mean): Divided attention (sequence comparison speed, dual condition): Darifenacin 15 mg (0.30) Oxybutynin ER 20 mg (0.06) Divided attention (sequence comparison efficacy): Darifenacin 15 mg (-2.19) Oxybutynin ER 20 mg (0.21) Divided attention (sequence comparison accuracy): Darifenacin 15 mg (2.21) Oxybutynin ER 20 mg (-0.17) Visual sequence comparison: Darifenacin 15 mg (0.12) Oxybutynin ER 20 mg (0.01) Divided attention (single task premature hits): Darifenacin 15 mg (0.12) Oxybutynin ER 20 mg (-0.27) Divided attention (task reaction time, dual condition): Darifenacin 15 mg (0.02) Oxybutynin ER 20 mg (0.06) Divided attention (premature hits, dual condition): Darifenacin 15 mg (0.12) Oxybutynin ER 20 mg (-0.27) Psychomotor/reaction time: Darifenacin 15 mg (-0.03) Oxybutynin ER 20 mg (0.01)	cognitive impairment but oxybutynin leads to cognitive impairment.
Kersten [49]	Cognitive Function	There was significant reduction in total ADS scores at baseline and at 8-week follow-up from 4 to 2 ($p<0.0001$) in intervention group. There was no significant mean difference between baseline and 8-week follow-up of CERAD immediate recall 0.54 (-0.91, 2.05) p=0.48; CERAD delayed recall -0.23 (-0.85, 0.38) p= 0.46; CERAD recognition 0.77 (-0.39, 1.94) p=0.19; MMSE 0.39 (-0.96, 1.75) p=0.57	Reduction of anti-cholinergic medications has no significant effects on cognitive function improvement.
Kersten [50]	Cognitive Function	Adjusted mean differences in comparison to ADS = 3 CERAD immediate recall, number of words: ADS = 4: 1.3 (-1.1, 3.8); ADS = 5: 1.0 (-1.8, 3.7); ADS ≥6: 0.2 (-2.9, 3.4) CERAD verbal delayed recall, number of words: ADS = 4: 0.2 (-1.1, 1.7); ADS =	Increasing ADS scores is not associated with decrease in cognitive function.

		5: 0.1 (-1.4, 1.6); ADS ≥6: -0.1 (-1.9, 1.6) CERAD verbal recognition, number of words: ADS = 4: -1.2 (-3.1, 0.7); ADS = 5: -0.6 (-2.7, 1.4); ADS ≥ 6: 0.1 (-2.0, 2.3) MMSE: ADS=4: 1.1 (-2.9, 2.8); ADS=5: 0.1 (-2.9, 2.8); ADS ≥6: -0.1 (-3.4, 3.1)	
Kolanowski [32]	Cognitive Function	There were no significant associations between ACB measures and mean engagement: Any ACB (p=0.302), any ACB 3 (p=0.126), ACB 3 score (p=0.412), Total ACB score (p=0.640). There was no significant difference between those with any ACB drug and those with none (p=0.350) or between those receiving any ACB 3 drug and those who did not p=0.877.	Use of anti-cholinergic medication is not associated with cognitive impairment.
Koyama [51]	Cognitive Function	Rate of change in mean ACB score at 10 year follow-up for cognitive status: Dementia 0.67 (SE=0.13); MCI 0.50 (SE=0.11); Normal 0.34 (SE=0.07) p<0.02	Higher anticholinergic load was significantly associated with poorer cognitive function at 10-year follow-up.
Lampela [52]	Cognitive Function	Higher anticholinergic scores associated with decrease in MMSE (p<0.01). In dementia patients anticholinergic scores were found to have no associateion with MMSE.	Use of anticholinergic medications is associated with cognitive impairment.
Lipton [28]	Cognitive Function	Memory scanning sensitivity: least squares mean differences from baseline were 0.056 (SD: 0.017) in Darifenacin group compared to 0.032 (SD: 0.017) in placebo group. Choice reaction time speed (m/s): least squares mean differences from baseline were 3.89 (SD: 4.72) in Darifenacin group compared to 2.70 (SD: 4.46) in placebo group. Delayed Word recognition sensitivity: least squares mean change from baseline was -0.003 (SD: 0.021) in Darifenacin group compared to 0.016 (SD: 0.020) in placebo group.	Use of darifenacin is not associated with significant difference in cognitive function.
Low [38]	Cognitive Function	Adjusted association between anticholinergic medication use and cognitive function: Simple reaction time F=0.1 p=0.733 Choice reaction time F=4.1 p=0.043 Immediate recall F=0.1 p=0.701 Delayed recall F=0.000 p=0.989 Digits backwards F=0.9 p=0.347 Mini-mental state examination F=1.9 p=0.167 Symbol digits modalities test F=7.1 p<0.008	Use of anti-cholinergic medication is associated with lower level of complex attention in the young-old but not with greater cognitive decline.
Merchant [18]	Cognitive Function	Adjusted association between use of ACB drugs and cognitive impairment: OR 2.66 (1.06-6.68).	Use of anti-cholinergic drugs is associated with increased risk of cognitive impairment.
Pasina [54]	Cognitive Function	Adjusted Mean Short Blessed Test (SBT) of patients treated with anticholinergic drugs according to ACB scale was 9.2 (95% CI 8.6-9.9) than those not treated with anticholinergic drugs 8.5 (95% CI 7.8-9.2) (p=0.05). Adjusted Mean SBT of patients treated with anticholinergic drugs according to ARS was 9.9 (95% CI 8.7-11.2) than those not treated with anticholinergic drugs 8.8 (8.2-9.4) (p=0.07)	Cumulative effects of anticholinergic drugs as assessed by ACB scale and ARS is associated with cognitive impairment.

Shah [56]	Cognitive Function.	Z score is calculated using a battery of 19 cognitive function tests in addition to the MMSE. No significant difference between prevalent and non-prevalent users. Annual rate of change = -0.007 z score units/year, SE = 0.012, p=0.6. Incident users in non-prevalent group have a more rapid dcline (difference = -0.034 z-score units/year, SE=0.008 p<0.001 compared to never users.	There is a gradation in annual rate of cognitive function decline amongst incident users compared to never users. However there was no significant difference between prevalent users and never users.
Shakakibara [55]	Cognitive Function	Baseline cognitive function = mean MMSE 21.8, mean FAB 10.7, mean ADAS-cog 14.8. At 3 month follow-up mean MMSE 22.1; mean FAB 11.1; mean ADAS-cog 14.4. No significance difference calculated.	Imidafenacin has no effect on cognitive function.
Uusvaara [57]	Cognitive Function	CERAD battery test: Low verbal fluency: DAP users 31.7% vs. non-users 18.1% p=0.008; Low naming test: Users 51.2% vs non-users 33.3% p=0.002; Low MMSE DAP users 24.7% vs. non-users 12.4% p=0.008; Low wordlist learning task: users 53.9% vs. 44.8% p=0.11; Low word list recall: Users 44.1% vs. 40.0% p=0.47; low wordlist recognition: users 35.3% vs non-users 32.4% p=0.59; low recall of constructional praxis: users 24.7% vs. non-users 19.0% p=0.24; low clock drawing users 40.9% vs non-users 31.7% p=0.10 After adjustment for age, sex and education low verbal fluency and naming remained statistically significant.	DAPs may be associated with specific impairments in cognitive functioning.
Wagg [42]	Cognitive Function	Solifenacin difference in: Power of attention -20.99 (95% CI: -68.58 – 26.61) Continuity of attention -0.51 (95% CI: -2.29 – 1.28) Quality of working memory -0.04 (95% CI: -0.21 – 0.13) Quality of episodic memory 4.66 (95% CI: -14.86 – 24.17) Speed of memory -77.92 (95% CI: -372.81 – 216.98) Oxybutynin difference in: Power of attention 17.51 (95% CI: -28.85 – 63.87) Continuity of attention -0.79 (95% CI: -2.12 – 0.54) Quality of working memory -0.05 (95% CI: -0.19 – 0.10) Quality of episodic memory -1.46 (95% CI: -18.98 – 16.06) Speed of memory 157.78 (95% CI: -182.02 – 497.58)	Use of solifenacin is not associated with increased risk of cognitive impairment but significant differences are observed for oxybutynin.
Wesnes [19]	Cognitive Function	Solifenacin difference in: Power of attention -0.44 (95% CI: -38.58 – 37.69) Continuity of attention 1.19 (95% CI: -0.47 – 2.85) Quality of working memory 0.07 (95% CI: -0.18 – 0.31) Quality of episodic secondary memory 9.21 (95% CI: -11.96 – 30.37) Speed of memory -114.71 (95% CI: -346.05 – 116.63) Oxybutynin difference in: Power of attention 46.50 (95% CI: 8.05 – 84.95) Continuity of attention -3.04 (95% CI: -4.70 - -1.38) Quality of working memory -0.44 (95% CI: -0.68 - -0.20) Quality of episodic secondary memory -16.86 (95% CI: -37.97 – 4.26) Speed of memory 199.68 (95% CI: -32.74 – 432.11)	Use of solifenacin is not associated with increased risk of cognitive impairment but significant differences are observed for oxybutynin.

Whalley [43]	Cognitive Function	Raven progressive matrices (mean): No drugs 30.8 (9.4) Prescribed drugs 28.6 (8.3) Mild-moderate exposure to anticholinergic 30.6 (8.5) Strong exposure to anticholinergic 21.6 (7.1), Univariate analysis of variance F=2.89 p=0.038. Block design (mean): No drugs 20.1 (6.9) Prescribed drugs 20.5 (7.2) Mild-moderate exposure to anticholinergic 18.5 (7.3) Strong exposure to anticholinergic 12.6 (5.8) Univariate analysis of variance F=3.22 p=0.025. Auditory verbal learning test (mean): No drugs 47.6 (14.1) Prescribed drugs 48.6 (12.5) Mild-moderate exposure to anticholinergic 48.8 (12.0) Strong exposure to anticholinergic 44.5 (9.9) Univariate analysis of variance F=0.28 p=0.838. Mini-mental state examination (mean): No drugs 28.6 (1.9) Prescribed drugs 28.1 (2.3) Mild-moderate exposure to anticholinergic 28.2 (1.4) Strong exposure to anticholinergic 26.8 (1.4) Kruskal-Wallis p=0.021	Use of anticholinergic drugs is associated with increased risk of cognitive impairment but not dementia.
Wilson [41]	Cognitive Function	Mini-mental state examination score (MMSE) were: None DBI: 23.7 (5.4); Low DBI: (>0 and <1): 22.9 (5.8); High DBI: (>1): 23.7(5.7)	Use of anti-cholinergic drugs is not associated with increased risk of cognitive impairment.
Yeh [58]	Cognitive Function	Difference in CR-ACHS at 12-week follow up: Intervention group = -0.5 vs Reference group = 0.1 p=0.014 Difference in MMSE at 12-week follow-up: Intervention group = -0.8 vs Reference group = -0.4 p=0.734	Reduction in anticholinergic drugs did not show in cognitive function improvement.
Outcome 2: Delirium			
Caeiro [47]	Delirium	Patients with delirium were more likely to have use of ACH before stroke OR 11.3 (95% CI: 1.19-108.2) and more likely to have ACH during hospitalization OR 5.82 (95% CI: 1.96-17.2).	Use of anti-cholinergic drugs is associated with increased risk of delirium.
Campbell [7]	Delirium	Risk of delirium among those prescribed definite anti-cholinergic medications: OR 0.43 (95% CI: 0.11 – 1.63).	Use of anti-cholinergic drugs is not associated with a significant difference in delirium.
Gaudreau [21]	Delirium	Unadjusted HR = 1.22 (0.65 to 2.30) p=0.53. Adjusted HR for history of delirium and liver metastases = 1.38 (0.73 to 2.60) p=0.32	Use of anti-cholinergic drugs is not associated with significant difference in delirium.
Luukkanen [20]	Delirium	Use of anti-cholinergic did not predict delirium (OR: 1.67; 95% CI: 0.87-3.21).	Use of anti-cholinergic drugs is not associated with a risk of development of delirium.
Pandharipande [36]	Delirium	The administration of anti-cholinergic was not associated in univariate analysis (p=0.54) or multivariate analysis (p=0.82) with delirium.	Use of anti-cholinergic drugs is not associated with the development of delirium.

Outcome 3: Physical Function			
Gnjidic [39]	Physical Function	Adjusted risk of functional outcomes with anticholinergic drug use: chair stands 0.35 (95% CI: -0.43-1.12); walking speed -0.02 (95% CI: -0.05-0.01); narrow walk -0.01 (95% CI: -0.04-0.02); balance -0.03 (95% CI: -0.11-0.05); grip strength -1.08 (95% CI: -1.99 - -0.17); instrument activities of daily living 0.13 (95% CI: -0.03-0.29)	No significant difference in chair stands, walking speed, narrow walk, balance and instrument activities of daily living.
Han [27]	Physical Function	Adjusted instrumental activities of daily living: mean effect estimate: 0.10 (95% CI: 0.04-0.17, p=0.001).	Use of anti-cholinergic drugs is associated with poorer performance on the instrument activities of daily living.
Hilmer [34]	Physical Function	Multiple regression for association of DBI at baseline and at 6 years (B and t-value): SPPB: -0.29 (p=0.008). Usual gait speed -0.04 (p=0.001). Grip strength -0.56 (p=0.08). The SPPB summary performance score (total 0-12) adds scores (0-4) for tests of standing balance, usual gait speed, and time to complete 5 repeated chair stands.7 Higher scores represent better function.	Use of anti-cholinergic drugs is associated with poorer performance on the instrument activities of daily living.
Kersten [50]	Physical Function.	Adjusted mean differences in anticholinergic end points between different subgroups of ADS score (4, 5 and ≥6) with reference to ADS score = 3. Barthel's index of activity of daily living: ADS = 4: 4.5 (-10.5, 19.6); ADS = 5: 15.67 (-1.3, 32.6); ADS ≥6: 19.11 (-0.2, 30.4)	Higher ADS scores are associated with higher ADL scores with no significant differences.
Lampela [52]	Physical Function	Higher anticholinergic scores associated with decrease in short-distance vision (p<0.01), ADL and IADL (p<0.001). In dementia patients anticholinergic scores were found to have negative association with short distance vision (p<0.01), IADL (p<0.01).	Higher anticholinergic scores are associated with reduced ADL and IADL scores.
Pasina [51]	Physical Function.	Adjusted mean BI with anticholinergic use according to ACB = 83.5 (95% CI 81.9-85.0) compared to those without anticholinergic use = 96.3 (84.4-88.1) (p=0.03). At 3 month follow up: adjusted mean BI score for users = 82.8 (95% CI 84.2-89.2); non-users = 86.7 (95% CI 84.2-89.2) (p=0.02) Adjusted mean BI with anticholinergic use according to ARS = 79.0 (95% 74.9-83.0) compared to no anticholinergic use = 85.2 (95% CI 84.0-86.4) (p=0.006). At 3 month follow up: adjusted mean BI score for users = 76.9 (95% CI 71.8-82.1); non-users = 85.2 (95% CI 83.5-86.9) (p=0.003)	Cumulative effects of anticholinergic drugs assessed by ACB and ARS scale is associated with functional impairment.
Wilson [41]	Physical Function	Functional status: No walking stick/frame use: DBI 0 87/189 (46%), >0 and <1 DBI 98/260 (37.7), DBI >1 52/153 (34%)	Use of anti-cholinergic drugs is associated with greater use of mobility aids.
Yeh [58]	Physical Function.	Difference in BI at 12-week follow-up: Intervention group = -0.5 vs Reference Group = -4.3 (p=0.116)	Reduction in anticholinergic burden did not show benefits in functional outcome improvements.

Outcome 4: Mortality

Agar [40]	Mortality	A log-rank test demonstrates there was no evidence that survival differed between the 3 groups (p>0.05).	Use of drugs with anti-cholinergic properties is not associated with any difference in mortality.
De Luise [35]	Mortality	Risk ratio of tiotropium use and total mortality OR 0.77 (95% CI: 0.56-0.78)	Tiotropium use is associated with lower mortality.
Fox [5]	Mortality	Odds ratio for mortality reported after adjusting for age, sex, baseline MMSE, education, social class, no. of non-anticholinergic medications, health conditions. Overall mortality OR = 1.26 (95% CI: 1.20-1.32) Definite anti-cholinergics OR = 1.68 (95% CI: 1.30-2.16) Possible anti-cholinergics OR = 1.56 (95% CI: 1.36-1.79).	There was a dose-response effect of ACB score associated with mortality at 2 years.
Kumpula [22]	Mortality	Cox hazards ratio for mortality is: ARS 1-2 vs 0: HR 1.08 (95% CI: 0.84-1.41); ARS ≥3 vs 0: HR 1.05 (95% CI: 0.75-1.46)	Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality.
Luukkanen [20]	Mortality	For whole cohort, use of anti-cholinergic was not an independent predictor of mortality (HR: 1.12; 95% CI: 0.75-1.68). This remained the same for those with pre-study diagnoses of dementia (HR: 1.41; 95% CI: 0.85-2.34).	Use of anti-cholinergic drugs is not associated with an increased risk of mortality.
Mangoni [53]	Mortality	Total all cause mortality at 3 months = 12.7%. Pre-admission cognitive impairment, in-hospital delirium, Katz ADL index, CCI, LOS, ARS score HR = 1.6 (1.2-2.2) p=0.004 and $DBI_{antichol}$ HR = 4.5 (1.2-16.7) p=0.02 were significantly associated. Pre-admission cognitive impairment and anticholinergic risk scale score HR = 2.2 (1.2-3.7) p=0.006 were independent predictors. Total all-cause mortality at 1-year was 25.4%. Living at home, in-hospital delirium, Katz index score, CCI, ARS HR = 1.4 (1.1-1.8) p=0.005 and $DBI_{antichol}$ 3.2 (1.1-9.4) p=0.04 were significantly associated. Living at home, in-hospital delirium and LOS were independent predictors.	Use of anti-cholinergic drug is associated with increased mortality.
Uusvaara [46]	Mortality	Adjusted Cox hazard ratio for risk of mortality with anticholinergic use: HR 1.57 (0.78 - 3.15, p=0.20).	Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality.
Wilson [11]	Mortality	Risk of mortality with low DBI and high DBI vs no DBI HR: Low DBI: HR 1.13 (0.82-1.57); High DBI: HR 1.19 (0.82-1.74)	Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards increased mortality.
Wilson [41]	Mortality	Multivariate HR for 1 year survival: Low DBI vs none: HR 1.13 (0.82-1.57); High	Use of drugs with anti-cholinergic properties is associated with a non-significant trend towards

	DBI vs none: HR 1.19 (0.82-1.74)	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; BI – Barthel's index; CCI – Charlson's Comorbidity Index, CI: confidence intervals; CERAD: consortium to establish registry for alzheimer's disease; Clinician-rated Anti-cholinergic Score (CR-ACHS); DAP: Drugs with anticholinergic properties; DBI: drug burden index; HR: hazard ratio; IADL – instrumental activities of daily living; LOS: Length of stay; MMSE: Mini-mental state examination; OR: Odd ratios; SD: standard deviation; SPPB: Short Physical Performance Battery Score