



Articles

Community-based Anticholinergic Exposure and Delirium: A Systematic Review

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Delirium

Background:

Anticholinergic medications adversely affect cognition and have been identified as a potential modifiable risk factor for delirium. Community-based anticholinergic exposure remains inadequately explored.

Objective:

To systematically review studies reporting association of community-based anticholinergic exposure and delirium incidence, prevalence, severity, and duration.

Methods:

A systematic review was conducted following PRISMA guidelines. Databases searched included PubMed, EMBASE, PsycINFO, CINAHL, and Web of Science (inception–November 2023). Eligible studies assessed community-based anticholinergic exposure and any of delirium incidence, prevalence, severity and delirium in adults (≥18 years). Two reviewers independently screened records assessed full-texts, and appraised quality using the Newcastle-Ottawa Scale.

Results:

Of 4311 studies, 24 met inclusion criteria. Eleven studies found a positive association between higher anticholinergic burden and incident delirium while 4 reported similar findings for prevalent delirium. Anticholinergic exposure was most commonly assessed using anticholinergic scales (n=22), of which, 9 used two or more scales. Exposure assessment was typically based on a single time point at or before admission (n=21). Three studies incorporated dose and duration of use in anticholinergic exposure assessment. Evidence on delirium severity and duration was limited; only one study addressed these outcomes reporting no significant relationship with anticholinergic use.

Conclusion:

Community-based anticholinergic burden appears to contribute to delirium risk, but variability in populations, measurement tools and study designs limits the generalizability of findings. Future research should focus on standardized exposure metrics, cumulative burden, and evaluate delirium severity and duration to inform evidence-based strategies for reducing delirium risk in vulnerable populations.

INTRODUCTION

Delirium is an acute neuropsychiatric syndrome characterized by confusion, attentional deficits, and a fluctuating cognitive impairment.¹ It is associated with substantial morbidity, functional decline, long-term cognitive deterioration, higher healthcare costs and mortality, contributing up to \$152 billion annually in the United States.¹⁻³ Delirium incidence varies widely across healthcare settings, affecting up to 20% of all hospitalized patients and up to 80% of those in intensive care or post-surgical environments.⁴ Older patients are particularly vulnerable, with the risk of delirium increasing by approximately 2% for every addi-

tional year beyond the age of 65.⁵ As the population ages and longevity increases,⁶ the number of vulnerable individuals at risk for delirium is expected to rise, emphasizing the need for enhanced understanding of risk factors and effective prevention strategies.

Delirium is a multifactorial condition resulting from a combination of predisposing and precipitating factors including medications.⁷ Evaluating medications is critical due to their ubiquitous use before, during and after hospitalization and the modifiability of their use. Medications are suggested to be the sole precipitant for 12-39% of cases of delirium.⁸ Medications with anticholinergic potential, in particular, have been identified as high-risk due to their antagonistic effects on acetylcholine, a neurotransmitter cru-

cial for cognitive functions often disrupted in delirium such as attention, sleep, and memory.⁹ The widespread prescription of anticholinergic drugs for a plethora of conditions including mental, neurological, respiratory, ophthalmic, and urological disorders,¹⁰ coupled with their known negative cognitive impact¹¹⁻¹³ underscores the need for a critical evaluation of their use in vulnerable populations.

Existing delirium research has predominantly focused on anticholinergic medication use within hospital settings, neglecting the anticholinergic burden that may carry from regularly prescribed medicines.¹⁴ To our knowledge, no review has specifically examined how community-based anticholinergic burden relates to delirium outcomes. By systematically evaluating existing literature in these underexplored settings, we aim to clarify the strength and consistency of this association. The main research question is whether anticholinergic burden of regularly used, community-based medications increases delirium occurrence severity, or duration. Such insights have the potential to refine clinical decision-making, guide prescribing practices, and ultimately inform strategies to prevent or mitigate delirium in vulnerable populations.

METHODS

A protocol for this review was prospectively registered with PROSPERO (CRD42023314206). This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA).¹⁵ The review was performed using Covidence®,¹⁶ an online tool designed to streamline the systematic review process by facilitating abstract screening, full-text screening, study selection, quality assessment, and data extraction.

DATA SOURCES AND SEARCH STRATEGY

A comprehensive literature search was conducted across multiple electronic databases including PubMed, EMBASE, PsycINFO, CINAHL, and Web of Science from their inception to November 2023. The search strategy was modified from similar searches created by Egberts et al¹⁷ with additional terms added. Terms related to delirium (e.g. "*delirium*", "*acute confusion*", "*cognitive dysfunction*") were combined with terms related to anticholinergic drugs (e.g. "*anticholinergic*"). The search terms and strategies for all databases are shown in Supplement B. Reference lists of identified articles and relevant reviews were manually searched to ensure comprehensive coverage.

ELIGIBILITY CRITERIA

Studies included if they (i) assessed anticholinergic burden of medicines taken prior to hospital or long-term care facility admission; (ii) reported any of incidence, prevalence, duration of delirium or delirium severity as an outcome; and (iii) included adult participants (≥18 years). Studies were excluded if they (i) focused exclusively on in-hospital anticholinergic exposure; (ii) were case reports, case series,

abstracts, study protocols editorials, or review articles; (iii) lacked primary data or clear delirium outcomes, (iv) studies that used a composite measure of sedative and anticholinergic burden, (v) studies that used a consolidated dementia-delirium outcome, (vi) studies with unclear exposure assessment period, (vii) studies not in English.

STUDY SCREENING AND SELECTION

All references identified by search queries were added to Covidence®¹⁶ and duplicates were removed. One author (H.K) screened titles and abstracts for potentially eligible studies. Two authors (H.K and N.K) independently assessed full-text articles against the eligibility criteria. Disagreements at any stage were resolved through consensus.

DATA EXTRACTION

Data was extracted independently by two reviewers using a standardized extraction form. Extracted information included study characteristics (authors, year of publication, country), study design, sample size, participant demographics, method for assessing anticholinergic burden, medication data source, delirium assessment tools, and main findings of each study with regards to the relationship between medications and the outcomes of interest.

QUALITY ASSESSMENT

Two reviewers independently assessed the methodological quality of included studies. Cohort and case-control studies were assessed using the Newcastle-Ottawa Scale (NOS).¹⁸ The Modified NOS scale was used for cross-sectional studies.¹⁹ Each study was evaluated for the adequacy of sample selection, comparability of groups and assessment of outcomes. The score ranged from 0 (lowest degree) to 9 (highest degree). Studies ≤ 4 stars, 5-6 stars, and ≥ 7 stars were defined as low, medium, and high quality respectively. In the event of disagreement on critical appraisal score, agreement was met through discussion between evaluators.

DATA ANALYSIS

The data extraction tables were reviewed to determine the most appropriate analysis technique to answer the research question. There was considerable heterogeneity in relation to population characteristics, methods, and data sources to obtain anticholinergic exposure, duration of exposure, follow-up period, outcome measurement and reporting of data. Therefore, a meta-analysis was not feasible. Accordingly, a qualitative narrative review of the literature was performed to assess the association between anticholinergic burden and delirium outcomes.

RESULTS

STUDY SELECTION

The initial literature search resulted in 4311 with 2437 remaining after duplicate removal. Screening excluded 2324

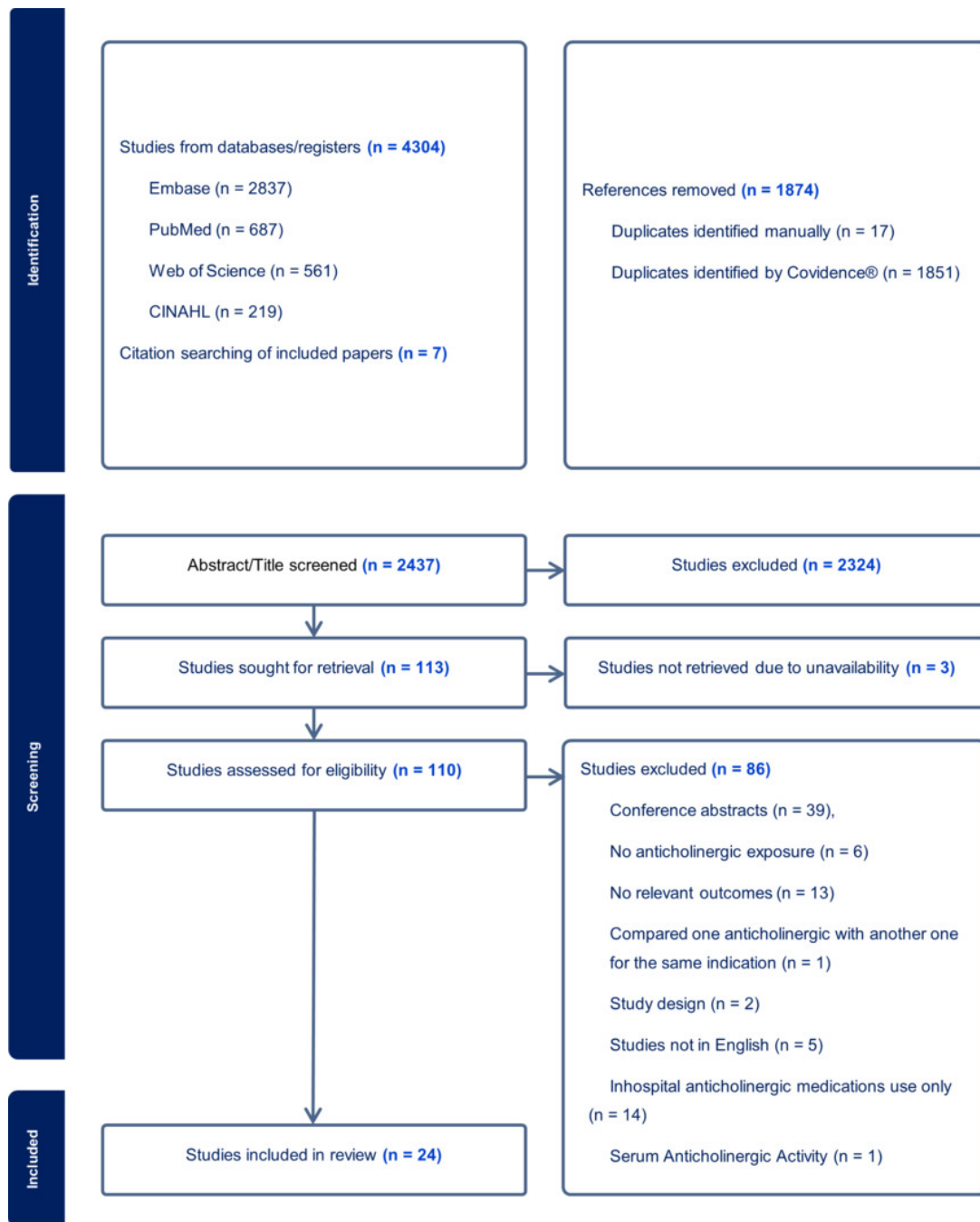


Figure 1. PRISMA flow diagram of the study selection process

records, leaving 110 full-text articles for eligibility assessment. Of these, 24 studies met the inclusion criteria and were included (Figure 1).

CHARACTERISTICS OF INCLUDED STUDIES

The 24 studies included were published between 2004 and 2023. They comprised 8 prospective cohorts,²⁰⁻²⁷ 6 retrospective cohorts,²⁸⁻³³ 5 cross-sectional studies,³⁴⁻³⁸ 3 case-controls,³⁹⁻⁴¹ 1 nested case-control,⁴² and 1 post-hoc analysis of a randomized control trial.⁴³ Studies were performed in 15 different countries with two being multi-country. In total, 673,938 participants were included (mean age range of 63-86.3, 45.3% male).

Seventeen of the included studies were conducted in hospital settings,^{20-23,25-27,31-34,36,38-41,43} with 6 specifically examining surgical patients.^{20-23,32,43} The remaining hospital studies focused on a range of populations including patients admitted to geriatric or medical wards,^{34,36,38} internal medicine wards,²⁶ and intensive care units (ICU),²⁷ as well as patients admitted for advanced cancer treatment,³¹ stroke,³⁹ emergency admissions,^{25,33,41} and rehabilitation.⁴⁰ Two studies were in a nursing homes^{24,35} and one at a hospice/home,³⁷ and four were population-based studies using health insurance records^{28-30,42} (Table 1). One study exclusively included patients with dementia,²⁸ while four excluded patients with dementia.^{20-22,32}

Table 1. Characteristics of included studies

Author, year	Study Design	Country	Population	Sample Size	Age, in years*	Male (n, %)	Delirium (n, %)**	Delirium Identification	Outcomes
<i>Hospital non-surgical</i>									
Caeiro, 2004 ³⁹	Case-control	Portugal	Acute stroke patients in neurology ward	74	63.6 (12.8)	47 (64)	22	DSM-IV, DRS	Prevalence
Ceppi, 2023 ⁴⁰	Case-control	Switzerland	Rehabilitation patients	625	77.2 (9.9) ^g , 64.6 (15.7) ^h	70 (55) ^g , 225 (45) ^h	125	Medical records	Incidence
Egberts, 2017 ³⁴	Cross-sectional	Netherlands	Acutely ill patients aged ≥ 65 in geriatric ward	905	81 (7.03)	437 (48.3)	215 (23.8%)	DSM-IV, DOSS	Prevalence
Lee, 2021 ³¹	Retrospective Cohort	South Korea	Stage IV solid cancer patients aged ≥ 65 in medical ward	430	72.6	265 (61.6)	35 (8.1%)	Medical records	Incidence
Moorey, 2016 ⁴¹	Case-control	United Kingdom	Patients aged ≥ 70 with unplanned medical admission	251	83.97 (6.6)	82 (32.7)	125 (49.8%)	CAM, DSM-IV	Prevalence
Naja, 2015 ²⁵	Prospective Cohort	France	Patients aged ≥ 75 admitted for various reasons often on an emergency basis	102	86.3 (5.8)	49 (48)	34.8%-60%	CAM	Prevalence
Pasina, 2019 ⁴⁴	Cross-sectional	Italy	Patients aged ≥ 65 patients in acute geriatric unit	477	85 (6.5) ^c , 83.4 (6.5) ^d	64 (42.4) ^c , 106 (41.8) ^d	151 (31.7%)	4A's Test	Prevalence
Rigor, 2020 ²⁶	Prospective Cohort	Portugal	Patients aged ≥ 65 in internal ward	198	79.9 (7.5)	106 (53.5)	56 (28.3%)	s-CAM	Incidence
Rawle, 2021 ³³	Retrospective Cohort	United Kingdom	Patients aged ≥ 70 and older admitted for ≥ 48 hr for unplanned emergency	577	83.2 (7.4)	237 (41)	175 (30%)	s-CAM	Prevalence by subtype (full syndromal, subsyndromal)
Vondeling, 2020 ²⁷	Prospective Cohort	Netherlands	Non-neurological patients admitted to ICU for > 24 hours	1,090	63 (15) ^c , 58 (16) ^d	328 (64) ^c , 328 (57) ^d	513 (47%)	Flowchart based on CAM-ICU	Incidence
Wahab, 2019 ³⁸	Cross-sectional	Malaysia	Patients aged ≥ 60 in geriatric and medical wards	145	71.51 (8.02)	70 (48.3)	Not reported	Medical records	Prevalence
<i>Surgical</i>									
Duprey, 2022 ²⁰	Prospective Cohort	United States	Patients aged ≥ 70 years undergoing major elective surgery	560	76.6 (5)	52 (39) ^c , 179 (42) ^d	134 (23.9%)	CAM	Incidence
Ferré, 2022 ¹⁵	Prospective Cohort	France	Patients aged ≥ 65 undergoing urgent surgery of hip fracture	67	78 [71-86]	24 (36)	36 (53.7%)	CAM	Incidence
Heinrich, 2021 ²²	Prospective Cohort	Germany, Netherlands	Patients aged ≥ 65 undergoing elective surgery with expected duration ≥ 60 min	837	74 [70-77] ^c , 71 [68-75] ^d	86 (52.1) ^c , 389 (57.9) ^d	165 (19.7%)	DSM-V, CAM, CAM-ICU, NuDESC	Incidence
Herrmann, 2022 ²³	Prospective Cohort	Germany	Patients ≥ 70 undergoing elective surgery with an expected duration ≥ 60 min	899	77.3 (4.9)	455 (50.6)	210 (23.4%)	CAM, DSM-V	Incidence
Mueller, 2020 ³²	Retrospective Cohort	Germany	Patients aged ≥ 65 scheduled for surgical treatment of gastrointestinal, genitourinary, or gynecological cancers	651	71.8 (4.9)	446 (68.5)	66 (10.1%)	CAM-ICU, NuDESC	Incidence
Tillemans, 2021 ⁴³	Post-hoc analysis of RCT	Netherlands	Patients ≥ 70 with intermediate or high risk for postoperative delirium admitted for acute or elective hip surgery	397	82.3 ^e , 82.6 ^f	13 (35.1) ^e , 8 (25.8) ^f	68 (15.8%)	CAM, DSM-IV	Incidence, severity (DRS-R-99), duration

Author, year	Study Design	Country	Population	Sample Size	Age, in years*	Male (n, %)	Delirium (n, %)**	Delirium Identification	Outcomes
<i>Nursing home or long-term care</i>									
Landi, 2014 ²⁴	Prospective Cohort	Italy	Long-term nursing home residents aged ≥ 65	1,490	83.56 [65.1-106.4]	28.5 (28.5)	Not reported	NH-CAM	Incidence
Oudewortel, 2021 ³⁵	Cross-sectional	European Multi-country ^m	Short- and long-stay nursing home residents	3,924	80 ^a , 84 ^b	1,059 (27)	643 (15.5%)	Approximated from recorded symptoms in SHELTER database	Prevalence
Pasina, 2021 ³⁷	Cross-sectional	Italy	Adults admitted and died in hospice or cared for at home by palliative care physicians	461	83 [76.5-88.6] ^c , 78.1 [71.7-84.9] ^d	235 (42)	124 (26.9%)	4A's Test	Prevalence
<i>Population based studies</i>									
Huang, 2012 ²⁹	Retrospective Cohort	Taiwan	Patients aged ≥ 65	72,556	73.98 (6.51) ⁱ , 74.3 (7.01) ^j	23,696 (43.17) ⁱ , 8,601 (48.68) ^j	534 (0.73%)	ICD-9 codes	Incidence
Ah, 2019 ⁴⁵	Retrospective Cohort	South Korea	Dementia patients > 60 who started a cholinesterase inhibitor	7,438	39% 60-74 yrs 60.9% ≥ 75 yrs	2,556 (34.4)	298 (4%)	ICD codes	Incidence
Hwang, 2019 ³⁰	Retrospective Cohort	South Korea	Persons aged ≥ 65	118,750	75.4 (6.6)	51,748 (43.6)	66 (0.05%)	ICD-10 codes	Incidence
Hwang, 2021 ⁴²	Nested Case-control	South Korea	Patients aged ≥ 65	461,034	76.1 (7.1)	180,351 (39.1)	719	ICD-10 codes	Incidence

CAM, Confusion Assessment Method; DRS, Delirium Rating Scale; DSM, Diagnostic Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; ICU, Intensive Care Unit; IQR, Interquartile range; Nu-DESC, Nursing Delirium Scale; SD, Standard Deviation; SHELTER, Services and Health for Elderly in Long TERM care; 4AT,

*Age reported as mean (SD or range) or median [Range]

** Percentage not reported for case-control studies

a. Men, b. Women, c. Delirium group, d. non-delirium group, e. Placebo with delirium, f. Haloperidol group, g. cases, h. controls, i. patients taking anticholinergics, j. patients not taking anticholinergics, k. Czech Republic, England, Finland, France, Germany, Italy, and the Netherlands

Details on the methodological quality of the studies included according to the NOS are provided in section B of supplement. Quality scores ranged from 3 to 9 stars (average 7.5 stars). The findings indicate that the evidence-base was largely moderate to high in methodological quality.

ASSESSMENT OF DELIRIUM

Delirium was using the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV or V, 6 studies),^{22,23,34,39,41,43} the Confusion Assessment Method in its various forms (CAM, 12 studies),^{20-27,32,33,41,43} diagnosis codes for delirium according to the international classification of diseases 9th and 10th edition (ICD-9 or 10, 4 studies),^{28-30,42} 4AT test (2 studies),^{36,37} medical record documentation (3 studies),^{31,38,40} and the Nu-DESC (1 study).²² One study used recorded pre-specified symptoms indicating acute mental status changes from a cross-sectional study.³⁵ Delirium incidence ranged between 66 of 118750 patients (0.05%)³⁰ to 36 of 67 (53.7%)²¹ and prevalence ranged between 124 of 461 (26.9%)³⁷ and 125 of 251 (49.8%)⁴¹ among included studies (Table 1).

Delirium severity was measured with the Delirium Rating Scale (DRS) in two studies,^{39,43} however only one⁴³ assessed the possible association between anticholinergic burden and severity. Delirium duration similarly was assessed by only one study.⁴³ In addition, one study further explored the impact of anticholinergic burden on subsyndromal delirium.³³

ANTICHOLINERGIC DRUG BURDEN MEASUREMENT

Among the 24 included studies, 22 used anticholinergic scales, with the remainder relying on anticholinergics listed in prior literature²¹ or pharmacological categories based on national drug formularies.³⁹ The most frequently utilized anticholinergic scales were the Anticholinergic Cognitive Burden scale (ACB, 12 studies),^{20,22,26,31,33-37,40-42} the Anticholinergic Drug Scale (ADS, 8 studies),^{20,22,27,32,38,41-43} and the Anticholinergic Risk Scale (ARS, 7 studies).^{22-24,29,34,35,42} Ah et al. (2019) modified the ACB scale²⁸ and Hwang et al. (2019) modified the ARS scale³⁰ to account for anticholinergics available in their study countries. Less common scales included the list of Chew³⁴ and Coupland's Anticholinergic Burden Score (ABS).^{23,46} One study²⁵ combined the ACB and ADS scales to account for the greatest number of possible anticholinergics. Fourteen studies used one scale^{24,26-33,36-38,40,43} while nine used multiple.^{20-23,25,34,35,41,42} Studies implemented scales by summing potency points (17 studies), or they were used to identify anticholinergic drugs and subsequently classify patients as users versus non-users (4 studies) or the number of anticholinergics taken by patients (7 studies) (Table 2).

Exposure assessment was typically based on a single time point (21 studies), most commonly at hospital admission (12 studies) (Table 2). Others specified distinct time windows for exposure assessment: Huang et al. (2012)²⁹ used an 1-year exposure period, Landi et al. (2014)²⁴ used a 7 day time-frame, Oudewortel et al. (2021)³⁵ considered 3 days, and Moorey et al. (2016)⁴¹ 48 hours. Duprey et

al. (2022)²⁰ considered patients taking anticholinergics if they reported them in an interview 2 weeks before planned hospital admission. Three studies did not specify the time point of anticholinergic assessment^{22,25,39} and sufficed to indicate medications taken before admission,^{25,39} or long-term medications taken regularly.²² Among studies using a single time point assessment, only one incorporated doses to quantify anticholinergic burden.²⁵ Longitudinal exposure measures incorporating dosage, duration, and anticholinergic potency was performed by only 3 studies,¹⁻³ all of which calculated an average daily burden score (Equation in Supplement.C). Ah et al. (2019)²⁸ calculated an average daily ACB score over 3 months, Hwang et al. (2019)³⁰ calculated an average ARS score over 3 months, and Hwang et al. (2021)⁴² calculated average KABS, ARS, ACB, and ADS over 30 days.

ANTICHOLINERGICS AND DELIRIUM OUTCOMES

HOSPITALIZED NON-SURGICAL POPULATIONS

In non-surgical hospitalized patients, four studies reported a positive association between higher anticholinergic burden measured at or before admission and incident delirium.^{26,27,31,40} Three of these studies used the ACB scale^{26,31,40} and one used the ADS²⁷ to identify medicines. The populations included patients in inpatient rehabilitation,⁴⁰ advanced cancer patients admitted to a medical ward,³¹ general internal medicine patients,²⁶ and patients admitted to the ICU²⁷ (Table 3).

Prevalent delirium was positively associated with anticholinergic burden measured at a single time point on or before hospitalization in three^{34,38,39} of seven^{25,33,34,36,38,39,41} studies, examining acutely ill patients admitted to geriatric wards,^{34,38} and stroke patients.³⁹ These three studies utilized different methods to quantify exposure: one used the ARS scale,³⁴ another categorized patient based on ADS-defined users versus non-users, and the third employed pharmacologic categories rather than standardized scales (Table 3).

SURGICAL POPULATIONS

In surgical populations, two^{23,32} of five^{20-23,32} studies demonstrated anticholinergic burden measured at or before admission was positively associated with incident delirium. Herrmann et al. (2022)²³ and Mueller et al. (2020)³² both reported a similar elevated adjusted-risk per anticholinergic scale point (54% and 49% respectively), although they were used different scales (ARS and ADS respectively). The remaining three surgical studies did not detect a similar association²⁰⁻²² (Table 3).

NURSING HOME AND LONG-TERM CARE RESIDENTS

In nursing home settings, Landi et al (2014)²⁴ reported a 16% higher risk of incident delirium for each additional ARS point measured at a single timepoint. Similarly Oudewortel et al. (2021),³⁵ observed a 17% higher risk of prevalent delirium for each additional ARS point and a 14%

Table 2. Description of anticholinergic exposure and summary findings

Study, year	Anticholinergic exposure assessment approach	Anticholinergic Scale Used	Exposure type and duration	Source of exposure ascertainment	Include dose or duration in exposure measurement	Findings
Hospital non-surgical						
Caeiro, 2004	Use versus non-use, Number of anticholinergic drugs	None	Single point – Before admission (unspecified)	Medical records	None	Pre-morbid intake of medications with anticholinergic activity is associated with delirium in stroke patients
Ceppi, 2023	Sum of scale points	ACB	Single point – At time of admission	Interview or questionnaire	None	High anticholinergic burden was a potential risk factor for incident delirium
Egberts, 2017	Sum of scale points, Number of anticholinergic drugs	ARS, ACB, List of Chew	Single point – At time of admission	Medical records or interview	None	Anticholinergic exposure measured with ARS, but not ACB or list of Chew, was associated with an increased prevalence of delirium on admission and increased post-discharge institutionalization
Lee, 2021	Sum of scale points	ACB	Single point – At admission	Medical records or interview	None	An increase in ACB during hospitalization was associated with delirium in older patients with cancer
Moorey, 2016	Sum of scale points	ACB, ADS	Single point – Drugs prescribed within 48 hours of admission	Medical records	None	Anticholinergic burden was not associated with delirium on admission
Naja, 2015	Sum of standardized doses multiplied by anticholinergic burden score	Combined ACB-ADS	Single point - Not mentioned	Medical records or interview	Dose	Pre-hospital anticholinergic burden was not associated with delirium at any day during hospital admission
Pasina, 2019	Sum of scale points	ACB	Single point – At admission	Interview or questionnaire	None	There was a dose-response relationship between anticholinergic burden and delirium, but its significance disappeared after adjustment for dementia and nutritional status
Rawle, 2021	Sum of scale points	ACB	Single point – At admission	Not mentioned	None	Anticholinergic burden was not associated with increased risk of delirium or mortality
Rigor, 2020	Sum of scale points, Number of anticholinergic drugs used	ACB	Single point – At admission	Medical records or interview	None	Pre-hospital anticholinergic burden was associated with delirium but not mortality
Vondeling, 2020	Sum of scale points	ADS	Single point – At admission	Medical records or interview	None	Exposure to drugs with anticholinergic effects before ICU admission increases the risk of developing delirium during critical illness
Wahab, 2019	Use versus non-use, Number of anticholinergic drugs used	ADS	Single point – At admission	Medical records or interview	None	Use of medicines with anticholinergic properties was associated with falls, confusion, and longer length of stay
Surgical						
Duprey, 2022	Sum of scale points, Number of anticholinergic drugs used	ACB, ADS	Single point – 2 weeks before surgery	Medical records or visual inspection of medications	None	No significant association between continuous ACB and ADS and incident delirium
Ferre, 2022	Sum of scale points	List from Duran et al. ⁴⁷ and Laroche et al. ⁴⁸ for drugs marketed in France	Single point – At time of admission	Not mentioned	None	Pre-hospital atropinic burden was not associated with delirium postoperatively
Heinrich, 2021	Sum of scale points, Use versus non-use	ARS, ACB, ADS	Single point – Long term medications taken at	Medical records or interview	None	There was no association between pre-operative anticholinergic load (ARS, ACB, ADS) and delirium

Study, year	Anticholinergic exposure assessment approach	Anticholinergic Scale Used	Exposure type and duration	Source of exposure ascertainment	Include dose or duration in exposure measurement	Findings
Herrmann, 2022	Sum of scale points, Number of anticholinergic drugs used	ARS, ABS from Coupland et al. ⁴⁶	time of study enrollment Single point – At admission	Interview or questionnaire	None	Preoperative anticholinergic burden was an independent risk factor of postoperative delirium in older adults
Mueller, 2020	Sum of scale points, Use versus non-use	ADS	Single point – At baseline	Interview or questionnaire	None	Higher preoperative anticholinergic burden following long-term medication use was independently associated with the development of postoperative delirium
Tillemans, 2021	Sum of scale points	ADS	Single point – At admission	Not mentioned	None	Anticholinergic burden was not associated with delirium duration and severity
Nursing home or long-term care						
Landi, 2014	Sum of scale points	ARS	Single point - Medications taken 7 days before baseline	Interview or questionnaire	None	Nursing home residents using anticholinergic medications were at higher risk of delirium
Oudewortel, 2021	Sum of scale points, Number of anticholinergic drugs used	ARS, ACB	Single point – Drugs used in the 3 days before baseline	Interview or questionnaire	None	ACB and ARS scales were associated with delirium in patients with dementia
Pasina, 2021	Sum of scale points	ACB	Single point – At admission	Interview or questionnaire	None	Anticholinergic burden was associated with increased risk of delirium
Population based						
Ah, 2019	Sum of standardized doses multiplied by anticholinergic burden score across duration	Modified ACB	3 months	Medical records	Dose and duration	High dose-adjusted anticholinergic burden measured by ACB was an independent prognostic factor for delirium in newly treated dementia patients
Huang, 2012	Use versus non-use	ARS	Single point during an observation period of 1-year	Medical records	None	Exposure to drugs on ARS scale was associated with higher odds of delirium
Hwang, 2019	Sum of standardized doses multiplied by anticholinergic burden score across duration	Modified ARS	92 days	Medical records	Dose and duration	High anticholinergic burden in older adults increases the risk of delirium visits
Hwang, 2021	Sum of standardized doses multiplied by anticholinergic burden score across duration	ARS, ACB, ADS, KABS	30 days	Medical records	Dose and duration	High anticholinergic burden as measured by KABS, ARS, ACB, and ADS was associated with emergency visits of delirium

ACB, Anticholinergic cognitive burden scale; ARS, Anticholinergic risk scale; ADS, Anticholinergic drug scale; ABS, Anticholinergic burden scale; KABS, Korean anticholinergic burden scale; ICU, Intensive care unit

Table 3. Results of Included Studies

Study, year	Anticholinergic scale	Drug Exposure; Exposure Period	Adjustments	Outcome	Results
<i>Hospital non-surgical</i>					
Ceppi, 2023	ACB	Anticholinergics taken by patient at hospital admission, single time point	Age, sex, rehabilitation discipline, index date and time span between admission and index date	Incident delirium	ACB ≥ 3 vs < 3 : OR 2.59 (1.41-4.73)*
Lee, 2021	ACB	Anticholinergics being taken by patients at hospital admission, single time point	Age, Sex, CCI, number of medications, length of stay, types of cancer, admission through emergency department, vital signs, laboratory results	Incident delirium	Patients with an increase in ACB score vs those with no increase: OR 13.45 (2.78-64.96)*
Rigor, 2020	ACB	Anticholinergics being taken by patients at hospital admission – single time point	Age, sex, CCI, dementia, number of comorbidities, number of outpatient drugs, number of inpatient drugs, number of outpatient ACB drugs, number of inpatient ACB drugs	Incident Delirium	ACB: Number of medications: OR 0.55 (0.27 – 1.13) Sum of points: OR 1.65 (1.09 – 2.51)*
Vondeling, 2020	ADS	Anticholinergics being taken by patients at hospital admission – single time point	Age, sex, drinking status, SOFA, APACHE IV, depression, diabetes, hypertension, sepsis or septic shock, cerebrovascular disease, cardiac failure, elective ICU admission (vs emergency), surgery before ICU admission	Incident delirium	ADS Sum of points: All patients: 1 vs 0: sHR 1.13 (0.91 - 1.40) ≥ 2 vs 0: sHR 1.32 (1.06 - 1.64)* Age ≥ 65 years, no severe sepsis and/or septic shock: 1 vs 0: sHR 1.52 (0.99 - 2.33)* ≥ 2 vs 0: sHR 2.15 (1.43 - 3.25)* Age ≥ 65 years, severe sepsis and/or septic shock: 1 vs 0: sHR 0.75 (0.47 - 1.20) ≥ 2 vs 0: sHR 0.84 (0.51 - 1.39)
Caeiro, 2004	None	ACH use vs non-use prior to admission - single time point	Non-neuroleptics ACH during hospitalization, medical complications, ACH taken before stroke and ICH	Prevalent delirium	ACH use vs non-use before stroke: OR 11.3 (1.19-108.2)* ARS: Use vs non-use: OR 1.73 (1.23 - 2.45)* Number of medications OR 1.38 (1.10 - 1.73)* Sum of points: 1-2 vs 0 OR 1.7 (1.16 - 2.49)* ≥ 3 vs 0 OR 1.83 (1.06 - 3.15)*
Egberts, 2017	ARS, ACB, List of Chew	Anticholinergics taken by patient at hospital admission, single time point	Age, sex, number of medications	Prevalent delirium	ACB: Use vs non-use: OR 1.1 (0.77 - 1.59) Number of medications: OR 1.07 (0.94 - 1.23) Sum of points: 1-2 vs 0: OR 0.99 (0.67 - 1.46) ≥ 3 vs 0: OR 1.39 (0.89 - 2.18) List of Chew: Use vs non-use: OR 1.09 (0.78 - 1.51) number of medications: OR 1.11 (0.94 - 1.31) Sum of points: 0.5-1 vs 0: OR 1 (0.71 - 1.43) ≥ 1.5 vs 0: OR 1.34 (0.85 - 2.11)

Study, year	Anticholinergic scale	Drug Exposure; Exposure Period	Adjustments	Outcome	Results
Moorey, 2016	ACB, ADS	Anticholinergics being taken by patients at hospital admission, single time point	Age, number of anticholinergics, polypharmacy, anticholinesterase use	Prevalent delirium	Non-significant, Not reported
Naja, 2015	Combined ACB - ADS	Anticholinergics being taken by patients before hospital admission, single time point	Age, sex, education, CCI, cognitive level (MMSE), sensorial disturbances, marital status, place of residence (with spouse or other family member, alone or in an institution), socioeconomic level before retirement, perceived health status on a numeric scale (0-10), number of previous hospitalizations, creatinine clearance, serum albumin	Prevalent delirium	Anticholinergic burden at home with delirium at day 1, day 3, day 5, day 8, day 15 Not significant
Pasina, 2019	ACB	Anticholinergics being taken by patients at hospital admission, single time point	Age, sex, dementia, cancer, mini nutritional assessment	Prevalent delirium	ACB sum of points: 1 vs 0: OR 0.93 (0.49-1.79) 2 vs 0: OR 1.01 (0.47-2.16) 3 vs 0: OR 1.81 (0.74-4.47) 4 vs 0: OR 2.19 (0.87-5.53) ≥5 vs 0: OR 2.73 (0.85-8.77)
Wahab, 2019	ADS	Anticholinergics being taken by patients at hospital admission, single time point	Age, sex, drinking status, smoking status, number of medications, comorbidities	Prevalent delirium	ADS use vs non-use: OR 3.6 (1.55-8.37)*
Rawle, 2021	ACB	Anticholinergics being taken by patients at hospital admission, single time point	Univariate	Subsyndromal Delirium prevalence, Full syndromal delirium prevalence	ACB sum of points: Subsyndromal Delirium 1 vs 0: OR 0.86 (0.49 - 1.51) 2 vs 0: OR 0.88 (0.42 - 1.82) ≥3 vs 0: OR 1.61 (0.89 - 2.94) Full Syndromal Delirium 1 vs 0: OR 1.06 (0.59 - 1.93) 2 vs 0: OR 0.72 (0.30 - 1.72) ≥3 vs 0: OR 1.49 (0.76 - 2.94)
<i>Surgical</i>					
Duprey, 2022	ACB, ADS	Anticholinergics taken by patients 2 weeks before surgery, single time point	Age, Sex, CCI, Surgery type, Baseline GCP, APACHE-II, The number of medications with anticholinergic activity	Incident delirium	ACB number of medications: RR: 1.03 (0.88-1.20) ADS number of medications: RR: 1.03 (0.87-1.22)
Ferre, 2022	Duran et al. ¹¹⁴ and Laroche et al. ¹¹⁵	Anticholinergics being taken by patients at hospital admission, single time point	CIRS-G frailty score, prehospital AB, In-hospital AB	Incident delirium	Non-significant, not reported ADS: Number of medications: OR 0.955 (0.62-1.46) Sum of points: OR 0.928 (0.74-1.15) ARS: Number of medications: OR 0.784 (0.37-1.63) Sum of points: OR 0.832 (0.56-1.22) ACB: Number of medications: OR 1.13 (0.762-1.68) Sum of points: OR 1.045 (0.84-1.29)
Heinrich, 2021	ARS, ACB, ADS	Long term medications taken regularly at time of study enrollment, single time point	Age, CCI, duration of anesthesia, number of long-term medications	Incident delirium	
Herrmann, 2022	ARS, ABS ⁶⁷	Long term medications taken for more than 3 days a week at hospital admission, single time	Age, sex, CCI, number of medications, Surgery type, ICU stay, preoperative serum creatinine, type of anesthesia, usage of heart-lung-machine	Incident delirium	ARS Sum of points: OR 1.54 (1.15-2.02)* ABS Number of medications:

Study, year	Anticholinergic scale	Drug Exposure; Exposure Period	Adjustments	Outcome	Results
		point			OR 2.74 (1.55-4.49)*
Mueller, 2020	ADS	Long term anticholinergics taken every day before hospital admission, single time point	Age, Sex, CCI, duration of anesthesia, ASA, severity of surgery, Number of prescribed long-term drugs	Incident delirium	ADS: sum of points: OR 1.50 (1.09-2.05)* use vs non-use: OR 2.21 (1.21-4.04)*
Tillemans, 2021	ADS, Dutch expert panel scale (0-2)	Anticholinergics being taken by patients at hospital admission, single time point	Univariate	Delirium duration and severity	Non-significant, Not reported
<i>Nursing home or long term care</i>					
Landi, 2014	ARS	Anticholinergics received by patients during 7 days preceding baseline assessment, single time point	Age, Sex, cognitive level (CPS), depression, schizophrenia, comorbidities, CIRS	Incident delirium during 1-year follow up	ARS sum of points: OR 1.16 (1.02-1.32)* Patients with dementia: ARS sum of points 1.17 (1.04 - 1.31)* ARS none, moderate, strong 1.26 (0.99 - 1.49) ACB sum of points 1.14 (1.06 - 1.23)* ACB none, moderate, strong 1.26 (1.11 - 1.44)*
Oudewortel, 2021	ARS, ACB	Anticholinergics received by patients for 3 days preceding baseline assessment – single time point	Age, CCI, cognitive level (CPS)	Prevalent delirium	Patients without dementia: ARS sum of points 1.07 (0.94 - 1.21) ARS none, moderate, strong 1.1 (0.86 - 1.43) ACB sum of points 1.07 (0.97 - 1.18) ACB none, moderate, strong 1.14 (0.94 - 1.38)
Pasina, 2021	ACB	Anticholinergics being taken by patients at hospital admission – single time point	Age, sex, dementia, cancer, karnofsky performance score, days of palliative assistance, care setting (hospice or home).	Prevalent delirium	ACB sum of points: 1 vs 0: OR 0.62 (0.16-2.43) 2 vs 0: OR 0.44 (0.11-1.72) 3 vs 0: OR 1.85 (0.52-6.61) 4 vs 0: OR 1.53 (0.39-6.00) ≥5 vs 0: OR 2.25 (0.69-7.28)
<i>Population based</i>					
Huang, 2012	ARS	Patients taking at least 1 anticholinergic during a 1-year observation period	Age, sex, CCI, number of medications, presence of chronic disease	Incident delirium during 6 month follow up	ARS use vs non-use: OR 1.51 (1.18-1.93)*
Ah, 2019	Modified ACB	Average daily ACB, 3 months	Age, sex, depression, diabetes, hyperlipidemia, stroke, hypertension, sedative drugs, parkinson's disease, use of prescription drugs with ginkgo extract during the first 90 days	Incident delirium during 1 year follow up	Average daily ACB score >3: HR 1.52 (1.17-1.96)*
Hwang, 2019	Modified ARS	Average daily ARS, 3 months	Age, sex, insurance type, comorbid conditions, sedative drugs, polypharmacy, excessive polypharmacy, exposure to sedative drugs, warfarin, insulin, digoxin	Incident delirium	Average daily ARS ≥2 vs ≤2: HR 2.05 (1.13 - 3.73)*

	Outcome	Results
Interventions prescribed for	during 3 month follow up	Average daily KABS 1 vs 0: 1.36 (1.12-1.66)* 2 vs 0: 1.91 (1.46-2.50)* ≥3 vs 0: 2.96 (2.28-3.83)*
		Average daily ARS 1 vs 0: 1.14 (0.92-1.41) 2 vs 0: 1.92 (1.32-2.77)* ≥3 vs 0: 2.32 (1.33-4.03)*
	Incident delirium during 6 month follow up	Average Daily ACB 1 vs 0: 1.05 (0.86-1.26) 2 vs 0: 1.57 (1.21-2.04) * ≥3 vs 0: 2.22 (1.69-2.90)*
		Average daily ADS 1 vs 0: 1.39 (1.15-1.68)* 2 vs 0: 1.56 (1.19-2.05)* ≥3 vs 0: 2.55 (1.91-3.40)*

scale; ICU, Intensive care unit; ACh, Anticholinergics; MMSE, Mini mental state examination; APACHE, Acute physiology and chronic health evaluation score; CIRS, Cumula-

higher risk for each ACB point, though this association was restricted to patients with dementia. In hospice or home care settings, one study identified a relationship between anticholinergic burden (ACB scale) and prevalent delirium³⁷ (Table 3).

POPULATION-LEVEL STUDIES

There were four population-based studies incorporating national health insurance claims that consistently supported an association between anticholinergic burden and delirium risk.^{28-30,42(p2)} Of these, three studies used an average daily anticholinergic score to characterize burden. Longer exposure durations and measures that accounted for dose and potency typically yielded stronger associations. Hwang et al. (2021)⁴² reported increased odds of delirium with higher categorized ACB, ARS, ADS, and KABS scores with dose-response relationships evident across scales. Similarly, Ah et al. (2019)²⁸ found that an average daily ACB score >3 increased the hazard of developing delirium (HR 1.52) (Table 3).

DELIRIUM SEVERITY AND DURATION

Only one study⁴³ specifically examined the relationship between anticholinergic drug burden and delirium severity or duration in surgical patients population, reporting no significant results.

DISCUSSION

This systematic review examined the relationship between pre-admission anticholinergic drug burden and delirium outcomes. Across 24 included studies, 11 identified a positive association between higher anticholinergic burden and increased risk of incident delirium, while 4 reported a similar association with prevalent delirium. However, substantial variability in measurement methods, populations, and study designs complicates drawing definitive conclusions.

A central challenge identified in this review was the absence of a standardized method to quantify anticholinergic exposure. Among the included studies, there were 7 unique scales employed (ACB, ADS, ARS, List of Chew, ABS, Duran and La roche, KABS), and 3 modified scales (mACB, mARS, ACB-ADS). These tools differ in their derivation, including medications, and potency scoring ratings. Nine studies^{20-23,25,34,35,41,42} used multiple scales reflecting the lack of a universally optimal tool. Measurement approaches varied even within the same scale: some studies assessed the number of anticholinergic medications²⁰ or categorized patients as users versus non-users,^{29,38,39}. Others summed potency scores, and either considered anticholinergic burden a continuous variable^{22-24,32} or categorical thresholds.^{27,33,36,37,40,42,44} Such methodological heterogeneity complicates cross-study comparisons and reduces the clinical utility of findings.

The most utilized tools were the ACB, ARS, and ADS scales, in line with prior research by Salahudeen et al. (2015).¹³ Among these, the ARS scale showed the most con-

sistent association with delirium, showing a positive relationship in 7 of 8 studies in line with a prior review.¹⁷ In contrast, the ACB and ADS scales were less consistent, showing associations in 5 of 12 and 4 of 8 studies, respectively. The ARS's inclusion of both central and peripheral anticholinergic effects may explain its higher predictive value. Higher anticholinergic burden scores (e.g., ARS>3) were consistently associated with delirium whereas lower scores had inconsistent effects.

Most of the studies in this review identified anticholinergic use at a single time point, commonly at hospital admission. Three studies^{29,42,45} however, measured anticholinergic use over an extended period, calculating an average ACB or ARS score by incorporating prescribed dosages over predefined durations. These studies consistently found a significant positive association between prolonged anticholinergic use and delirium risk. Specifically, two studies^{30,45} examined 3-month exposure periods, and one⁴² used a 30-day period. This suggests that long-term anticholinergic burden may offer greater predictive value for delirium risk. Notably, no study has used cumulative total standardized doses to assess delirium, a method that is not solely dependent on scale scores^{44,49} and could provide a more nuanced understanding of dose-response effects independent of specific scale scores. Research in related fields, such as dementia, has demonstrated that cumulative medication exposure over several years can significantly increase dementia risk.^{46,49} Further studies are needed to see if a similar relationship exists for delirium.

A notable gap in the current literature is the limited focus on core outcomes⁵⁰ of delirium beyond incidence or prevalence. Only one study in this review examined the relationship between anticholinergic burden and delirium severity and it found no significant association⁴³ between the ADS and delirium severity as measured by the (DRS-R-98). In an earlier study by Han et al. (2001)⁵¹ examining in-hospital anticholinergic burden among older inpatients, anticholinergic exposure was significantly associated with delirium severity, as measured with the Delirium Index. Given that delirium severity and duration may affect mortality,⁵² cognitive and functional decline,⁵³ and being discharged home,⁵⁴ future research should incorporate standardized severity measures, and evaluate whether anticholinergics influence the depth or persistence of delirium symptoms.

There are several limitations to this study. First, the studies included in this review used retrospective cohort designs or cross-sectional analyses, which limit the ability to infer causality. Although many of the studies controlled for potential confounders, such as age, comorbidities, and polypharmacy, there remains the possibility of residual confounding. For example, patients taking anticholinergic medications may have underlying conditions (e.g., dementia, urinary incontinence) that independently increase their risk for delirium. While the studies tried to adjust for such factors, the observational nature of most studies precludes definitive conclusions about the causative role of anticholinergic burden in the development of delirium. Finally, the potential for publication bias also exists, as studies with

null findings may be less likely to be published and included in the review. Other than the variability in measurement of anticholinergic burden, heterogeneity in the study designs, populations, and methodologies poses a significant challenge for drawing definitive conclusions. Studies varied in terms of the populations studied (e.g., general hospital populations, patients undergoing surgery, cancer patients, and dementia patients) and settings (hospital, nursing home, hospice). Furthermore, differences in the tools, employed to assess delirium (e.g., CAM, DSM criteria, ICD codes) may contribute to the inconsistent findings across studies. Lastly, delirium itself is a complex syndrome with the potential to include multiple neurobiological mechanisms.⁹ While a disruption of cholinergic function can be sufficient to trigger delirium in some, this work does not clarify whether anticholinergic medications are sufficient to result in delirium or serve to increase vulnerability for a different mechanism to result in delirium.

This review has several strengths, including a comprehensive search strategy across multiple databases and the inclusion of a wide range of study designs and populations. By focusing specifically on outpatient and nursing home anticholinergic exposure, this review addresses a gap in the literature, as most prior studies have concentrated on anti-

cholinergic use during hospital stays or have not clearly described time of anticholinergic exposure measurement. For example, Vondeling et al. (2020)²⁷ in ICU patients reported a significantly higher risk of delirium in patients with outpatient prehospital ADS scores ≥ 2 , whereas in a previous study of a similar population Wolters et al. (2015)⁵⁵ the ADS scale of inpatient medicines was not associated with delirium at any level.

CONCLUSION

In conclusion, while this review supports an association between elevated anticholinergic burden and delirium, variability in measurement methods, limited longitudinal data, and a focus predominantly on incidence and prevalence rather than severity or duration restricts the generalizability and clinical applicability of the findings. Addressing these gaps through standardized methodologies, comprehensive exposure assessments, and prospective studies will be critical to understanding the true impact of anticholinergic burden on delirium and informing evidence-based interventions.

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REFERENCES

1. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers*. 2020;6(1):1-26. doi:[10.1038/s41572-020-00223-4](https://doi.org/10.1038/s41572-020-00223-4)
2. Witlox J, Eurelings LSM, de Jonghe JFM, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443-451. doi:[10.1001/jama.2010.1013](https://doi.org/10.1001/jama.2010.1013)
3. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-Year Health Care Costs Associated With Delirium in the Elderly Population. *Archives of Internal Medicine*. 2008;168(1):27-32. doi:[10.1001/archinternmed.2007.4](https://doi.org/10.1001/archinternmed.2007.4)
4. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-922. doi:[10.1016/S0140-6736\(13\)60688-1](https://doi.org/10.1016/S0140-6736(13)60688-1)
5. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-26. doi:[10.1097/00000542-200601000-00005](https://doi.org/10.1097/00000542-200601000-00005)
6. Morris JC. Neurodegenerative Disorders of Aging: The Down Side of Rising Longevity. *Mo Med*. 2013;110(5):393-394.
7. Reynish EL, Hapca SM, De Souza N, Cvorov V, Donnan PT, Guthrie B. Epidemiology and outcomes of people with dementia, delirium, and unspecified cognitive impairment in the general hospital: prospective cohort study of 10,014 admissions. *BMC Med*. 2017;15:140. doi:[10.1186/s12916-017-0899-0](https://doi.org/10.1186/s12916-017-0899-0)
8. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age and Ageing*. 2011;40(1):23-29. doi:[10.1093/ageing/afq140](https://doi.org/10.1093/ageing/afq140)
9. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International Journal of Geriatric Psychiatry*. 2018;33(11):1428-1457. doi:[10.1002/gps.4823](https://doi.org/10.1002/gps.4823)
10. Ghossein N, Kang M, Lakhkar AD. Anticholinergic Medications. In: *StatPearls*. StatPearls Publishing; 2021. Accessed December 12, 2021. <http://www.ncbi.nlm.nih.gov/books/NBK555893/>
11. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clinical interventions in aging*. 2009;4:225-233.
12. Risacher SL, McDonald BC, Tallman EF, et al. Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. *JAMA Neurol*. 2016;73(6):721-732. doi:[10.1001/jamaneurol.2016.0580](https://doi.org/10.1001/jamaneurol.2016.0580)
13. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr*. 2015;15(1):31. doi:[10.1186/s12877-015-0029-9](https://doi.org/10.1186/s12877-015-0029-9)
14. Pasina L, Djade CD, Lucca U, et al. Association of anticholinergic burden with cognitive and functional status in a cohort of hospitalized elderly: comparison of the anticholinergic cognitive burden scale and anticholinergic risk scale: results from the REPOSI study. *Drugs Aging*. 2013;30(2):103-112. doi:[10.1007/s40266-012-0044-x](https://doi.org/10.1007/s40266-012-0044-x)
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:[10.1136/bmj.n71](https://doi.org/10.1136/bmj.n71)
16. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. <http://www.covidence.org>
17. Egberts A, Moreno-Gonzalez R, Alan H, Ziere G, Mattace-Raso FUS. Anticholinergic Drug Burden and Delirium: A Systematic Review. *Journal of the American Medical Directors Association*. 2021;22(1):65-73.e4. doi:[10.1016/j.jamda.2020.04.019](https://doi.org/10.1016/j.jamda.2020.04.019)
18. Ottawa Hospital Research Institute. Accessed April 12, 2024. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
19. Moskalewicz A, Oremus M. No clear choice between Newcastle–Ottawa Scale and Appraisal Tool for Cross-Sectional Studies to assess methodological quality in cross-sectional studies of health-related quality of life and breast cancer. *Journal of Clinical Epidemiology*. 2020;120:94-103. doi:[10.1016/j.jclinepi.2019.12.013](https://doi.org/10.1016/j.jclinepi.2019.12.013)
20. Duprey MS, Devlin JW, Griffith JL, et al. Association Between Perioperative Medication Use and Postoperative Delirium and Cognition in Older Adults Undergoing Elective Noncardiac Surgery. *Anesth Analg*. 2022;134(6):1154-1163. doi:[10.1213/ANE.0000000000005959](https://doi.org/10.1213/ANE.0000000000005959)

21. Ferré F, Piel-Julian ML, Tincres F, et al. A High Postoperative Atropinic Burden is Associated with Postoperative Delirium in Elderly Patients with Hip Fracture: Results of the Prospective, Observational, ATROPAGE Trial. *Clin Interv Aging*. 2022;17:1931-1938. doi:[10.2147/CIA.S372400](https://doi.org/10.2147/CIA.S372400)
22. Heinrich M, Nottbrock A, Borchers F, et al. Preoperative medication use and development of postoperative delirium and cognitive dysfunction. *Clin Transl Sci*. 2021;14(5):1830-1840. doi:[10.1111/cts.13031](https://doi.org/10.1111/cts.13031)
23. Herrmann ML, Boden C, Maurer C, et al. Anticholinergic Drug Exposure Increases the Risk of Delirium in Older Patients Undergoing Elective Surgery. *Frontiers in Medicine*. 2022;9. doi:[10.3389/fmed.2022.871229](https://doi.org/10.3389/fmed.2022.871229)
24. Landi F, Dell'Aquila G, Collamati A, et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. *J Am Med Dir Assoc*. 2014;15(11):825-829. doi:[10.1016/j.jamda.2014.08.002](https://doi.org/10.1016/j.jamda.2014.08.002)
25. Naja M, Zmudka J, Hannat S, Liabeuf S, Serot JM, Jouanny P. In geriatric patients, delirium symptoms are related to the anticholinergic burden. *Geriatr Gerontol Int*. 2015;16(4):424-431. doi:[10.1111/ggi.12485](https://doi.org/10.1111/ggi.12485)
26. Rigor J, Rueff Rato I, Ferreira PM, et al. Prehospital Anticholinergic Burden Is Associated With Delirium but Not With Mortality in a Population of Acutely Ill Medical Patients. *Journal of the American Medical Directors Association*. 2020;21(4):481-485. doi:[10.1016/j.jamda.2019.12.018](https://doi.org/10.1016/j.jamda.2019.12.018)
27. Vondeling AM, Knol W, Egberts TCG, Slooter AJC. Anticholinergic drug exposure at intensive care unit admission affects the occurrence of delirium. A prospective cohort study. *European Journal of Internal Medicine*. 2020;78:121-126. doi:[10.1016/j.ejim.2020.04.062](https://doi.org/10.1016/j.ejim.2020.04.062)
28. Ah YM, Suh Y, Jun K, Hwang S, Lee JY. Effect of anticholinergic burden on treatment modification, delirium and mortality in newly diagnosed dementia patients starting a cholinesterase inhibitor: A population-based study. *Basic Clin Pharmacol Toxicol*. 2019;124(6):741-748. doi:[10.1111/bcpt.13184](https://doi.org/10.1111/bcpt.13184)
29. Huang KH, Chan YF, Shih HC, Lee CY. Relationship between potentially inappropriate anticholinergic drugs (PIADs) and adverse outcomes among elderly patients in Taiwan. *Journal of Food and Drug Analysis*. 2012;20(4):930-937. doi:[10.6227/jfda.2012200423](https://doi.org/10.6227/jfda.2012200423)
30. Hwang S, Jun K, Ah YM, Han E, Chung JE, Lee JY. Impact of anticholinergic burden on emergency department visits among older adults in Korea: A national population cohort study. *Arch Gerontol Geriatr*. 2019;85:103912. doi:[10.1016/j.archger.2019.103912](https://doi.org/10.1016/j.archger.2019.103912)
31. Lee JH, Lim J, Han SJ, et al. Clinical outcomes associated with anticholinergic burden in older hospitalized patients with advanced cancer: a single-center database study. *Supportive Care in Cancer*. 2021;29(8):4607-4614. doi:[10.1007/s00520-021-06008-z](https://doi.org/10.1007/s00520-021-06008-z)
32. Mueller A, Spies CD, Eckardt R, et al. Anticholinergic burden of long-term medication is an independent risk factor for the development of postoperative delirium: A clinical trial. *J Clin Anesth*. 2020;61:109632. doi:[10.1016/j.jclinane.2019.109632](https://doi.org/10.1016/j.jclinane.2019.109632)
33. Rawle MJ, McCue L, Sampson EL, Davis D, Vickerstaff V. Anticholinergic Burden Does Not Influence Delirium Subtype or the Delirium-Mortality Association in Hospitalized Older Adults: Results from a Prospective Cohort Study. *Drugs and Aging*. 2021;38(3):233-242. doi:[10.1007/s40266-020-00827-1](https://doi.org/10.1007/s40266-020-00827-1)
34. Egberts A, van der Craats ST, van Wijk MD, Alkilabe S, van den Bemt PMLA, Mattace-Raso FUS. Anticholinergic drug exposure is associated with delirium and postdischarge institutionalization in acutely ill hospitalized older patients. *Pharmacol Res Perspect*. 2017;5(3):e00310. doi:[10.1002/prp2.310](https://doi.org/10.1002/prp2.310)
35. Oudewortel L, Roest HG van der, Onder G, et al. The Association of Anticholinergic Drugs and Delirium in Nursing Home Patients With Dementia: Results From the SHELTER Study. *Journal of the American Medical Directors Association*. 2021;22(10):2087-2092. doi:[10.1016/j.jamda.2021.05.039](https://doi.org/10.1016/j.jamda.2021.05.039)
36. Pasina L, Colzani L, Cortesi L, et al. Relation Between Delirium and Anticholinergic Drug Burden in a Cohort of Hospitalized Older Patients: An Observational Study. *Drugs Aging*. 2019;36(1):85-91. doi:[10.1007/s40266-018-0612-9](https://doi.org/10.1007/s40266-018-0612-9)
37. Pasina L, Rizzi B, Nobili A, Recchia A. Anticholinergic load and delirium in end-of-life patients. *Eur J Clin Pharmacol*. 2021;77(9):1419-1424. doi:[10.1007/s00228-021-03125-w](https://doi.org/10.1007/s00228-021-03125-w)
38. Wahab IA, Akbar B, Zainal ZA, Che Pa MF, Naina B. The Use of Medicines with Anti-cholinergic Properties and Their Health Impacts among Hospitalised Malaysian Geriatric Patients. *Malays J Med Sci*. 2019;26(2):77-87. doi:[10.21315/mjms2019.26.2.9](https://doi.org/10.21315/mjms2019.26.2.9)

39. Caeiro L, Ferro JM, Claro MI, Coelho J, Albuquerque R, Figueira ML. Delirium in acute stroke: a preliminary study of the role of anticholinergic medications. *Eur J Neurol*. 2004;11(10):699-704. doi:[10.1111/j.1468-1331.2004.00897.x](https://doi.org/10.1111/j.1468-1331.2004.00897.x)
40. Ceppi MG, Rauch MS, Spöndlin J, Gantenbein AR, Meier CR, Sándor PS. Potential Risk Factors for, and Clinical Implications of, Delirium during Inpatient Rehabilitation: A Matched Case-Control Study. *J Am Med Dir Assoc*. 2023;24(4):519-525.e6. doi:[10.1016/j.jamda.2023.01.012](https://doi.org/10.1016/j.jamda.2023.01.012)
41. Moorey HC, Zaidman S, Jackson TA. Delirium is not associated with anticholinergic burden or polypharmacy in older patients on admission to an acute hospital: an observational case control study. *BMC Geriatr*. 2016;16:162. doi:[10.1186/s12877-016-0336-9](https://doi.org/10.1186/s12877-016-0336-9)
42. Hwang S, Chung JE, Jun K, Ah YM, Kim KI, Lee JY. Comparative associations between anticholinergic burden and emergency department visits for anticholinergic adverse events in older Korean adults: a nested case-control study using national claims data for validation of a novel country-specific scale. *BMC Pharmacology and Toxicology*. 2021;22(1). doi:[10.1186/s40360-020-00467-6](https://doi.org/10.1186/s40360-020-00467-6)
43. Tillemans MPH, Butterhoff-Terlingen MH, Stuffken R, Vreeswijk R, Egberts TCG, Kalisvaart KJ. The effect of the anticholinergic burden on duration and severity of delirium in older hip-surgery patients with and without haloperidol prophylaxis: A post hoc analysis. *Brain Behav*. 2021;11(12):e2404. doi:[10.1002/brb3.2404](https://doi.org/10.1002/brb3.2404)
44. Lozano-Ortega G, Szabo SM, Cheung A, et al. An Evaluation of Longitudinal Measures of Anticholinergic Exposure for Application in Retrospective Administrative Data Analyses. *Advances in Therapy*. 2019;36(9):2247-2259. doi:[10.1007/s12325-019-01035-z](https://doi.org/10.1007/s12325-019-01035-z)
45. Ah YM, Suh Y, Jun K, Hwang S, Lee JY. Effect of anticholinergic burden on treatment modification, delirium and mortality in newly diagnosed dementia patients starting a cholinesterase inhibitor: A population-based study. *Basic Clin Pharmacol Toxicol*. 2019;124(6):741-748. doi:[10.1111/bcpt.13184](https://doi.org/10.1111/bcpt.13184)
46. Coupland CAC, Hill T, Denning T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia. *JAMA Intern Med*. 2019;179(8):1084-1093. doi:[10.1001/jamainternmed.2019.0677](https://doi.org/10.1001/jamainternmed.2019.0677)
47. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol*. 2013;69(7):1485-1496. doi:[10.1007/s00228-013-1499-3](https://doi.org/10.1007/s00228-013-1499-3)
48. Laroche ML, Sirois C, Reeve E, Gnjidic D, Morin L. Pharmacoepidemiology in older people: Purposes and future directions. *Therapie*. 2019;74(2):325-332. doi:[10.1016/j.therap.2018.10.006](https://doi.org/10.1016/j.therap.2018.10.006)
49. Gray SL, Anderson ML, Dublin S, et al. Cumulative Use of Strong Anticholinergic Medications and Incident Dementia. *JAMA Intern Med*. 2015;175(3):401-407. doi:[10.1001/jamainternmed.2014.7663](https://doi.org/10.1001/jamainternmed.2014.7663)
50. Rose L, Burry L, Agar M, et al. A Core Outcome Set for Research Evaluating Interventions to Prevent and/or Treat Delirium in Critically Ill Adults: An International Consensus Study (Del-CORs). *Crit Care Med*. 2021;49(9):1535-1546. doi:[10.1097/CCM.0000000000005028](https://doi.org/10.1097/CCM.0000000000005028)
51. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med*. 2001;161(8):1099-1105. doi:[10.1001/archinte.161.8.1099](https://doi.org/10.1001/archinte.161.8.1099)
52. Lindroth H, Khan BA, Carpenter JS, et al. Delirium Severity Trajectories and Outcomes in ICU Patients. Defining a Dynamic Symptom Phenotype. *Annals ATS*. 2020;17(9):1094-1103. doi:[10.1513/AnnalsATS.201910-764OC](https://doi.org/10.1513/AnnalsATS.201910-764OC)
53. Richardson S, Murray J, Davis D, et al. Delirium and Delirium Severity Predict the Trajectory of the Hierarchical Assessment of Balance and Mobility in Hospitalized Older People: Findings From the DECIDE Study. *The Journals of Gerontology: Series A*. 2022;77(3):531-535. doi:[10.1093/gerona/glab081](https://doi.org/10.1093/gerona/glab081)
54. Rosgen BK, Krewulak KD, Stelfox HT, Ely EW, Davidson JE, Fiest KM. The association of delirium severity with patient and health system outcomes in hospitalised patients: a systematic review. *Age Ageing*. 2020;49(4):549-557. doi:[10.1093/ageing/afaa053](https://doi.org/10.1093/ageing/afaa053)
55. Wolters AE, Zaal IJ, Veldhuijzen DS, et al. Anticholinergic Medication Use and Transition to Delirium in Critically Ill Patients: A Prospective Cohort Study. *Crit Care Med*. 2015;43(9):1846-1852. doi:[10.1097/CCM.0000000000001094](https://doi.org/10.1097/CCM.0000000000001094)