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REVIEW

Association between anticholinergic (atropinic) drug exposure and cognitive function in longitudinal studies among individuals over 50 years old: a systematic review

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Abstract

Purpose With increasing age, adults are often exposed to anticholinergic drugs and are prone to potential adverse drug reaction, among which cognitive impairment. If the short-term cognitive effects of anticholinergic drugs are well established, their long-term cognitive effects have less been studied.

Objective To provide a systematic review of longitudinal studies which assessed the effect of anticholinergic exposure on cognition in individuals over 50 years.

Materials We searched the MEDLINE database for studies with a minimal 6-month follow-up, assessing anticholinergic exposure through a biological measure or a clinical list and reporting at least one cognitive outcome. We used the modified Newcastle-Ottawa scale and additional criteria regarding the anticholinergic exposure to assess studies' methodological quality. Given the heterogeneity of the studies, we performed a systematic review.

Results Among the 1574 references retrieved, 25 studies were included. Anticholinergic medications were mostly defined through the Anticholinergic Cognitive Burden Scale ($n = 14/25$). Six studies evaluated baseline drug collection, 14 used longitudinal aggregated measure, and 5 multiple drug exposure measures over time. Seventeen studies assessed anticholinergic burden. Cognitive function was assessed by mild cognitive impairment/dementia incidence ($n = 15$) or neuropsychological tests ($n = 14$). Most studies were of poor quality and retrieved discordant results. However, studies with good quality ($n = 4$) suggested a relationship between anticholinergic drug exposure and/or burden and cognitive function.

Conclusion Our review suggests a deleterious effect of anticholinergic exposure on mid/long-term cognitive function but should be confirmed in studies with improved methodology. Meanwhile, prescription of anticholinergic drugs should remain cautious.

Keywords Anticholinergic drug exposure · Anticholinergic burden · Cognitive decline · Longitudinal study · Systematic review

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Introduction

Anticholinergic drugs are widely prescribed for common symptoms and diseases such as bradycardia, motion sickness, overactive bladder, anxiety. Despite their adverse drug reactions (sleepiness, constipation, mydriasis, delirium, cognitive effect) [1], they are often increasingly prescribed with age, with estimated prevalences of anticholinergic exposition ranging from 7.5 to 80% [2–6]. Older adults are particularly vulnerable to adverse drug reactions because of renal and hepatic function alterations [7–9]. Moreover, the cognitive change occurring during aging may be impacted by anticholinergic exposure; given the role of the cholinergic mediator on memory in the hippocampus system. The middle-aged and older adult population is frequently concerned by memory complaints and worried about it [10, 11]. Therefore, the use of anticholinergic drugs in middle-aged and older adults raises some concern.

Biological methods [12] and clinical scales [13–21] have been developed to measure drugs' anticholinergic activity and therefore patient's anticholinergic exposure. Generally, these methods score anticholinergic drug activity from 0 (meaning no anticholinergic activity) to a score ranging from 1 to 4 with increasing anticholinergic activity. Consequently, there is considerable variation between studies in (i) the drugs considered as having anticholinergic activity, (ii) the anticholinergic score affected to the same drug. As no consensus is validated concerning the method used, variability is expected in (iii) the method used to assess concomitant anticholinergic exposure, which is called the anticholinergic burden, and (iv) the method used to assess longitudinal anticholinergic exposure.

Several cross-sectional studies have assessed the association between anticholinergic exposure and cognitive outcomes [6, 22–29], taking into account, or not, anticholinergic burden. They suggest an association between anticholinergic exposure and cognitive impairment such as delirium or confusion [30]. Meanwhile, the long-term cognitive effects of anticholinergic exposure have scarcely been assessed and are of great interest since anticholinergic drugs may be used over long periods of time in some indications.

Therefore, the main aim of this review was to assess the longitudinal effects of anticholinergic exposure on cognitive function among people over 50 years old. Furthermore, we aimed to describe heterogeneity between studies and if the methods used to measure anticholinergic exposure affected the results.

Methods

Eligibility criteria

English articles of minimal of 6-month follow-up observational studies (cohort or nested case-control) conducted on subjects aged 50 years old and over, evaluating the effect of anticholinergic exposure assessed through an anticholinergic drug scale/list on any cognitive outcome (cognitive function, MCI, dementia) were included in our study (see appendix 1).

We excluded studies focusing on subjects with neurodegenerative diseases and/or psychiatric disorders susceptible to affect cognitive function, dealing with cognitive disorders limited to delirium or restricted to evaluate a specific drug class (e.g., drugs for overactive bladder, antidepressants).

Search strategy

Studies were traced through the MEDLINE database to 7 May 2018. The relevant keywords include dementia, cognition, Alzheimer, cholinergic antagonist, antimuscarinic, or atropinic (see appendix 2).

Data extraction

Eligibility of each study was assessed by one epidemiologist reviewer (LA). Study selection was based on title, abstract and full text, if necessary. Publications which possibly met inclusion criteria were collected by the main reviewer. Any doubt was resolved by consensus with another independent reviewer (AG). Besides, the bibliography of the selected articles was checked to identify any potential eligible studies not already retrieved.

Data collection and quality criteria assessment

Characteristics of the included studies, cognitive measures, anticholinergic drug exposure as well as longitudinal anticholinergic measure and anticholinergic burden were described. Initially, study quality was assessed through the modified Newcastle-Ottawa scale for cohorts or case-control studies (eight items evaluated) [31]. But, as this scale presented a single item related to drug exposure, we evaluated supplementary criteria (independently of the modified Newcastle-Ottawa scale for cohorts or case-control studies items) regarding population setting, length of follow-up (> 4 year), cognitive outcomes assessed (MCI or dementia vs cognitive scores), anticholinergic exposure and scales and confounders management; considering the highest quality scores to studies which took into account the six criteria (see appendix 3).

We separately described the retrieved studies with the highest methodological quality (i.e., studies meeting these six criteria).

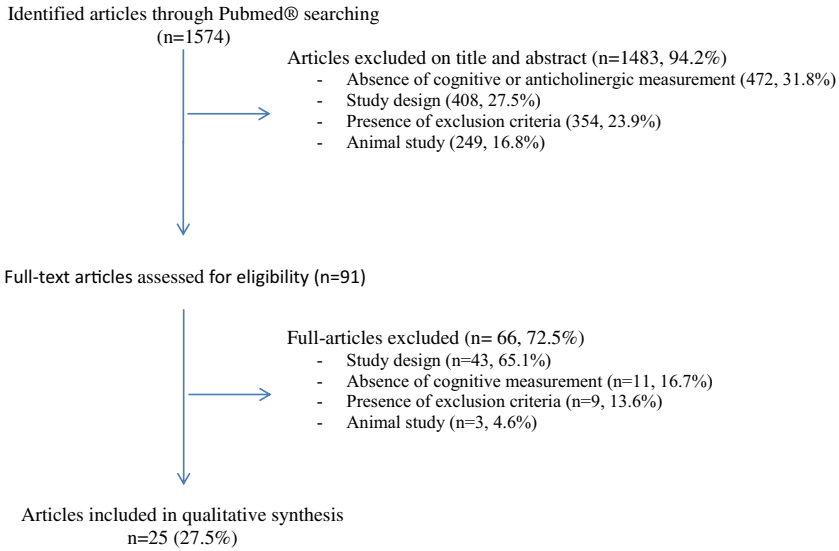

Fig. 1 Study selection flow-chart

Results

Characteristics of studies

Design and objectives

Among 1574 citations retrieved, 91 full texts were assessed for eligibility and among them 25 were included in our review (Fig. 1). Eighteen included articles used prospective data [18, 21, 32–47] from cohorts, and the 7 remaining were retrospective cohorts or nested case-control studies [48–54].

For 21 studies [18, 21, 32–39, 42–44, 46–50, 52–54], the main objective was to evaluate the effect of anticholinergic exposure on cognitive functions and 3 of them used a new-user design.

Setting and follow-up

Fourteen studies were conducted in Northern America [18, 32, 34, 36, 39–41, 44, 46, 47, 49–51, 54], 7 in Europe [21, 33, 35, 38, 43, 45, 48], 2 in Australia [37, 42], and 2 in Asia [52, 53] (see appendix 4). Most of the studies included participants during the 2000s [18, 32–34, 37, 38, 41–45, 48, 49, 51–54], and 2 studies during the early 2010s [34, 53]. Two studies were restricted to women [40, 41], 4 to men [18, 37, 51, 53], and 6 focused on other specific populations such as older Catholics nuns, priests or lay brothers [46], African-Americans [32], indigent, uninsured or underinsured US people [49, 50, 54], or from outpatient incontinence clinics [39]. The remaining studies ($n = 13$) included community-dwelling middle-aged or older adults.

All articles assessed adults over 60 or 65 years old, except 2 which included middle-aged adults (≤ 65 years) [34, 42]. Sample sizes ranged from 102 [39] to 324,703 subjects [48]. Follow-up varied from 6 months [53] to more than 10 years [36, 46].

Only 4 studies presented the highest quality assessment (meeting all 6 criteria listed above). They included North American [34, 36], Australian [42], or European participants [38] free of dementia in prospective cohorts conducted between 1994 and 2013. Among them, 2 studies [34, 42] enrolled older adults, whereas the 2 others included 50- to 65-year-old adults.

Drugs assessment

Drug exposure was collected during face-to-face interviews with a trained staff ($n = 16$), through a dispensing drug database ($n = 5$) [36, 49, 50, 52, 54] and through medical records [48, 55]. No details were given for the remaining two [51, 53]. The exposure period was the period concomitant to the visits or covered a short period before the visit (maximal 30 days prior to the assessment). In studies based on medical records or dispensing databases, the exposure period varied between 1 and 20 years before the cognitive outcome measurement [36, 48–50, 52, 54, 55].

In face to face interviews, drug use was primarily recorded by checking the bottles, containers, or medical prescriptions ($n = 9$) [21, 32, 34, 37, 40, 41, 43, 45, 47].

An exposure confirmation was required in case of unreliable reports for the self-reported drugs collection [21, 33, 35, 39, 43, 45]; 4 used proxies ((i) close informant, (ii) medical record, or (iii) pharmacist confirmation), and 2 checked bottles or containers.

Anticholinergic drugs definition

Twenty of 25 studies used an anticholinergic drug list (validated in a clinical setting) (see appendix 4), among which 3

studies compared several scales [39, 48, 52]. Twelve different anticholinergic lists were used comprising 7 validated lists [13–16, 18, 19, 21]; the anticholinergic cognitive burden (ACB) [15] was the most commonly used ($n = 14$), followed by the Drug Burden Index (DBI) [19] ($n = 3$), the Anticholinergic Drug Scale (ADS) [13] ($n = 2$), the Anticholinergic Risk Scale (ARS) [14] ($n = 2$), the Ancelin list [21] ($n = 2$), the clinician-rated anticholinergic score [18] ($n = 1$), and the chew list [16] ($n = 1$). The five remaining lists of anticholinergic drugs were constructed by the authors using various methods such as pharmacological reference [33], experts consensus [36], or pre-existing list of anticholinergic drugs non-validated in a clinical setting [43].

Anticholinergic drugs exposure measure

Six studies assessed anticholinergic exposure restricted to baseline measurements, whereas 15 used a longitudinal approach. The four remaining studies used both methods.

Unique measure of anticholinergic exposure (see Tables 1 and 2) Twenty studies assessed a unique measure of anticholinergic exposure through two different ways. Six studies [35, 41, 44, 45, 47, 53] exclusively studied baseline exposure. Conversely, 14 studies [21, 32–34, 36, 38, 39, 43, 46, 48, 49, 51, 54, 55] used a single aggregated measure summarizing the whole follow-up period. Studies identified three or four different patterns of exposure over time, considering or not the anticholinergic burden: anticholinergic prevalent users [46], intermittent users [32], continuous users [21, 33, 42, 43], discontinuous users [33, 42, 51], incident users [42, 46, 48], and never users. In other studies, the categorization depended on maximal anticholinergic score and duration [54] or the total sum of anticholinergic scores [52].

Multiple measures of anticholinergic exposure (see Tables 1 and 2) Five studies [37, 40, 42, 50, 52] used multiple anticholinergic measures collected during the follow-up (drug exposure at each visit). Low et al. [42] compared anticholinergic users and non-users at each visit (representing 2 evaluations over 4 years), whereas two others took into account the dose and the anticholinergic burden over time [50, 52], one other assessed the sum of anticholinergic scores [40], and the last one used the dose and the duration at each visit [37].

Anticholinergic burden measurement (i.e., method used to assess concomitant anticholinergic exposure) (see Table 2)

Seventeen studies evaluated the anticholinergic burden. Four studies evaluated the anticholinergic burden during baseline visit [32, 35, 41, 44], one used the number of drugs according to the maximal score [32], three used the drugs' maximal score [32, 35, 44] or the sum of all anticholinergic scores [32, 35, 41].

The other ones used a longitudinal measure of the anticholinergic burden. First, the measure could be used by a unique measure defined by the maximal score used during the study [21, 34] as well as the anticholinergic score change [39] or by the sum of anticholinergic score over time [34]. To finish, the anticholinergic burden could be evaluated by the sum of anticholinergic drugs at different visits [38, 42, 50, 52].

New-user design

Only three studies [42, 46, 48] used a new user design and among them, only one [48] evaluated anticholinergic burden.

Cognition assessment (see appendix 4)

Cognitive assessment was mainly prospectively collected during each follow-up visit, ranging from 1 to more than 10 visits (2 studies [49, 54] underwent a single assessment visit at 12 months).

Cognitive function was assessed by several methods, and multiple outcomes could be reported in a single study (Table 1). These methods were the following:

- A single neuropsychological test ($n = 6$):
  - Global cognition measured using the MMSE ($n = 3$) [35, 37, 53] the Community Instrument for Dementia ($n = 1$) [54] or the Saint Louis University Mental Status ($n = 1$) [51],
  - Memory using the Hopkins Verbal recall test ($n = 1$) [18].
- A battery of neuropsychological tests, each of them being analyzed separately ($n = 7$) [21, 33, 39, 41–43, 47]. These tests concerned several cognitive function dimensions, such as attention, executive function, memory, fluency, and visuo-spatial ability.
- An aggregation of several neuropsychological tests summarized in a single measure, evaluating global cognition or specific function such as episodic memory function ($n = 1$) [46].
- Mild cognitive impairment (MCI) incidence ($n = 9$) [21, 32, 34, 40, 42, 44, 49, 50, 54] assessed from 1 to 10 years after baseline visit. MCI was defined using various methods: diagnosis and statistical manual IV, modified Peterson Criteria, Stockholm group consensus, or cognitive impairment no dementia.
- Incident dementia or Alzheimer's disease (AD) incidence ($n = 13$) [21, 32–34, 36, 38, 40, 44, 49, 52, 54, 56]. Dementia or AD was defined using a standardized

Table 1 Association with anticholinergic drug use and cognitive outcome, without any consideration for the anticholinergic burden ($n = 14$ studies)

Anticholinergic categories	Cognitive outcome							
	Memory[a]	Fluency[b]	Visuo-spatial abilities[c]	Attention and executive functions[d]	Global cognition[e]	Incidence of MCI/Cognitive Impairment	Incidence of dementia/ Alzheimer dementia	Incidence of MCI/Cognitive Impairment / dementia/ Alzheimer dementia
Baseline anticholinergic exposure. Baseline collection of drugs assessed with longitudinal cognitive outcome								
Non-anticholinergic vs anticholinergic users								
Any anticholinergic drugs used	Discordant (Bottiggi) Significant for men and non-significant for women (Carrière) Non-significant (Shah)	Significant for women and non-significant for men (Carrière)		Discordant (Bottiggi) Non-significant (Carrière)	Non-significant (Bottiggi) Non-significant (Carrière) Non-significant (Shah) Significant (Wu)	Significant (Ritchie)	Non-significant (Campbell 2010)	Non-significant (Campbell 2010)
Number of any anticholinergic drugs used					Non-significant (Cruz-Oliver)			
Longitudinal anticholinergic exposure. Longitudinal collection of drugs assessed with longitudinal cognitive outcome								
Anticholinergic users vs non-anticholinergic users								
Any anticholinergic drugs used	Non-significant (Low) Non-significant (Papenberg)	Non-significant (Papenberg)		Discordant (Low) Non-significant (Papenberg)	Non-significant (Low) Non-significant (Papenberg)	Non-significant (Low)		Significant (Jessen)
Prevalent users	Non-significant (Shah)				Non-significant (Shah)			
New users	Non-significant (Low) Significant (Shah)			Discordant (Low)	Non-significant (Low) Significant (Shah)	Non-significant (Low)		
Continuous users: anticholinergic users for all waves or at baseline and another visit	Discordant (Ancelin) Significant for men and non-significant for women (Carrière). Non-significant (Low)Discordant (Papenberg)	Significant (Ancelin) Significant for women and Non-significant for men (Carrière). Non-significant (Papenberg)	Significant (Ancelin)	Significant (Ancelin) discordant for men and non-significant for women (Carrière). Non-significant (Low)Non-significant (Papenberg)	Discordant (Carrière) Non-significant (Low) Non-significant (Papenberg)	Significant (Ancelin) Non-significant (Low)	Non-significant (Ancelin) Discordant (Carrière)	
Discontinuous users: exposure at baseline visit only	Non-significant (Carrière) Non-significant (Low)	Non-significant (Carrière)		Non-significant (Carrière) Discordant (Low)	Non-significant (Carrière) Significant (Cruz-Oliver) Non-significant (Low)	Non-significant (Low)		

Table 1 (continued)

Anticholinergic categories	Cognitive outcome							
	Memory[a]	Fluency[b]	Visuo-spatial abilities[c]	Attention and executive functions[d]	Global cognition[e]	Incidence of MCI/Cognitive Impairment	Incidence of dementia/ Alzheimer dementia	Incidence of MCI/Cognitive Impairment / dementia/ Alzheimer dementia
Total standard daily dose[f] (duration and dosage)								
Score > 0 and ≤ 0.5							Significant (Hsu)	
Score >0.5 and ≤ 1							Significant (Hsu)	
Continuous daily dose (with duration)	Discordant (Kashyap)			Discordant (Kashyap)	Discordant (Jamsen) Non-significant (Kashyap)			

Abbreviation: *MCI* mild cognitive impairment; *Significant* significant association between cognition and anticholinergic exposure found for all analyses; *Discordant* significant association between cognition and anticholinergic exposure depended of cognition definition/anticholinergic exposure/statistical analyses/adjustment used; *Non-significant* no association between cognition and anticholinergic exposure found for all analyses; > superior to; ≤ inferior or equal to

[a] Memory function was tested by number of face recall, visuo-spatial span, narrative recall total, naming total recall, primary verbal memory, delayed free recall of name, implicit memory, total number of correct name face association, word list memory test total word correct, word list memory test recognition discriminability, word list memory test delayed recall, learning over trial, Benton Visual Retention Test, Hopkins Verbal Learning Test Revisited, Grober and Buschke test, Rey Osterrnieth Complex Figure Test Recall, California Verbal Learning Test-II Immediate Recall, backward digit span, immediate-delayed recall, digit backward modalities

[b] Fluency was tested by verbal fluency, object naming, Isaac Set Test, category/verbal/letter fluency

[c] Visuo-spatial abilities were analyzed by construction total

[d] Attention and executive functions were tested by Simple Reaction Time, attention, logical reasoning, Trail Making Test A or B, Stroop Test, Choice Reaction Time, two papers and pencil test, digit cancelation, pattern comparison, and Symbol Digit Modality Test

[e] Global cognition was analyzed by the Mini-Mental State Examination, The Saint Louis University Mental Status Examination, Mattis Dementia Rating Scale, Montreal Cognitive Assessment, z-score of neuropsychological tests, Community-Screening Instrument for Dementia, and the Six-Item Screener

[f] Standard daily dose = $\Sigma = D/(\delta + D)$ (D = total daily dose of drugs and δ the minimum efficacy daily dose)

Table 2 Association with anticholinergic burden and cognitive outcome, taking into account the anticholinergic burden (n = 17 studies)

Anticholinergic categories	Cognitive outcome							
	Memory[a]	Fluency[b]	Visuo-spatial abilities[c]	Attention and executive functions[d]	Global cognition[e]	Incidence of MCI/Cognitive Impairment	Incidence of dementia/Alzheimer dementia	Incidence of MCI/ cognitive impairment/ dementia/Alzheimer dementia
Baseline anticholinergic exposure. Baseline collection of drugs assessed with longitudinal cognitive outcome								
Non-anticholinergic vs anticholinergic users								
Number of anticholinergic drugs used with score = 1							Non-significant (Campbell 2010)	
Number of anticholinergic drugs used with score ≥ 2							Discordant (Campbell 2010)	
Maximal anticholinergic drug score								
Maximal score = 1					Non-significant (Fox)			
Maximal score ≥ 2					Significant (Fox)		Discordant (Campbell 2010)	
Categorical sum of anticholinergic drugs score					Non-significant (Fox)			
Continuous sum of anticholinergic drugs score	Discordant (Koyama 2014)	Discordant (Koyama 2014)		Non-significant (Koyama 2014)	Non-significant (Fox) Non-significant (Koyama 2014)		Non-significant (Campbell 2010)	
Non-users (score ≤ 1) vs anticholinergic users								Significant (Risacher)
Longitudinal anticholinergic exposure								
Non-anticholinergic vs anticholinergic users								
Any anticholinergic drugs used							Significant (Jessen)	
Maximal anticholinergic drug score							Maximal score = 1 significant (Jessen) Significant (Richardson)	Significant (Chuang)
Maximal score ≥ 2							Non-significant (Chuang)	
Maximal score = 2	Non-significant (Ancelin)	Non-significant (Ancelin)	Non-significant (Ancelin)	Non-significant (Ancelin)			Non-significant (Jessen) Significant (Richardson)	
Maximal score = 3	Non-significant (Ancelin)	Non-significant (Ancelin)	Non-significant (Ancelin)	Non-significant (Ancelin)			Significant (Jessen) Significant (Richardson)	
Maximal score = 4								Significant (Jessen)

Table 2 (continued)

Anticholinergic categories	Cognitive outcome							
	Memory[a]	Fluency[b]	Visuo-spatial abilities[c]	Attention and executive functions[d]	Global cognition[e]	Incidence of MCI/Cognitive Impairment	Incidence of dementia/Alzheimer dementia	Incidence of MCI/ cognitive impairment/ dementia/Alzheimer dementia
1 or 2 anticholinergic drugs used ≥ 90 consecutive days for a maximal score = 1					Non-significant (Cai)	Non-significant (Cai)	Non-significant (Cai)	
≥ 3 anticholinergic drugs used ≥ 90 consecutive days for a maximal score = 1					Non-significant (Cai)	Significant (Cai)	Non-significant (Cai)	
At least 1 anticholinergic drugs used ≥ 60 consecutive days for a maximal score ≥ 2					Significant (Cai)	Non-significant (Cai)	Non-significant (Cai)	
Categorical sum of anticholinergic drugs score (adjusted on the standardized daily dose)								Significant (Hsu)
Categorical standardized daily dose (dose, score and duration)								
Maximal score = 1								
Prevalent users								Significant (Richardson)
Incident users								Significant (Richardson)
Maximal score = 2								
Prevalent users								Discordant (Richardson)
Incident users								Significant (Richardson)
Maximal score = 3								
Prevalent users								Significant (Richardson)
Incident users								Significant (Richardson)
Score ≥ 2								Discordant (Gray)
Intermittent users for score ≥ 2								
At least one anticholinergic exposure during all the study but not for all waves or prevalent users but non-exposed during follow-up visits								Significant (Campbell 2010)
Continous users for score ≥ 2								
Anticholinergic users for all waves or at baseline and for another visit								Non-significant (Campbell 2010)

Table 2 (continued)

Anticholinergic categories	Cognitive outcome							
	Memory[a]	Fluency[b]	Visuo-spatial abilities[c]	Attention and executive functions[d]	Global cognition[e]	Incidence of MCI/Cognitive Impairment	Incidence of dementia/Alzheimer dementia	Incidence of MCI/ cognitive impairment/ dementia/Alzheimer dementia
Total standard daily dose of multiplied by score (score, duration, and dosage)							Non-significant (Campbell 2018)	
Total standard daily dose of multiplied by score ≥ 2 (duration and dosage)						Significant (Campbell 2018)		
Mean total daily anticholinergic multiplied by score (score and duration)	Discordant (Han)							Significant (Campbell 2016)
Mean sum of anticholinergic drugs score							Significant (Richardson)	Significant (Koyama 2013)
Mean sum of anticholinergic drugs score change								Significant (Koyama 2013)
Score change > 1	Discordant (Kashyap)			Non-significant (Kashyap)	Non-significant (Kashyap)			

Abbreviation: *MCI* mild cognitive impairment; *Significant* significant association between cognition and anticholinergic exposure found for all analyses; *Discordant* significant association between cognition and anticholinergic exposure depended of cognition definition/anticholinergic exposure/statistical analyses/adjustment used; *Non-significant* no association between cognition and anticholinergic exposure found for all analyses; > superior to; ≥ superior or equal to; ≤ *inferior or equal to; = equal to*

[a] Memory function was tested by number of face recall, visuo-spatial span, narrative recall total, naming total recall, primary verbal memory, delayed free recall of name, implicit memory, total number of correct name face association, word list memory test total word correct, word list memory test recognition discriminability, word list memory test delayed recall, learning over trial, Benton Visual Retention Test, Hopkins Verbal Learning Test Revisited, Grober and Buschke test, Rey Osterrnieth Complex Figure Test Recall, California Verbal Learning Test-II Immediate Recall, backward digit span, immediate-delayed recall, digit backward modalities

[b] Fluency was tested by verbal fluency total, Isaac Set Test, category/verbal/letter fluency

[c] Visuo-spatial abilities were analyzed by construction total

[d] Attention and executive functions were tested by Simple Reaction Time, attention, logical reasoning, Trail Making Test A or B, Stroop Test, Choice Reaction Time, two papers and pencil test, digit cancelation, pattern comparison, Symbol Digit Modality Test eGlobal cognition was analyzed by the Mini-Mental State Examination, The Saint Louis University Mental Status Examination, Mattis Dementia Rating Scale, Montreal Cognitive Assessment, *z* -score of neuropsychological tests, community-screening instrument for dementia, and the Six-Item Screener,

[f] Standard daily dose = $\Sigma = D/(\delta + D)$ (D = total daily dose of drugs and δ the minimum efficacy daily dose)

diagnosis, except for two studies which collected this information through medical records [52, 56].

Statistical analysis (see appendix 4)

Twenty-two studies considered categorical outcomes such as the incidence of dementia or cognitive impairment (determined by a cut-off on neuropsychological tests or by the comparison of quantiles), with 5 of them studying the time to event, using Cox proportional hazard models [33, 34, 36, 38, 44]. Conversely, eight studies considered continuous outcomes such as the cognitive score or the change in the cognitive score from baseline and four took into account repeated cognitive measures in mixed linear models [18, 42, 46, 47].

Concerning the adjustment performed, two studies reported crude associations (the relationship between anticholinergic use and cognitive function was not their main goal) [39, 45] and three adjusted on a limited set of covariates (mainly age, sex, and education level) [46, 47, 51]. Most of the studies also adjusted on comorbidities, physical conditions, Fried criteria [18, 21, 32–37, 40–44, 49, 53, 54], baseline cognitive level, apoE4 phenotype, and number of non-anticholinergic drugs. Lastly, five studies assessed different sets of covariates [33, 34, 49, 54, 56]. One study [52] considered comorbidities as time-varying covariables in analyses.

Baseline anticholinergic prevalence

Anticholinergic exposure prevalence at baseline varied, based on the study and anticholinergic scale used from 7.7 to 57.3%. The prevalence was lower in studies conducted among the community-dwelling population of priests, nuns, and lay brothers population (< 20%) and in male veterans (29.7% at baseline). The highest prevalence (57.3%) was found in the study conducted among 70-year-olds or more African-American (living at home or institutionalized in Indianapolis) included from Medicare and using the ACB list [32].

In these studies, anticholinergic exposure appeared as more frequent in women, in participants with lower education level, in subjects more depressed, more prone to polypharmacy and with more comorbidities.

Association between anticholinergic measure and cognition

The relationship between anticholinergic exposure and cognition is presented according to anticholinergic exposure measurement in Tables 1 and 2, the latter presenting the studies taking into account the anticholinergic burden.

Among studies which did not take into account the anticholinergic burden (Table 1, $n = 14$), all but two studies showed non-significant or both significant and non-significant associations between baseline use of any anticholinergic drug (compared to no use) and cognitive function.

Studies that considered a longitudinal anticholinergic measure over the follow-up also found non-significant, or both significant and non-significant associations between anticholinergic exposure and cognitive function. However, most studies that compared continuous users of anticholinergic drugs to non-users found significant associations between anticholinergic exposure and cognitive function.

Last, studies that compared new users of any anticholinergic drugs to non-users found discordant results, with significant results for the longest study [42, 46].

Among studies which assessed anticholinergic burden (Table 2, $n = 17$), discordant associations between baseline exposure and cognitive function were found [21, 39, 41, 42, 55].

When considering longitudinal exposure, results were mostly non-significant, whatever the cognitive outcomes. However, studies assessing high anticholinergic burden defined at baseline [35, 44] or exposed to high anticholinergic burden during follow-up [34, 52, 54] reported poorer cognitive function.

The single new user design evaluating this relationship [56] reported a significant association between new-anticholinergic users (for any new-anticholinergic exposure with a score > 1) and dementia (defined through medical records).

Lastly, among the studies with a methodological quality score ≥ 6 (see Table 2 and appendix 4), a relationship appeared between high anticholinergic burden and dementia or MCI incidence compared no anticholinergic use, except for middle-aged adults.

Discussion

This review retrieved 25 longitudinal studies assessing the relationship between anticholinergic exposure and cognitive function with various methods used to define cognition and anticholinergic exposure.

In most studies, cognitive function was assessed through neuropsychological tests, and ACB was the most commonly used scale. If these 25 studies brought about discordant results, the results yielded from the limited number of high-quality studies which could be considered as the most informative to answer our review question and suggest an effect of anticholinergic burden exposure on cognitive deterioration among older adults.

Further discussion is needed about the methodological reasons for such apparent discrepancy.

First, there were very few studies with a new-user design, and only one evaluated the anticholinergic burden

[48]. In this context, as we usually ignore if baseline anticholinergic users were prevalent or incident users, as well as the duration of anticholinergic used preceding baseline visit, a potential depletion of the susceptible phenomenon [57], as well as an indication bias, are highly probable. Moreover, baseline prevalent anticholinergic users were probably at lower risk of adverse effects than the overall user population. Further studies using new-user design are needed to control such bias.

Second, studies used different lists to define anticholinergic drugs, and a low to moderate concordance between ADS, ARS, and ACB has been reported [58, 59]. Consequently, the list choice impacts the anticholinergic burden, since the anticholinergic score of the same drug may vary according to the anticholinergic scale. Moreover, anticholinergic association on cognition could be limited by some non-anticholinergic users, exposed to non-anticholinergic drugs suspected to have cognitive effect (benzodiazepines). Among the available scales, the ACB scale [15] may be particularly relevant to address our question since it has been specifically constructed to identify anticholinergic drugs with effects on cognition. It has also been validated in a clinical setting. However, results using the ACB scale were also discordant.

Third, the use of the measure of a longitudinal anticholinergic exposure might also explain the divergent results observed in the studies. There is no consensual method to estimate longitudinal atropinic exposure, and the methods used varied, which could have impacted the results. However, few authors [50, 56] simultaneously used the anticholinergic score, the duration, and the drugs' dose as a longitudinal anticholinergic measure, and found a significant cognitive deterioration among users with the highest burden. Conducting studies comparing different anticholinergic longitudinal measures (such as duration, dose, and anticholinergic score) would be informative. The Muscarinic Acetylcholinergic Receptor Antagonist Exposure Scale has recently been published; it is taking into account the anticholinergic score as well as the dosage [60].

Fourth, the cognitive functions based on neuropsychological tests did not seem to be affected by anticholinergic exposure [21, 33, 41, 43]. Nonetheless, anticholinergic exposure seemed to be associated with a sub-dimension of memory, i.e., the episodic memory [43, 46], which may be explained by the role of the cholinergic system in episodic memory, particularly in the hippocampus system [61].

The definition of cognitive decline also could explain the discrepancy of our results. Indeed, cognitive decline measured by a change or by a cut-off based on cognitive tests showed discordant results. The clinical relevance of such tests might be questionable as they might be insufficiently sensitive to detect a cognitive decline among middle-aged or older adults. The measure of cognition using a composite score of different tests might be a solution, as it has been shown to be sensitive enough to evidence early cognitive change among cognitively intact older adults [62], as Shah et al. [46] shown, using a composite *z*-score outcome and reporting a significant cognitive deterioration among anticholinergic new-users compared to non-users.

Last, the age of the studied population as well as the window of exposure and the exposure duration might also explain these results. The two studies that followed middle-aged adults during 4 and 6 years [34, 42] did not find any association between anticholinergic exposure and dementia incidence. The lack of association reported among middle-aged adults may be driven by (i) a lower dementia risk in this population compared to older adults [63] and/or (ii) a lower anticholinergic cognitive sensibility effect [64].

Our review presents some weaknesses. First, the search strategy was limited to one database. However, relevant articles not indexed in MEDLINE may also have been included if they were cited by at least one selected article. Second, articles were included and reviewed by a single reviewer. However, in order to avoid potential selection bias, a second reviewer counterchecked any article when necessary. Third, there was no available validated scale to accurately assess the methodological quality of the studies based on our review question. Therefore, we focused on some criteria that we thought are particularly important in our review.

In light of our results, some recommendations can be made for future research. Clinical trials or cohorts are required to longitudinally evaluate the effect of anticholinergic burden on cognitive function. But, in order to extrapolate the results and limit a healthy user effect, community-dwelling middle-aged, or older adults who represent the target population should be included, especially participants at risk of cognitive impairment who are rarely included in research studies (e.g., participants with low educational level, low income, several comorbidities, nursing home residents [50, 65]). A new-user design is also required. Second, clinically relevant cognitive outcomes should be favored, such as dementia or MCI incidence. Third, the collection of all drug exposure during the whole study period is necessary to avoid potential misclassification bias and using a longitudinal definition of drug exposure. Using a time-varying drug exposure in the statistical analysis would also reduce the risk of misclassification bias. Without any recommendation about the anticholinergic scale or method of measurement of anticholinergic burden during longitudinal studies, the Muscarinic Acetylcholinergic Receptor Antagonist Exposure Scale, which takes into account the anticholinergic score as well as the dosage [60], sounds promising and comparing various methods could be useful.

Conclusion

Our literature search highlights the heterogeneity of the available studies and the complexity to assess the long-term cognitive effects of anticholinergics drugs. However, the most recent and the most reliable studies are suggesting a deleterious cognitive effect of anticholinergic drugs but future studies are still required. Meanwhile, anticholinergic prescription should remain cautious especially since alternatives are usually available.

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Compliance with ethical standards

Conflict of interest Andre Laurine, Gallini Adeline, Montastruc François, Montastruc Jean-Louis, Piau Antoine, Lapeyre-Mestre Maryse, and Gardette Virginie have no conflicts of interest directly relevant to the content of this study.

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