



# Increased risk of incident dementia following use of anticholinergic agents: A systematic literature review and meta-analysis

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## Abstract

**Background/rationale:** Long-term treatment with anticholinergic agents may increase the risk of cognitive impairment or dementia. This systematic literature review and meta-analysis aimed to assess the impact of  $\geq 3$  months of exposure to anticholinergics as a class on the risk of dementia, mild cognitive impairment, and change in cognitive function. The impact of anticholinergic agents specifically used to treat overactive bladder was also evaluated.

**Materials and Methods:** A systematic literature review was conducted to identify English language articles evaluating the impact of anticholinergic use for  $\geq 3$  months on dementia or cognitive function in adult patients. Databases searched included PubMed, Embase, and the Cochrane Library. Meta-analyses were conducted using random-effects models; 95% confidence intervals (CIs) and 95% prediction intervals (PIs) were reported.

**Results:** A total of 2122 records were identified. Out of those, 21 studies underwent qualitative synthesis and 6 reported endpoints relevant for

inclusion in a meta-analysis assessing the risk of incident dementia. The overall rate ratio for incident dementia was 1.46 (95% CI: 1.17–1.81; 95% PI: 0.70–3.04;  $n = 6$ ). The risk of incident dementia increased with increasing exposure ( $n = 3$ ). In addition, two studies from the meta-analysis reported an increased risk of dementia with  $\geq 3$  months of use of bladder antimuscarinics (adjusted odds ratios ranged from 1.21 to 1.65, depending on exposure category).

**Conclusion:** Anticholinergic use for  $\geq 3$  months increased the risk of dementia on average by an estimated 46% versus nonuse. This relationship was consistent in studies assessing overactive bladder medications. The risk of developing dementia should be carefully considered in the context of potential benefit before prescribing anticholinergics.

#### KEYWORDS

bladder antimuscarinics, cognitive dysfunction, cognitive impairment, incontinence, overactive bladder

## 1 | INTRODUCTION

The healthcare cost of dementia is substantial, estimated at \$290 billion in the United States in 2019 alone.<sup>1</sup> The prevalence of dementia doubles every 5 years after the age of 65 and reaches 30% or more among those over the age of 80.<sup>2</sup> This trend is expected to continue, with the prevalence of dementia estimated to double by 2030.<sup>3</sup> In addition to dementia, approximately 22% of people in the United States over the age of 70 have cognitive impairment without dementia.<sup>4</sup>

Anticholinergic drugs are prescribed for various indications, including those occurring in patients at high risk for cognitive impairment or dementia, such as those over the age of 65. There is growing evidence that long-term treatment with anticholinergic drugs or those with anticholinergic properties increases the risk of dementia,<sup>5–8</sup> which has led to recommendations to limit the use of these agents.<sup>9,10</sup> Further, drugs with higher anticholinergic activity, such as the antimuscarinic agent oxybutynin, include precautions in their prescribing information regarding central nervous system anticholinergic effects. The oxybutynin label recommends caution in patients with pre-existing dementia treated with cholinesterase inhibitors because it can exacerbate symptoms.<sup>11</sup> Results of a recent meta-analysis, however, suggest that the link between anticholinergics and cognitive impairment/dementia has not been fully established.<sup>12</sup> That review was limited by short average follow-up time (12 weeks) and few studies available to assess the outcome of dementia. Other studies have shown that the risk with these agents is greater with longer cumulative exposure time.<sup>13</sup> This could be due to

increased Alzheimer-like pathology over time, as a study conducted in Parkinson's patients reported 2.5-fold greater amyloid plaque densities, as well as increased neurofibrillary tangle densities in patients treated with antimuscarinic medications for  $\geq 2$  years compared with untreated patients or shorter exposures.<sup>14</sup>

This systematic literature review assessed the impact of  $\geq 3$  months of anticholinergic use on the risk of incident dementia (multiple subtypes), incident mild cognitive impairment, and change in cognitive function. A meta-analysis was performed for incident dementia. In addition, the impact of agents used specifically for the treatment of overactive bladder (OAB) was evaluated.

## 2 | MATERIALS AND METHODS

### 2.1 | Systematic literature review

#### 2.1.1 | Search strategy and selection criteria

The systematic literature review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),<sup>15</sup> and the Meta Analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidance.<sup>16</sup> The protocol was registered in the PROSPERO database (registration number: CRD42020149910).<sup>17</sup>

Using PubMed, Embase, and Cochrane Library databases, studies published before August 8, 2019 were

identified using a search strategy that incorporated terms for measures of occurrence/association, anticholinergic drugs, and dementia/cognitive impairment (see Table S1–S3 for full search queries). Searches were conducted using title, abstract, or keyword field searches, and results were filtered for the English language (PubMed, Embase) and human studies (PubMed). No search restrictions were applied based on publication year. A manual search of key publications and references was conducted to ensure relevant articles were not overlooked.

All articles were independently screened by two reviewers (KI and ST). Titles and abstracts were reviewed during the first phase of screening and, if the studies met the inclusion criteria, they were carried forward to the full-text review. Studies deemed to be out-of-scope based on the full-text review were excluded with a documented rationale. Included studies met the following criteria: (1) examined the impact of anticholinergic drug use for  $\geq 3$  months on dementia or cognitive function in adult patients; (2) was a randomized controlled trial (RCT), case-control study, or cohort study; (3) contained an adequate description of the methods used; and (4) was a primary publication. Studies were excluded if they only assessed serum anticholinergic activity, utilized a combined scale of drug burden that did not specify the risk for exposure to anticholinergic agents only, examined acute outcomes such as delirium or state of acute cognitive dysfunction, or if full-text was not available. Discrepancies between reviewers were discussed and resolved through consensus at each stage or a third reviewer was consulted (CG). Study search results and initial deduplication were managed using Endnote software (version X8.1), and search review and study selection were coordinated using Covidence software.

### 2.1.2 | Data extraction and risk of bias assessment

One reviewer extracted study information using an abstraction form with predefined fields on source, study design, population, analysis, confounders, anticholinergic drug exposure, outcome assessments, results, and study limitations. Another reviewer independently verified the extracted data against the original publications. The data items followed guidance from the Cochrane Handbook.<sup>18</sup> Articles were independently assessed for risk of bias by two reviewers using the Cochrane Risk of Bias Tool<sup>18</sup> for RCTs and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) for observational studies.<sup>19</sup> Any disagreements regarding extraction or risk of bias were settled by consensus between the reviewers.

### 2.1.3 | Meta-analysis

All studies from the qualitative review were considered for inclusion in the meta-analysis if they met all other criteria, contained a comparison group that had no anticholinergic drug use, and reported either a relative effect measure estimate (hazard ratio, relative risk, or odds ratio) with 95% confidence interval (CI), an absolute difference measure (risk difference, rate difference, or prevalence difference) with 95% CI, a mean difference of scores or difference of mean change scores with 95% CIs or the summary statistics that would allow derivation of these estimates. Where information was missing in relevant publications, the corresponding author was contacted to request the data.

Clinical trials and observational studies were reviewed separately to identify studies that were similar with regard to exposure and outcomes (e.g., incident dementia [all subtypes], incident mild cognitive impairment, and change in cognitive function). Dementia subtypes included Alzheimer's disease, Lewy body dementia, and vascular dementia. Studies assessing anticholinergics used to treat OAB were considered for a separate meta-analysis.

For a common measure of association, hazard ratios and risk ratios were assumed to approximate the rate ratio (RR), as were odds ratios from case-control studies after verifying incidence density sampling and rare disease assumptions. Covariate-adjusted estimates were used when available to minimize confounding. Unadjusted estimates were calculated when necessary and used when adjusted estimates were not reported. For studies with multiple eligible estimates, the comparison with the strongest anticholinergic exposure pattern (i.e., highest number of anticholinergic medications or longest exposure) was used for primary analyses and the weakest eligible  $\geq 3$ -month exposure pattern in the sensitivity analysis. Estimates from studies using daily dose indices (e.g., total standardized daily dose and defined daily dose) were combined where possible.

Meta-analyses were conducted using random-effects models for the outcomes. Funnel plot asymmetry was assessed visually and using  $p$  values for Begg and Mazumdar's log-rank test<sup>20</sup> and the Egger regression test.<sup>21</sup> All plausible explanations were considered, including publication bias, study characteristic associations, or chance. Duval and Tweedie's trim and fill imputation method was also used to assess funnel plot symmetry and estimate the effect "corrected" for hypothetical publication bias.<sup>22,23</sup> Consistency of study results was assessed using homogeneity tests with Cochran's  $Q$  statistic<sup>24</sup> and 95% CIs and 95% prediction intervals (PIs) were reported.<sup>25</sup>  $I^2$  was also calculated for reference. Among meta-analyzed studies, an influence analysis

was conducted to determine whether any single study was particularly impactful on the summary results.

The assessment tool or definition of dementia used in each study included in the meta-analysis is indicated in Table 1. Study characteristics are shown in Table 1 and were investigated using stratified and meta-regression analyses, and characteristic categorizations were chosen for contextual value or to ensure a minimum of two studies in each category. Stratified estimates were produced by running the meta-regression model twice, the second time with dichotomized study characteristics variables coded inversely. Model intercepts formed stratified estimates. Because the count of meta-analyzable studies was too small to conduct multiple meta-regression, each study characteristic was evaluated individually in one-covariate models. The covariate coefficients were used to estimate the relative differences between study characteristic RRs. This ratio of RRs and its corresponding 95% CI was used to estimate the magnitude and direction of the heterogeneity associated with each study characteristic. All analyses were conducted with STATA v.16 (Stata Corporation LP; College Station, TX).

### 3 | RESULTS

#### 3.1 | Systematic literature review

The electronic search returned 2092 articles. An additional 30 were identified from a hand search of other sources, and 132 duplicates were deleted. Out of the 1990 records screened based on their titles and abstracts, 316 were included in the full-text assessment. Out of those, 295 were excluded based on the inclusion/exclusion criteria (Figure 1). Ultimately, 21 studies were included for qualitative synthesis (Table S4).

Across the 21 studies evaluated, 8 of 9 incident dementia studies, 4 of 4 incident Alzheimer's disease studies, 2 of 2 incident mild cognitive impairment studies and 7 of 11 cognitive impairment/decreased performance studies reported an increased risk with anticholinergic use, either overall or for at least one anticholinergic exposure category.

#### 3.2 | Meta-analysis

##### 3.2.1 | Main analysis

Of the outcomes assessed (dementia, mild cognitive impairment, and change in cognitive function), only the dementia category had a sufficient number of studies to allow meta-analysis, with six of the nine observational studies reporting on dementia deemed appropriate for

inclusion (Table 1). Data from the three case-control and three cohort studies represented 645,865 patients across five countries. Three of these studies required that patients were over the age of 65 years, the remaining three studies had lower thresholds for inclusion (45 years, 55 years, and 60 years). All studies had moderate risk of bias. Given that there is no clear consensus on which drugs are considered to have anticholinergic properties, the studies varied in their exposure definitions. All six dementia studies assessed the impact across anticholinergic agents. Given the limited number of articles, a meta-analysis could not be conducted for individual dementia subtypes, incident mild cognitive impairment, or change in cognitive function; the results reported here, therefore, reflect the collective outcomes for multiple dementia subtypes, such as Alzheimer's disease, Lewy body dementia, and vascular dementia, among others, referred to hereafter as "incident dementia." Specific definitions for dementia varied by study.

The estimate of the average RR for incident dementia was 1.46 (95% CI: 1.17–1.81; 95% PI: 0.70–3.04; Figure 2) and ranged from 1.05 to 2.63 across the six studies. Three of these studies examined anticholinergic exposures in terms of daily dosing information. Two studies reported total standardized daily doses (TSDD) and one reported defined daily doses (DDD), which were assumed to be equivalent for analysis. The three levels of anticholinergic exposure were considered based on the categories described in the included publications: TSDD/DDD = 90–365 ( $n = 3$ ), TSDD/DDD = 365–1095 ( $n = 2$ ), and TSDD/DDD > 1095 ( $n = 2$ ). Compared to no anticholinergic dose exposure, all three dosing exposure levels were associated with increased incident dementia (Figure 3). The strength of the association increased with increasing exposure level comparisons, with higher dosing comparisons producing summary RRs 1.19- and 1.32-times higher than the lowest exposure comparison.

The point estimate results for incident dementia RRs were generally consistent with the main analysis when performing subgroup analysis and meta-regression to examine the impact of study characteristics (Table 2). There were positive associations on the average for each category assessed.

Based on an influence analysis (Table S5), no single study was exceedingly influential on the results. The pooled estimate (RR = 1.46) was most impacted by the removal of the Park et al.<sup>28</sup> study (RR = 1.29) and Richardson et al.<sup>29</sup> study (RR = 1.58).

Begg and Egger's tests yielded  $p > 0.8$  (Figure S1). Using the trim and fill method, two hypothetically missing studies were imputed, and the random-effects summary RR was 1.63.

TABLE 1 Qualitative summary of studies included in the meta-analysis assessing the impact of anticholinergic agent use on incident dementia

Study	Design	Study setting/participants	Patient characteristics	Drug exposure assessment	Dementia assessment	Follow-up/study duration	Risk of bias	Reported association
Ancelin 2006 <sup>26</sup>	Prospective cohort	General practitioner patients (France) N = 327	>60 years 77% women among users	Prevalent use at baseline and 1 year after	Neurologic examination based on DSM-III-R criteria <sup>a</sup>	7 years	Moderate	No
Coupland 2019 <sup>8</sup>	Nested case-control	QResearch database (UK) N = 284,343	≥55 years 63% women	10 years: 1–11 years before index date	Clinical code for dementia recorded in practice records or Office of National Statistics death records, or prescription for donepezil, galantamine, memantine, or rivastigmine	N/A	Moderate	Yes
Gray 2015 <sup>13</sup>	Prospective cohort	Sampled patients (GroupHEALTH, USA) N = 3434	≥65 years 60% women	≥10 years of GroupHEALTH care plan enrollment	Cognitive Abilities Screening Instrument used. If score was ≤85, patient had a diagnostic evaluation for dementia <sup>b</sup>	Mean (SD) follow-up: 7.3 (4.8) years	Moderate	Yes/no depending on level of TSDD
Hong 2019 <sup>27</sup>	Retrospective cohort	National Health Insurance Research Database (Taiwan) N = 21,934	≥45 years 52% women	1 year after index date	ICD-9-CM diagnosis code for dementia and record of mental function examination within the same visit <sup>c</sup>	Mean (SD) follow-up: 5.9 (3.4) years among unexposed, 5.7 (3.4) years among exposed	Moderate	Yes
Park 2017 <sup>28</sup>	Nested case-control	National Health Insurance Service (South Korea) N = 11,124	≥65 years 72% women	2 years before index date	ICD-10-CM diagnosis code for dementia	N/A	Moderate	Yes
Richardson 2018 <sup>29</sup>	Nested case-control	Clinical Practice Research Datalink (UK) N = 324,703	65–99 years 63% women	Median (IQR, range) = 7.1 (4.0–11.3, 1–16) years before index date	Read code for dementia or prescription for memantine, donepezil, rivastigmine, galantamine, or tacrine if diagnosis of dementia was recorded within 12 months	N/A	Moderate	Yes

Abbreviations: CM, clinical modification; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; IQR, interquartile range; NINCDS-ADRD, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

<sup>a</sup>When examination was not possible, medical records were examined in collaboration with the patient's general practitioner to determine presence/absence of dementia.

<sup>b</sup>A study neurologist, geriatrician, or internist performed a physical/neurologic examination, as well as neuropsychological testing. Results of the assessment, laboratory testing, and clinical data from medical records were reviewed for diagnosis using DSM-IV and NINCDS-ADRD criteria. Patients diagnosed with incident dementia had at least one follow-up examination to confirm the dementia diagnosis.

<sup>c</sup>Mental function examinations to confirm dementia diagnosis included the Clinical Dementia Rating, Cognitive Abilities Screening Instrument, or Mini-Mental State Examination.

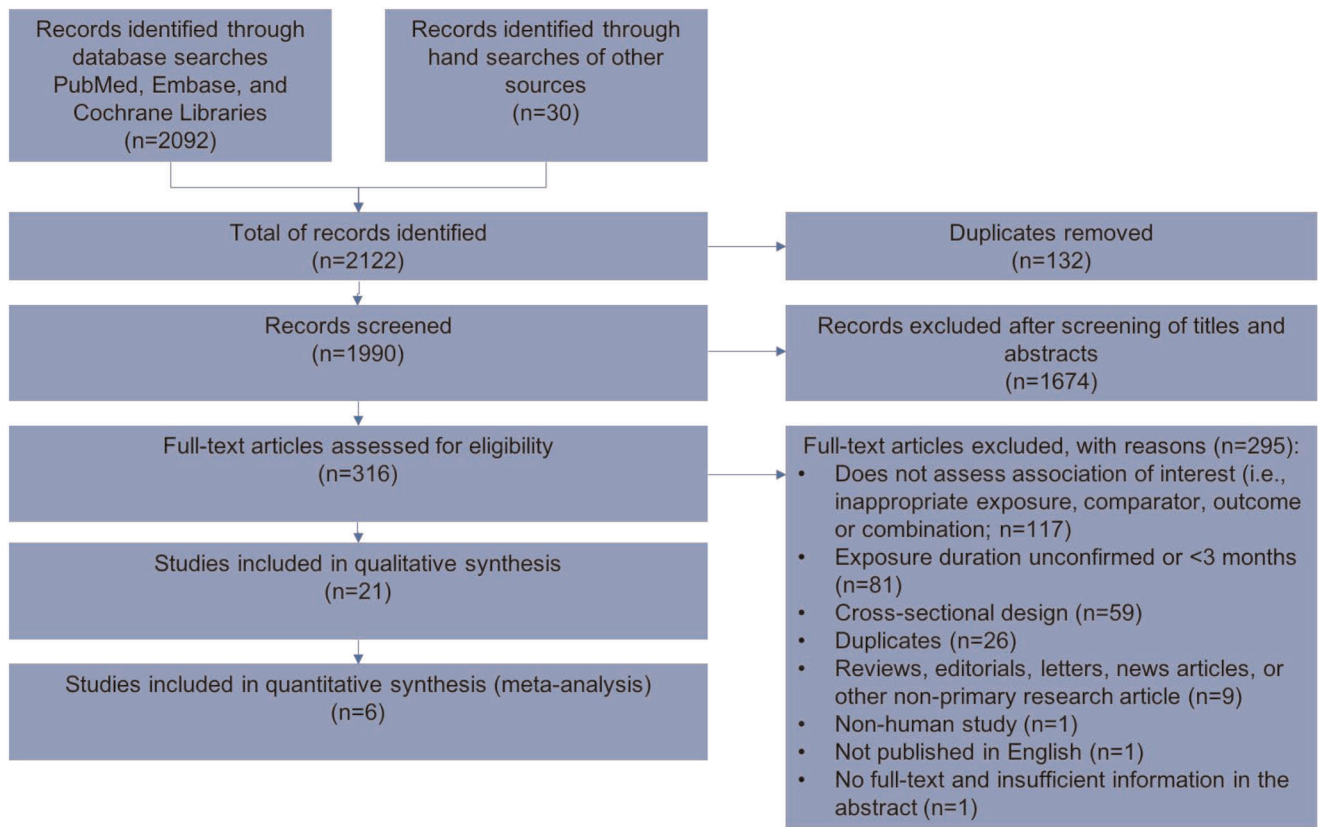


FIGURE 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

### 3.2.2 | Sensitivity analysis

A sensitivity analysis using study estimates from the comparisons using the weakest eligible exposure pattern resulted in a somewhat decreased summary RR (RR = 1.30; 95% CI: 1.14–1.48; 95% PI: 0.87–1.95; Figure S2).

### 3.2.3 | OAB medications

Two studies included in the meta-analysis specifically examined the impact of OAB medications on dementia, so a meta-analysis was not performed for this medication class. The nested case-control studies by Coupland et al.<sup>8</sup>

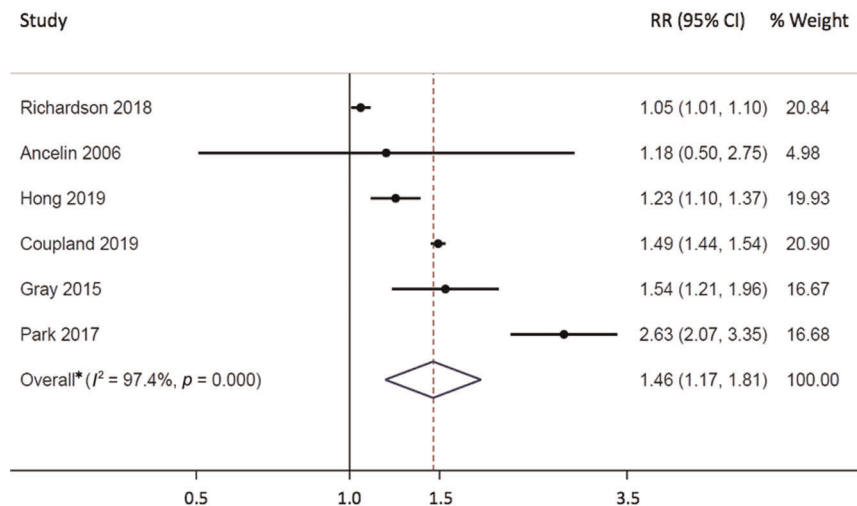
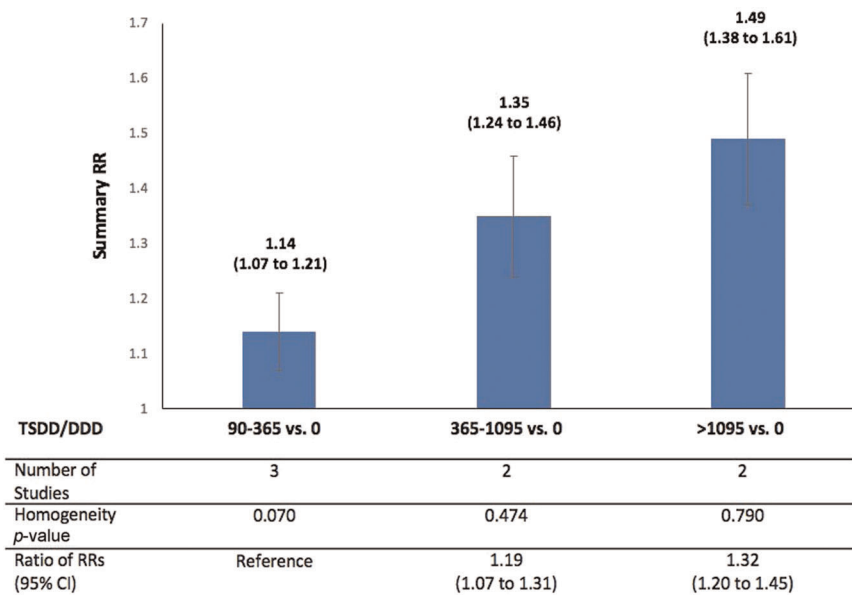


FIGURE 2 Forest plot of estimated rate ratios for the association between  $\geq 3$  months of anticholinergic use and incident dementia. The CI reflects a random error in estimating the mean but does not reflect the spread of the random-effects distribution. The PI reflects heterogeneity and random estimation error and maybe informally interpreted as the interval within which we expect the true value estimated from a future study to lie. CI, confidence interval; PI, prediction interval; RR, rate ratio. \*95% PI = 0.70–3.04



**FIGURE 3** Stratified analysis and meta-regression of three observational studies investigating the relationship between  $\geq 3$  months of anticholinergic use assessed by total standardized daily dose/defined daily dose and dementia. Daily dose indices were assumed to be equivalent. CI, confidence interval; DDD, defined daily doses, defined as the number of maintenance daily doses prescribed during the drug exposure period. The World Health Organization's (WHO) Collaborating Centre for Drug Statistics Methodology assigns daily dose values to drugs based on the average maintenance daily dose for the drug's primary indication in adult patients.<sup>29</sup> RR, rate ratio; TSDD, total standardized daily doses, defined as the sum of standardized daily doses (tablet strength \* number of dispensed tablets divided by minimum recommended dose per day for older adults) from all anticholinergic pharmacy fills in the exposure assessment period.<sup>8,13</sup>

and Richardson et al.<sup>29</sup> reported an increased risk of dementia with  $\geq 3$  months of use of bladder antimuscarinics (i.e., darifenacin, fesoterodine, flavoxate, oxybutynin, propiverine, solifenacin, tolterodine, and trospium). Adjusted odds ratios ranged from 1.35 to 1.65<sup>8</sup>

and 1.21 to 1.35<sup>29</sup> (Table S4). The risk tended to be greater in higher exposure categories (i.e., comparisons including  $> 365$  TSDD/DDD). The risk of dementia from OAB medications was higher than the overall risk across anticholinergic agents for all of the TSDD/DDD

**TABLE 2** Stratified analysis and meta-regression of seven observational studies investigating the relationship between  $\geq 3$  months of anticholinergic exposure and dementia

Study characteristic	Category	Studies	Homogeneity, <i>p</i>	Summary RR (95% CI)	Ratio of effect metrics (95% CI)
Design	Case control	3	0.000	1.57 (1.06–2.34)	Reference
	Cohort	3	0.247	1.33 (0.85–2.10)	0.85 (0.46–1.55)
Lag	None	2	0.000	1.76 (1.11–2.79)	Reference
	$\geq 1$ -year lag in outcomes	4	0.000	1.31 (0.93–1.86)	0.75 (0.42–1.33)
Minimum age at enrollment	<65 years	3	0.004	1.32 (0.85–2.05)	Reference
	$\geq 65$ years	3	0.000	1.59 (1.06–2.39)	1.20 (0.66–2.18)
Enrollment start years	Before 2000	2	0.552	1.42 (0.77–2.60)	Reference
	After 2000	4	0.000	1.48 (1.04–2.10)	1.04 (0.52–2.10)
Sex	<70% female	4	0.000	1.30 (1.05–1.60)	Reference
	$\geq 70$ % female	2	0.074	2.27 (1.47–3.51)	1.75 (1.08–2.85)

Abbreviations: CI, confidence interval; RR, rate ratio.

comparisons in both studies, with the exception of the >1460 comparison in Richardson et al.<sup>8,29</sup>

## 4 | DISCUSSION

In the present systematic literature review, over 316 of 2100 identified articles were reviewed evaluating the impact of  $\geq 3$  months of anticholinergic use on cognitive outcomes. Out of those, 21 studies were qualitatively synthesized and 6 met the a priori criteria for inclusion. With considerable evidence of heterogeneity, the use of anticholinergic agents for  $\geq 3$  months was found to increase the risk of dementia on average by 46% relative to the risk given with nonuse. This increased risk of dementia was reported in the two studies from the meta-analysis that specifically evaluated anticholinergic medications used to treat OAB. These results are consistent with three previously published reviews,<sup>30–32</sup> as well as recommendations from the American Geriatrics Society regarding limiting prescribing of anticholinergic agents in older adults.<sup>9</sup> In addition to corroborating prior findings, the current analysis expands upon prior reviews by updating the literature and providing a meta-analysis of the results.

Through subgroup analyses of study characteristics, anticholinergic use was associated with an increased risk of incident dementia in studies of patients 65 years of age and older, as well as in younger patients. Hong et al.<sup>27</sup> found that the patients 45–75 years old had a greater relative risk of incident dementia (adjusted hazard ratio [aHR] = 1.27, 95% CI: 1.15–1.39) than those  $\geq 75$  years old (aHR = 1.13, 95% CI: 1.01–1.27). Given the greater baseline risk in older patients, it is unclear whether the estimated absolute effects would be greater in younger patients as well. A similar direction of modification was seen in a study by Joung et al.<sup>33</sup> who found that use of strong anticholinergics (per Beers Criteria or those with an Anticholinergic Cognitive Burden [ACB] score of 2 or 3) increased the risk of Alzheimer's disease, but the association on the ratio scale was stronger in the younger age group (all subjects with  $\geq 120$  doses/year vs. 0–9 doses/year: aHR = 1.39, 95% CI: 1.30–1.50; 60–64 years subgroup with  $\geq 120$  doses/year vs. 0–9 doses/year: aHR = 1.83, 95% CI: 1.56–2.14). It is unclear whether the estimated absolute effect would be modified by age in the same direction. Nonetheless, these results suggest that the risk of dementia with anticholinergic use should be considered for patients above and below 65 years of age. When examining the risk based on sex, there was an increased risk of dementia with anticholinergic use in each subgroup of studies (<70% women and  $\geq 70\%$  women), consistent with an effect in both sexes. Hong et al.<sup>27</sup> found that the increased risk on the ratio scale was similar for men and women (men: aHR = 1.21, 95% CI: 1.09–1.35;

women: aHR = 1.15, 95% CI: 1.04–1.27). As with age, estimated sex disparity in absolute effects is dependent on baseline risk. Based on these results, the cognitive impact of anticholinergics appears to span age (middle-aged and older adults) and sex groups, but additional studies are needed to further elucidate this relationship.

Cumulative exposure modified the increased risk presented by anticholinergics in the current analysis, with greater increases at higher exposure categories. The strength of anticholinergic activity, which could not be assessed in our analysis, has been found to play a role in the risk of negative effects on cognition.<sup>29,33,34</sup> One study estimated the adjusted hazard ratio for incident dementia in patients with a total ACB score  $\geq 3$  versus  $< 3$  to be as high as 4.18 (95% CI: 1.43–12.21).<sup>34</sup> This is particularly relevant to certain populations, such as OAB, as anticholinergic medications for treating OAB (e.g., tolterodine, oxybutynin, darifenacin, fesoterodine, and solifenacin) have the highest anticholinergic burden score.<sup>8,29</sup> Further, when compared to  $\beta$ -3 agonists—a nonantimuscarinic OAB treatment—anticholinergic medications increased the risk of incident dementia (HR = 1.23, 95% CI: 1.12–1.35).<sup>35</sup> It is not yet established whether the use of anticholinergic agents is a reversible risk factor for cognitive impairment or dementia, particularly with regard to specific patient segments and duration of exposure or strength of anticholinergic activity.

Beyond dementia, anticholinergic agents may pose additional risks. In retrospective studies, high anticholinergic exposure was associated with a 40%<sup>36,37</sup> or a 31%<sup>36,37</sup> increased risk of falls or fractures and a 36% increased rate of all-cause mortality,<sup>36,37</sup> potentially leading to increased healthcare resource use.<sup>38,39</sup> Anticholinergic agents can also cause delirium, constipation, and urinary retention.<sup>39</sup> Despite these risks, the prescribing of anticholinergics remains high. Estimates suggest that in older adults, the prevalence of anticholinergic use ranges from 9% to 56%, depending on the anticholinergic scale used.<sup>38,40–42</sup> Gray et al.<sup>13</sup> reported an increased risk of incident dementia across all anticholinergic agents, noting that bladder antimuscarinics represented 10.5% of all TSDDs, the third-highest following antidepressants (63.1%) and antihistamines (17.2%).<sup>13</sup>

Some limitations need to be considered in the context of this analysis. First, definitions of exposures and outcomes varied, limiting the number of studies included in the meta-analysis, as well as the ability to assess outcomes beyond dementia. Interactions that may have been present across variables of interest could not be explored given the limited number of studies. Second, many studies did not specifically examine or report results by exposure duration and were therefore excluded. Third, because publications were limited to those in the English language, the results might not represent the full body of published literature. Lastly, the examination of specific anticholinergic drugs beyond those



used to treat OAB was outside of the scope of this study. Despite these limitations, however, the current study presents a comprehensive and methodologically rigorous review of the impact of  $\geq 3$  months of anticholinergic use on incident dementia using information from three databases. PICOTS criteria were used to frame the question of interest and a systematic approach was undertaken to synthesize the results. Data from 645,865 patients across five countries were pooled for the meta-analysis, representing a large, diverse sample. Additionally, results were remarkably robust to sensitivity analysis, as well as influence analysis. This study substantially contributes to the literature on the topic by examining the impact of longer-term therapy.

## 5 | CONCLUSION

The use of anticholinergic agents for  $\geq 3$  months appears to increase the risk of dementia by an estimated 46% on average compared with nonuse. This relationship was consistent in studies assessing bladder antimuscarinics, likely due to their high anticholinergic activity. Whether the use of anticholinergic agents is a reversible risk factor is an important area of future research; however, given the substantially increased risk of developing dementia associated with anti-cholinergic agents, physicians should carefully weigh the risk versus the potential benefits before prescribing.

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### AUTHOR CONTRIBUTIONS

All investigators were involved in the conception/design of the study. KI and ST collected and assembled the data. ST performed the data analysis. All authors were involved in the interpretation of the results. KI and ST drafted the manuscript, with all authors revising it critically for intellectual content and providing final approval.

### DISCLOSURES

Roger R. Dmochowski is a consultant for Urovant Sciences. Urovant Sciences contracted with CERobs Consulting, LLC, a consulting firm with focus on real world evidence, outcomes research, epidemiology and clinical outcome assessments, including patient reported outcomes; Sydney Thai, Kristy Iglay, and Charles Poole consulted on this project through CERobs Consulting, LLC; Cynthia Girman

is the President of CERobs Consulting, LLC; Larry Radican is an employee of Peloton Advantage, an OPEN Health Company, which was contracted through CERobs Consulting, LLC. Ekene Enemchukwu is a consultant for Urovant Sciences and Astellas. Silvia Tee has no conflicts of interest to report. Susann Varano is the Principal Investigator for Clinical Research Consulting and Adjunct Professor at Sacred Heart University and University of Bridgeport. Paul N. Mudd Jr. is an employee of Urovant Sciences and is a shareholder.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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