Short-term cognitive effects of anticholinergics in patients with neurogenic lower urinary tract dysfunction: A systematic review and meta-analysis

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Abstract. Neurogenic lower urinary tract dysfunction (NLUTD) is common in individuals with neurological disorders, leading to bladder overactivity and incontinence. Anticholinergic medications are frequently prescribed for symptom control, but concerns exist regarding potential cognitive impairments. The present systematic review and meta-analysis aimed to evaluate the short-term cognitive effects of anticholinergics in patients with NLUTD. PubMed, Embase, Cochrane Library and Scopus (inception to February 2025) were searched for randomized controlled trials and observational studies assessing short-term cognitive outcomes in patients with NLUTD treated with anticholinergics. Study characteristics, anticholinergic type/dosage, and standardized cognitive measures were extracted. A random-effects model was used to calculate pooled effect sizes (standardized mean differences, SMDs), and heterogeneity was assessed via the Q-statistic, τ^2, and precision interval analysis. A total of three studies involving 139 participants (22 comparisons) met inclusion criteria. The overall pooled SMD for cognitive performance was -0.33 (95% CI: -0.72 to 0.06; P=0.10), indicating a non-significant trend toward negative cognitive effects. Subgroup analyses showed notable impairments in memory, executive function and attention, while global measures exhibited minimal change. Heterogeneity was high (Q=162.25; P<0.001), likely due to differences in patient populations, anticholinergic agents and cognitive assessments. Although short-term use of anticholinergic medications may negatively impact certain cognitive domains in patients with NLUTD, the pooled effect was not statistically significant under a random-effects model. These findings emphasize the importance of cautious agent selection and the need for further, larger-scale studies to clarify long-term cognitive safety. Future research should also assess alternative therapies, such as β3-adrenergic agonists, which have notably fewer adverse central effects.

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Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is a common complication in individuals with conditions such as spinal cord injuries, multiple sclerosis (MS) and other neurologic disorders, often presenting with symptoms of overactive bladder, incontinence and voiding dysfunction (1,2). Anticholinergic medications, which inhibit muscarinic receptors to reduce detrusor muscle overactivity, are frequently employed as first-line pharmacological interventions to manage these symptoms (1,3). However, the widespread distribution of muscarinic receptors in the central nervous system raises concerns regarding potential cognitive side effects, particularly in vulnerable populations (2,4).

Cognitive impairments, including memory loss, attention deficits and decreased processing speed, have been reported with anticholinergic use, especially in older populations (2,5,6). Studies show that anticholinergic medications cross the blood-brain barrier, contributing to brain atrophy and increased dementia risk (2,7). A cohort study by Wang *et al* (2) found that cumulative exposure to bladder-specific anticholinergics was associated with an elevated risk of dementia, emphasizing the need for careful therapeutic balancing between symptom management and cognitive safety.

In cognitive research, functions are commonly categorized into key domains: Memory, attention and processing speed, executive functions, visuospatial ability and global cognition (8). NLUTD studies often use standardized tools to assess these domains. For instance, the Mini-Mental State Examination (MMSE) is a 30-point scale examining orientation, recall, attention, language and constructional ability (9). The Symbol Digit Modalities Test (SDMT) is widely used, particularly in neurological populations, to evaluate attention and processing speed (10). More specialized tests, such as the

Frontal Assessment Battery (FAB) or the Trail Making Test, are used to evaluate executive functioning, and instruments such as the Montreal Cognitive Assessment (MoCA) assess multiple domains, including visuospatial abilities (9). By briefly outlining these tools and domains, a clear conceptual framework that supports analyses of cognitive outcomes was established.

In populations with neurogenic bladder dysfunction, the cognitive burden of anticholinergics may be particularly problematic due to pre-existing neurological vulnerabilities. Sakakibara *et al* (4) demonstrated that although some anticholinergic agents, such as imidafenacin, may present lower cognitive risks, others such as oxybutynin and tolterodine have been linked to significant declines in memory and executive function. Similarly, Morrow *et al* (7) highlighted a substantial impact on processing speed and memory in patients with MS treated with anticholinergic medications, with impairments detected using standardized cognitive tests.

Despite their therapeutic efficacy in alleviating NLUTD symptoms, the long-term cognitive consequences of anticholinergic medications remain a critical area of investigation. Emerging evidence suggests that alternative treatments, such as β3-adrenergic agonists like mirabegron, may provide effective symptom control with fewer cognitive side effects, as demonstrated in comparative studies (1). Trbovich *et al* (1) found improved cognitive outcomes and comparable efficacy when switching from anticholinergics to mirabegron in individuals with neurogenic bladder dysfunction.

The present systematic review and meta-analysis aim to comprehensively evaluate the cognitive effects of anticholinergic medications in patients with NLUTD, synthesizing data from clinical trials and observational studies. By examining the extent and nature of cognitive impairments across various populations and drug types, the present study seeks to inform clinical decision-making and highlight potential therapeutic alternatives that minimize cognitive risks.

Materials and methods

Study design. The present study is a systematic review and meta-analysis conducted to evaluate the cognitive effects of anticholinergic medications in patients with NLUTD. The review adhered to the guidelines outlined in the PRISMA statement to ensure comprehensive reporting and transparency. The study protocol was registered in accordance with best practices for meta-analyses (11).

Search strategy and selection criteria. A systematic search was conducted across major electronic databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Cochrane Library (https://www.cochrane.org/) and Scopus (https://www.scopus.com/), from inception to February 2025. The search terms included combinations of the following: 'anticholinergics', 'cognitive impairment', 'neurogenic bladder', 'neurogenic lower urinary tract dysfunction', 'cognition' and 'urinary tract dysfunction'. No language restrictions were applied. The reference lists of included studies and relevant review articles were manually screened to identify additional studies. Inclusion criteria were: i) Studies assessing the cognitive effects of anticholinergic medications in patients with NLUTD, ii) randomized controlled trials, cohort studies, case-control studies and cross-sectional studies, iii) studies reporting cognitive outcomes, including memory, executive function, or overall cognition, and iv) only studies involving anticholinergic monotherapy delivered via oral administration were eligible for inclusion. Exclusion criteria were: i) Studies not involving NLUTD or anticholinergic medications, ii) animal or *in vitro* studies, iii) conference abstracts, case reports and reviews without primary data, and iv) studies using combination therapies (for example, anticholinergics plus β3-agonists), non-oral administration routes (for example, transdermal patches), and studies enrolling participants with clinically diagnosed cognitive impairment at baseline to reduce potential confounding.

Data extraction. Two independent reviewers (HZ and YW) screened titles and abstracts to identify relevant studies. Discrepancies were resolved through discussion. Full-text articles were retrieved and evaluated against the inclusion criteria. The following data were extracted using a standardized form: i) Study characteristics: author, year, study design, sample size and population characteristics; ii) intervention details: Type, dosage and duration of anticholinergic use; iii) cognitive outcomes: type of cognitive test used (for example, MMSE and SDMT); and iv) risk of bias and confounders: assessed using the Newcastle-Ottawa Scale (NOS).

Statistics. All statistical analyses were performed using Comprehensive Meta-Analysis software version 3. The primary outcome was the standardized mean difference (SMD) in cognitive test scores between patients receiving anticholinergics and those not exposed to the medications. A random-effects model was used due to the expected heterogeneity across studies, with effect sizes reported as point estimates and 95% confidence intervals (CIs). Heterogeneity was assessed using the Q statistic and precision interval analysis. Tau-squared (τ^2) was calculated to estimate between-study variance. Instead of relying solely on I^2 to quantify heterogeneity, the present meta-analysis employed precision interval analysis. While I^2 is commonly used to measure the percentage of variability due to heterogeneity, it has limitations, particularly when the number of studies is small or when effect sizes vary widely (12). Precision interval analysis focuses on the width of the CI and how much uncertainty surrounds the estimate, offering a more robust measure of how precise the combined effect size is. The width of the precision interval indicates whether the heterogeneity among studies affects the reliability of the meta-analysis conclusion (13). Sensitivity analyses were conducted by excluding studies with a high risk of bias and recalculating pooled estimates. Subgroup and moderator analyses were performed based on population characteristics (for example, age and sex groups) and type of cognitive test. The Begg and Mazumdar rank correlation test and Egger's regression intercept were used to identify publication bias. The Classic fail-safe N and Orwin's fail-safe N were calculated to assess the robustness of the results. Forest plots were generated to visualize effect sizes, and the funnel plot was used to assess publication bias. The significance of heterogeneity was tested using P-values, where $P<0.05$ was considered to indicate significant heterogeneity.

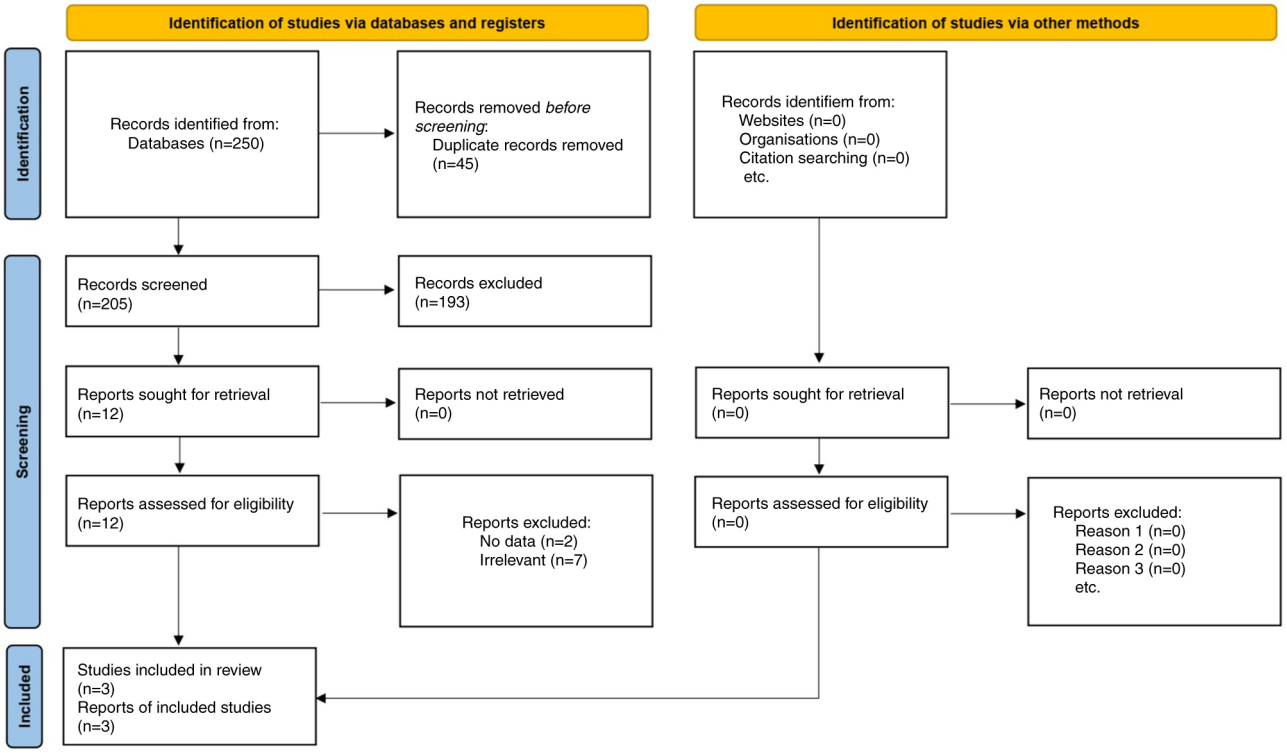


Figure 1. PRISMA flow diagram of study selection. The study selection process is illustrated, detailing the number of studies identified, screened, and excluded at each stage, along with the final inclusion of studies in the meta-analysis.

Results

Study selection. A systematic literature search of four major electronic databases (PubMed, Embase, Cochrane Library and Scopus) yielded 250 potentially relevant articles. After removing 45 duplicates, 205 articles underwent title and abstract screening, of which 12 were considered for full-text review. A total of 9 articles were excluded for not meeting the inclusion criteria (for example, lack of NLUTD focus, no anticholinergic intervention, or insufficient cognitive data). Ultimately, 3 studies (4,7,14) fulfilled the eligibility criteria, providing 22 independent comparisons. Two additional studies were excluded because they did not report sufficient data for the analysis (1,2). The entire selection process followed PRISMA guidelines and is outlined in Fig. 1.

General characteristics of included studies. The selected studies included 139 participants across various clinical settings, focusing on patients with NLUTD due to conditions such as spinal cord injury (SCI), MS and neurologic overactive bladder (OAB). The mean age of participants ranged from 25 to 70 years, with follow-up durations between 3 and 12 weeks. The studies examined both traditional anticholinergic agents (for example, oxybutynin and tolterodine) and newer, selective agents (for example, solifenacin and imidafenacin). Treatment durations ranged from 3 months to 12 weeks. Cognitive outcomes were assessed using standardized tests, including the SDMT, MMSE and FAB (Table I).

Primary outcome: Cognitive decline. The meta-analysis of 22 comparisons yielded a pooled SMD of -0.33 (95% CI: -0.72 to 0.06; Fig. 2A) under a random-effects model, indicating a trend toward negative cognitive effects of anticholinergic medications that did not reach statistical significance (P=0.10). By contrast, a complementary fixed-effects analysis produced a statistically significant SM -0.178 (95% CI: -0.314 to -0.041; P=0.011), suggesting a small but significant overall effect. However, given the substantial between-study heterogeneity (Q=162.25, df=21, P<0.001; τ^2=0.738; τ=0.859; Fig. 2B), the random-effects model was prioritized. This model accounts for both within- and between-study variance and provides a more conservative and generalizable estimate, particularly appropriate when true effect sizes are expected to vary due to differences in patient populations, anticholinergic agents and cognitive assessment tools. Notably, domain-specific impairments were more evident in memory and executive function, while global cognitive measures showed minimal or non-significant effects. To explore potential sources of heterogeneity, subgroup and sensitivity analyses were subsequently performed.

Sensitivity analysis. The sensitivity analysis, as shown in Fig. 3, demonstrated that the overall effect size remained stable, with the pooled SMD ranging between -0.25 and -0.41 after sequential removal of individual studies. No single study had an outsized influence on the overall results, confirming the robustness of the meta-analysis. Minor variations in effect size were observed when removing studies assessing attention outcomes, such as total errors and omissions from Krebs *et al* (14), but these changes did not significantly alter the overall conclusions. Similarly, the removal of global cognitive outcomes [(for example, MMSE, FAB and ADAS-cog

in Sakakibara *et al* (4)] had minimal impact on the pooled estimates, reflecting the limited influence of non-significant global measures on the overall effect. The stability of the results across sensitivity analyses underscores the consistent negative impact of anticholinergic medications on cognitive outcomes, particularly in memory, attention and executive function.

Secondary outcomes: Subgroup analysis results. The subgroup analysis revealed significant variability in the cognitive effects of anticholinergic medications across different domains. Attention outcomes showed a significant pooled (SMD) of 0.752 (95% CI: 0.108 to 1.395, P=0.022), indicating impaired attentional processes. Executive function outcomes demonstrated moderate impairment with a pooled SMD of -0.948 (95% CI: -1.755 to -0.141, P=0.046). Memory outcomes also indicated significant negative effects, with a pooled SMD of -0.645 (95% CI: -1.269 to -0.022, P=0.043), affecting both short-term and long-term memory. Global cognitive function showed no significant impact, with a pooled SMD of -0.031 (95% CI: -0.311 to 0.249, P=0.837). Visuospatial performance had a pooled SMD of -0.645 (95% CI: -1.563 to 0.273, P=0.165), suggesting a trend toward impairment that did not reach statistical significance. These findings highlight the greatest cognitive impairments in attention, executive function, and memory, while global and visuospatial domains were less impacted (Fig. 4).

Publication bias. The funnel plot in Fig. 5 illustrates the distribution of studies based on their effect sizes and standard errors, providing a visual assessment of publication bias. The plot shows slight asymmetry, with a concentration of studies on the left side (negative effect sizes), suggesting a possible overrepresentation of studies reporting negative cognitive effects. Begg's rank correlation test was statistically significant (P=0.009), while Egger's regression test was not (P=0.12). This discrepancy is not uncommon in meta-analyses with a small number of studies. Empirical evidence indicates that Begg's test may be more sensitive but less specific in small samples, whereas Egger's test is more conservative and better controls type I error under conditions of heterogeneity and continuous outcomes. Importantly, the trim-and-fill method estimated only two potentially missing studies, with negligible impact on the pooled SMD, indicating that the overall effect size remained stable after adjustment. Based on the mild funnel plot asymmetry, the modest number of imputed studies, and the limited change in effect size, we conclude that any potential publication bias is unlikely to meaningfully influence the meta-analysis results.

Heterogeneity. The precision interval analysis shown in Fig. 6 highlights the uncertainty surrounding the pooled effect size of anticholinergic medications on cognitive outcomes. The mean effect size was -0.33, with a 95% CI ranging from -0.72 to 0.06, indicating that the overall effect approaches but does not achieve statistical significance. The precision interval, which extends from -2.17 to 1.51, demonstrates substantial uncertainty due to between-study variability. This wide precision interval suggests that while there is evidence of a negative cognitive impact, the true effect size may vary considerably

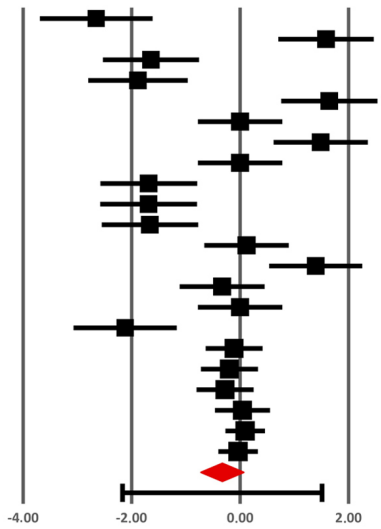
Table I. Study characteristics and interventions in the meta-analysis.

First author/s, year	Study design	Sample size (n)	Population characteristics	Anticholinergic agent(s)	Dosage	Duration of treatment	Cognitive tests used	(Refs.)
Krebs *et al*, 2017	Prospective controlled cohort	29	Patients with spinal cord injury with neurogenic lower urinary tract dysfunction during post-acute rehabilitation phase	Solifenacin, fesoterodine, darifenacin	Variable, based on agent	3 months	Verbal learning test, Stroop test, word fluency test	(14)
Morrow *et al*, 2018	Randomized controlled trial	69	Patients with multiple sclerosis and bladder dysfunction	Oxybutynin, tolterodine	Oxybutynin (5-10 mg/day), Tolterodine (4 mg/day)	12 weeks	Symbol Digit Modalities Test (SDMT), BiCAMS battery	(7)
Sakakibara *et al*, 2013	Prospective cohort	62	Patients with neurologic overactive bladder due to various conditions (for example, Parkinson's, Alzheimer's, white matter lesions)	Imidafenacin	0.2 mg/day (0.1 mg twice daily)	3 months	Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), ADAS-cog	(4)

The key characteristics of the studies included in the meta-analysis were summarized, including the study design, sample size, anticholinergic interventions, cognitive assessments, and risk of bias ratings.

A

Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Krebs et al., 2017 a	Executive function	Perseveration	-2,653	0,523	0,274	-3,678	-1,627	-5,068	0,000
Krebs et al., 2017 b	Visuospatial performance	Block design	1,585	0,443	0,196	0,717	2,453	3,581	0,000
Krebs et al., 2017 c	Visuospatial performance	Picture completion	-1,643	0,446	0,199	-2,518	-0,769	-3,682	0,000
Krebs et al., 2017 d	Visuospatial performance	Gestalt closure	-1,883	0,462	0,214	-2,790	-0,977	-4,073	0,000
Krebs et al., 2017 e	Attention	Auditory	1,645	0,446	0,199	0,770	2,520	3,684	0,000
Krebs et al., 2017 f	Attention	Visual	0,000	0,391	0,153	-0,766	0,766	0,000	1,000
Krebs et al., 2017 g	Attention	Total errors	1,486	0,437	0,191	0,630	2,342	3,403	0,001
Krebs et al., 2017 h	Attention	Total omissions	0,000	0,391	0,153	-0,766	0,766	0,000	1,000
Krebs et al., 2017 i	Memory	Total recall	-1,685	0,449	0,202	-2,565	-0,805	-3,753	0,000
Krebs et al., 2017 j	Memory	Delayed recall	-1,687	0,449	0,202	-2,567	-0,807	-3,756	0,000
Krebs et al., 2017 k	Memory	Immediate recall	-1,663	0,448	0,200	-2,540	-0,786	-3,715	0,000
Krebs et al., 2017 l	Attention	Total number	0,120	0,391	0,153	-0,647	0,886	0,306	0,760
Krebs et al., 2017 m	Attention	Total errors	1,395	0,431	0,186	0,549	2,241	3,233	0,001
Krebs et al., 2017 n	Executive function	Test time	-0,331	0,393	0,155	-1,102	0,439	-0,843	0,399
Krebs et al., 2017 o	Executive function	Test errors	0,000	0,391	0,153	-0,766	0,766	0,000	1,000
Krebs et al., 2017 p	Executive function	Fluency	-2,120	0,480	0,230	-3,060	-1,179	-4,419	0,000
Morrow et al., 2018 a	Executive function	SDMT	-0,111	0,262	0,069	-0,624	0,402	-0,423	0,673
Morrow et al., 2018 b	Memory	BVMTR	-0,197	0,262	0,069	-0,711	0,317	-0,752	0,452
Morrow et al., 2018 c	Memory	CLVT2	-0,277	0,263	0,069	-0,792	0,238	-1,054	0,292
Sakakibara et al., 2013 a	Global	MMSE	0,043	0,253	0,064	-0,452	0,538	0,170	0,865
Sakakibara et al., 2013 b	Global	FAB	0,093	0,180	0,032	-0,259	0,445	0,518	0,605
Sakakibara et al., 2013 c	Global	ADAS-cog	-0,037	0,180	0,032	-0,389	0,315	-0,205	0,837
Pooled			-0,330	0,201	0,040	-0,723	0,064	-1,642	0,101
Prediction Interval			-0,330			-2,170	1,510		



B

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Lower limit	Upper limit
		Effect size and 95% confidence interval					Test of null (2-Tail)		Prediction Interval	
Fixed	22	-0,178	0,069	0,005	-0,314	-0,041	-2,556	0,011		
Random effects	22	-0,330	0,201	0,040	-0,723	0,064	-1,642	0,101	-2,170	1,510

Figure 2. (A) Forest plot displaying SMDs and 95% CIs for each cognitive outcome assessed across 22 comparisons from three studies. Each square represents the point estimate of an individual outcome, with square size proportional to its weight. Horizontal lines indicate the 95% CI. Cognitive domains include executive function, attention, memory, visuospatial performance and global cognition. The red diamond at the bottom represents the pooled SMD under a random-effects model, with its width reflecting the 95% CI. (B) Summary table comparing the pooled effect estimates under fixed-effects and random-effects models. The random-effects model was prioritized due to substantial heterogeneity. The prediction interval under the random-effects model is also reported, indicating the range within which true effects of future studies may lie. SMDs, standardized mean differences; CI, confidence interval.

Study name	Subgroup within study	Outcome	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics with study removed						
Krebs et al., 2017 a	Executive function	Perseveration	-0,231	0,193	0,037	-0,609	0,147	-1,199	0,230
Krebs et al., 2017 b	Visuospatial performance	Block design	-0,413	0,198	0,039	-0,802	-0,025	-2,088	0,037
Krebs et al., 2017 c	Visuospatial performance	Picture completion	-0,270	0,201	0,041	-0,664	0,125	-1,339	0,181
Krebs et al., 2017 d	Visuospatial performance	Gestalt closure	-0,259	0,199	0,040	-0,650	0,131	-1,302	0,193
Krebs et al., 2017 e	Attention	Auditory	-0,416	0,197	0,039	-0,803	-0,029	-2,105	0,035
Krebs et al., 2017 f	Attention	Visual	-0,346	0,209	0,044	-0,756	0,063	-1,656	0,098
Krebs et al., 2017 g	Attention	Total errors	-0,410	0,199	0,040	-0,800	-0,020	-2,060	0,039
Krebs et al., 2017 h	Attention	Total omissions	-0,346	0,209	0,044	-0,756	0,063	-1,656	0,098
Krebs et al., 2017 i	Memory	Total recall	-0,268	0,201	0,040	-0,662	0,126	-1,333	0,183
Krebs et al., 2017 j	Memory	Delayed recall	-0,268	0,201	0,040	-0,662	0,126	-1,332	0,183
Krebs et al., 2017 k	Memory	Immediate recall	-0,269	0,201	0,040	-0,663	0,125	-1,336	0,181
Krebs et al., 2017 l	Attention	Total number	-0,352	0,209	0,044	-0,761	0,057	-1,685	0,092
Krebs et al., 2017 m	Attention	Total errors	-0,407	0,200	0,040	-0,798	-0,015	-2,034	0,042
Krebs et al., 2017 n	Executive function	Test time	-0,331	0,209	0,044	-0,740	0,079	-1,581	0,114
Krebs et al., 2017 o	Executive function	Test errors	-0,346	0,209	0,044	-0,756	0,063	-1,656	0,098
Krebs et al., 2017 p	Executive function	Fluency	-0,250	0,197	0,039	-0,637	0,136	-1,268	0,205
Morrow et al., 2018 a	Executive function	SDMT	-0,343	0,214	0,046	-0,762	0,075	-1,607	0,108
Morrow et al., 2018 b	Memory	BVMTR	-0,339	0,214	0,046	-0,757	0,080	-1,586	0,113
Morrow et al., 2018 c	Memory	CLVT2	-0,335	0,213	0,046	-0,753	0,084	-1,567	0,117
Sakakibara et al., 2013 a	Global	MMSE	-0,351	0,214	0,046	-0,770	0,067	-1,645	0,100
Sakakibara et al., 2013 b	Global	FAB	-0,356	0,219	0,048	-0,786	0,074	-1,623	0,105
Sakakibara et al., 2013 c	Global	ADAS-cog	-0,349	0,221	0,049	-0,782	0,083	-1,583	0,113
Pooled			-0,330	0,201	0,040	-0,723	0,064	-1,642	0,101
Prediction Interval			-0,330	0,000	0,000	-2,170	1,510	0,000	0,000

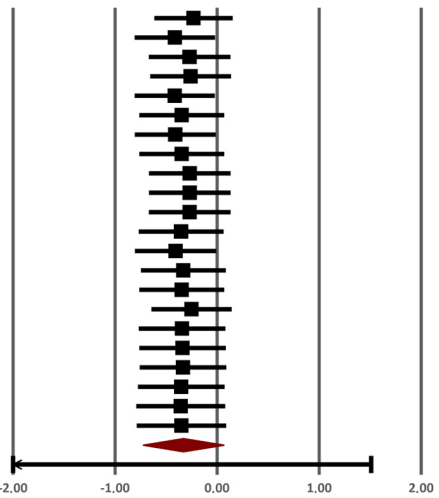


Figure 3. Sensitivity analysis: Effect of study removal on overall results. This plot shows the stability of the pooled effect size by sequentially removing individual studies. The consistency of the effect size suggests the robustness of the meta-analytic findings.

across different populations and study contexts. This further emphasizes the need for additional targeted studies to reduce uncertainty and improve estimation of the true effect of anticholinergics on cognitive function.

Moderator analysis. The moderator analysis evaluated the relationship between the proportion of female participants in the included studies and the observed SMD in cognitive outcomes, as shown in the regression plot (Fig. 7).

Group by Subgroup within study	Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Attention	Krebs et al., 2017 e	Attention	Auditory	1,645	0,446	0,199	0,770	2,520	3,684	0,000
Attention	Krebs et al., 2017 f	Attention	Visual	0,000	0,391	0,153	-0,766	0,766	0,000	1,000
Attention	Krebs et al., 2017 g	Attention	Total errors	1,486	0,437	0,191	0,630	2,342	3,403	0,001
Attention	Krebs et al., 2017 h	Attention	Total omissions	0,000	0,391	0,153	-0,766	0,766	0,000	1,000
Attention	Krebs et al., 2017 l	Attention	Total number	0,120	0,391	0,153	-0,647	0,886	0,306	0,760
Attention	Krebs et al., 2017 m	Attention	Total errors	1,395	0,431	0,186	0,549	2,241	3,233	0,001
Attention	Pooled			0,752	0,328	0,108	0,108	1,395	2,289	0,022
Attention	Prediction Interval			0,752			-1,368	2,871		
Executive function	Krebs et al., 2017 a	Executive function	Perseveration	-2,653	0,523	0,274	-3,678	-1,627	-5,068	0,000
Executive function	Krebs et al., 2017 n	Executive function	Test time	-0,331	0,393	0,155	-1,102	0,439	-0,843	0,399
Executive function	Krebs et al., 2017 o	Executive function	Test errors	0,000	0,391	0,153	-0,766	0,766	0,000	1,000
Executive function	Krebs et al., 2017 p	Executive function	Fluency	-2,120	0,480	0,230	-3,060	-1,179	-4,419	0,000
Executive function	Morrow et al., 2018 a	Executive function	SDMT	-0,111	0,262	0,069	-0,624	0,402	-0,423	0,673
Executive function	Pooled			-0,986	0,495	0,245	-1,955	-0,016	-1,993	0,046
Executive function	Prediction Interval			-0,986			-4,608	2,637		
Global	Sakakibara et al., 2013 a	Global	MMSE	0,043	0,253	0,064	-0,452	0,538	0,170	0,865
Global	Sakakibara et al., 2013 b	Global	FAB	0,093	0,180	0,032	-0,259	0,445	0,518	0,605
Global	Sakakibara et al., 2013 c	Global	ADAS-cog	-0,037	0,180	0,032	-0,389	0,315	-0,205	0,837
Global	Pooled			0,031	0,113	0,013	-0,191	0,253	0,274	0,784
Global	Prediction Interval									
Memory	Krebs et al., 2017 i	Memory	Total recall	-1,685	0,449	0,202	-2,565	-0,805	-3,753	0,000
Memory	Krebs et al., 2017 j	Memory	Delayed recall	-1,687	0,449	0,202	-2,567	-0,807	-3,756	0,000
Memory	Krebs et al., 2017 k	Memory	Immediate recall	-1,663	0,448	0,200	-2,540	-0,786	-3,715	0,000
Memory	Morrow et al., 2018 b	Memory	BVMTR	-0,197	0,262	0,069	-0,711	0,317	-0,752	0,452
Memory	Morrow et al., 2018 c	Memory	CLVT2	-0,277	0,263	0,069	-0,792	0,238	-1,054	0,292
Memory	Pooled			-1,029	0,360	0,129	-1,734	-0,324	-2,860	0,004
Memory	Prediction Interval			-1,029			-3,565	1,507		
Visuospatial performance	Krebs et al., 2017 b	Visuospatial performance	Block design	1,585	0,443	0,196	0,717	2,453	3,581	0,000
Visuospatial performance	Krebs et al., 2017 c	Visuospatial performance	Picture completion	-1,643	0,446	0,199	-2,518	-0,769	-3,682	0,000
Visuospatial performance	Krebs et al., 2017 d	Visuospatial performance	Gestalt closure	-1,883	0,462	0,214	-2,790	-0,977	-4,073	0,000
Visuospatial performance	Pooled			-0,645	1,126	1,269	-2,853	1,563	-0,573	0,567
Visuospatial performance	Prediction Interval			-0,645			-28,692	27,402		
Overall	Pooled			-0,031	0,100	0,010	-0,228	0,165	-0,311	0,756
Overall	Prediction Interval			-0,031			-1,835	1,773		

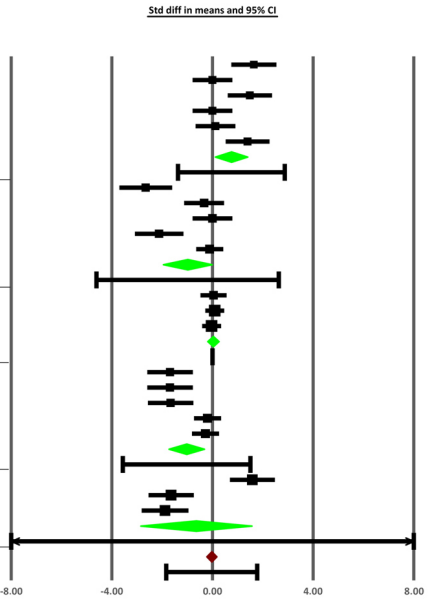


Figure 4. Subgroup analysis of cognitive domains. The forest plot displays the pooled effect sizes for different cognitive domains, including attention, memory, executive function, visuospatial performance and global cognition. Diamonds represent pooled standardized mean differences within each subgroup. CI, confidence interval.

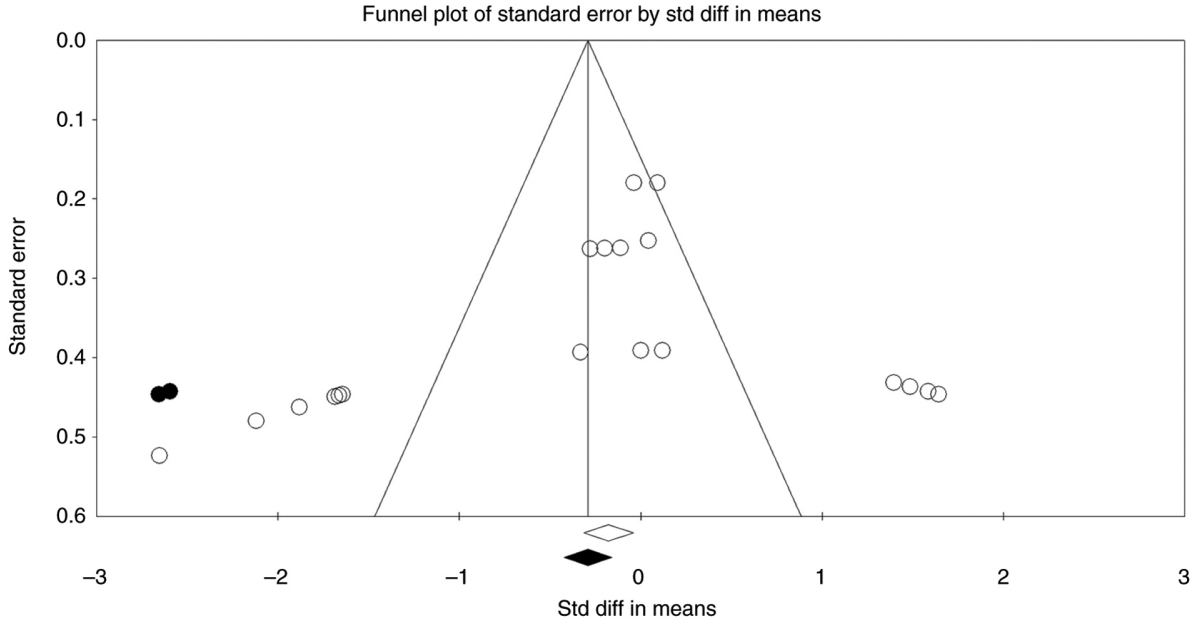


Figure 5. Funnel plot of standard error by standardized mean differences. The funnel plot assesses publication bias by plotting the standard error against the effect size for individual studies. Asymmetry indicates potential bias, further analyzed using Begg's and Egger's tests.

The regression model yielded a positive slope of 0.033 (95% CI: 0.014 to 0.053, P<0.001), indicating a significant association between sex distribution and the magnitude of cognitive decline. As the proportion of female participants increased, the observed cognitive impact of anticholinergic medications diminished, suggesting that females may be less susceptible to adverse cognitive effects compared with males. The intercept of -1.753 (P<0.001) reflects the baseline SMD when the male proportion is minimal. The significant Q-value (P<0.001) supports the robustness of this association, with a tau-squared value of 1.096 reflecting the variance explained by sex as a moderator. This analysis highlights the importance of considering sex as a key factor in understanding differential cognitive responses to anticholinergic medications.

The moderator analysis also assessed the relationship between the participants' mean age in the studies and the observed SMD in cognitive outcomes (Fig. 8). The regression analysis yielded a significant positive slope of 0.036 (95% CI: 0.01623 to 0.05669, P<0.001), indicating that as the mean age of participants increased, the magnitude of cognitive decline associated with anticholinergic use was reduced. The

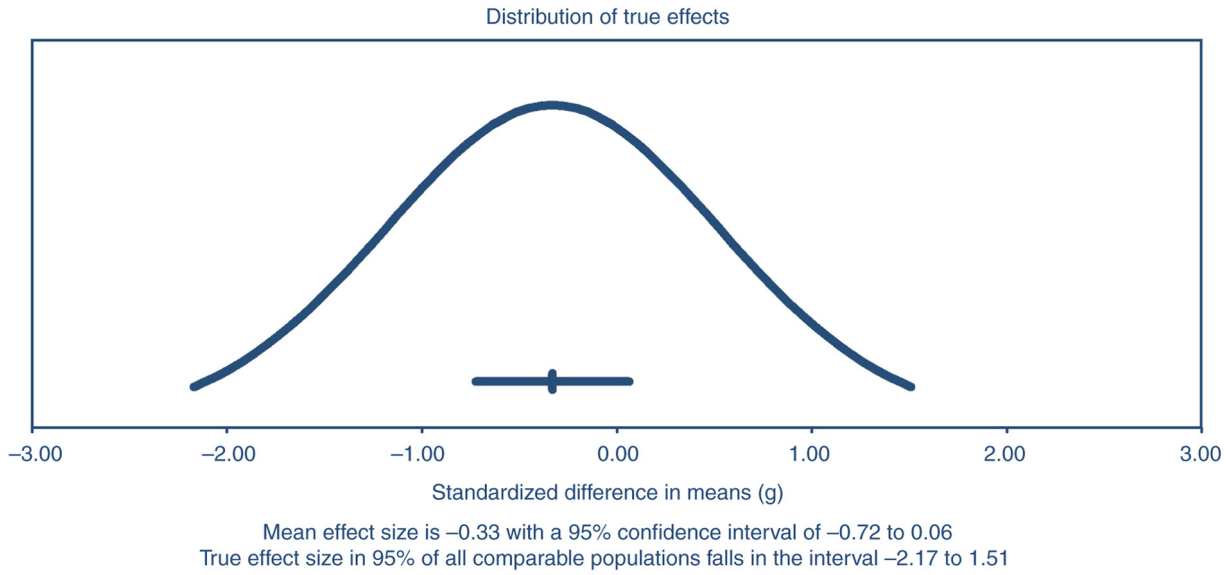


Figure 6. Distribution of true effects (precision interval analysis). This plot shows the distribution of true effect sizes with a mean effect of -0.33 and a 95% confidence interval of -0.72 to 0.06. The precision interval extends from -2.17 to 1.51, reflecting uncertainty due to between-study variability.

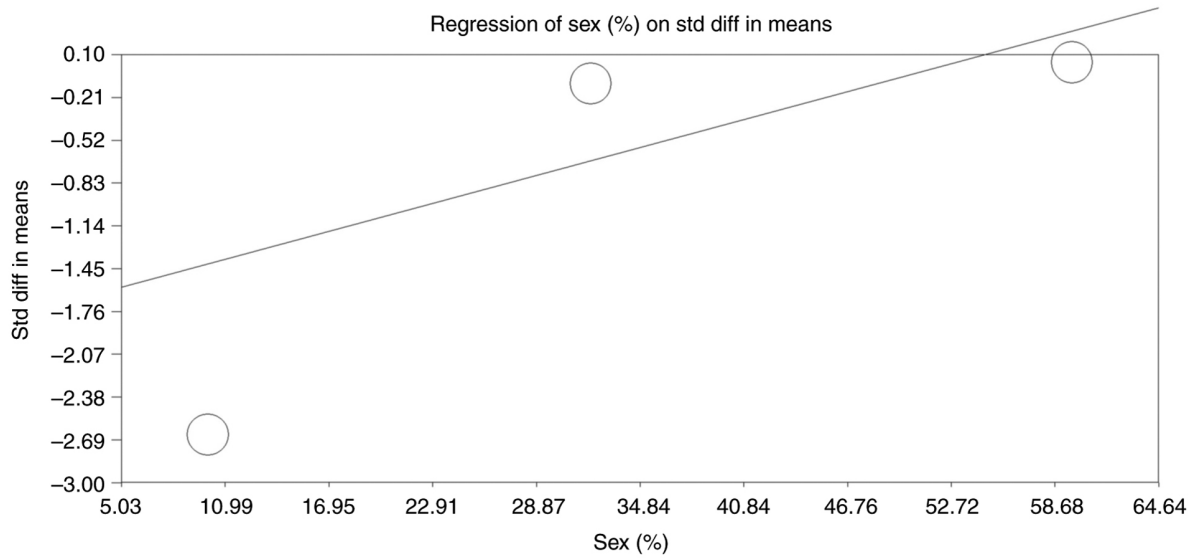


Figure 7. Moderator analysis: Regression of sex (%) on standardized mean differences. The regression plot illustrates the relationship between the proportion of male participants and the observed effect size. The positive slope suggests that higher male representation is associated with reduced cognitive decline.

intercept value of -2.414 (P<0.001) reflects the baseline SMD at a younger mean age. The significant Q-value (P<0.001) suggests that age significantly moderated the cognitive impact of anticholinergics, with younger participants experiencing more severe cognitive decline. The tau-squared value of 0.961 indicates considerable between-study variability explained by differences in mean age. This analysis highlights age as a critical moderator, suggesting that younger individuals may be more susceptible to anticholinergic-induced cognitive impairments compared with older adults.

Quality assessment. The quality of the included studies was assessed using the NOS, with scores ranging from 6 to 8 out of a maximum of 9. Morrow *et al* (7) received the highest score (8/9), reflecting its randomized design, comprehensive outcome assessment, and high comparability between groups. Krebs *et al* (14) scored 7/9, with points deducted for limited blinding and potential confounders. Sakakibara *et al* (4) received a score of 6/9 due to potential selection bias, limited blinding, and reduced comparability across groups. Overall, the studies demonstrated moderate to high methodological quality, ensuring reliable data for meta-analysis (Table II).

Discussion

The present systematic review and meta-analysis investigated the cognitive effects of anticholinergic medications in individuals with NLUTD. The primary findings suggest a trend toward negative cognitive impact-particularly in the domains

Table II. Quality assessment using the NOS.

First author/s, year	Selection (4)	Comparability (2)	Outcome (3)	Total score	(Refs.)
Krebs *et al*, 2017	++++	+-	++-	7/9	(14)
Morrow *et al*, 2018	++++	++	+++	8/9	(7)
Sakakibara *et al*, 2013	+++ -	--	++-	6/9	(4)

The quality assessment of each included study was presented using the NOS, with individual columns representing key evaluation domains. The total score reflects the study's methodological rigor, with a maximum of 9 points. NOS, Newcastle-Ottawa Scale.

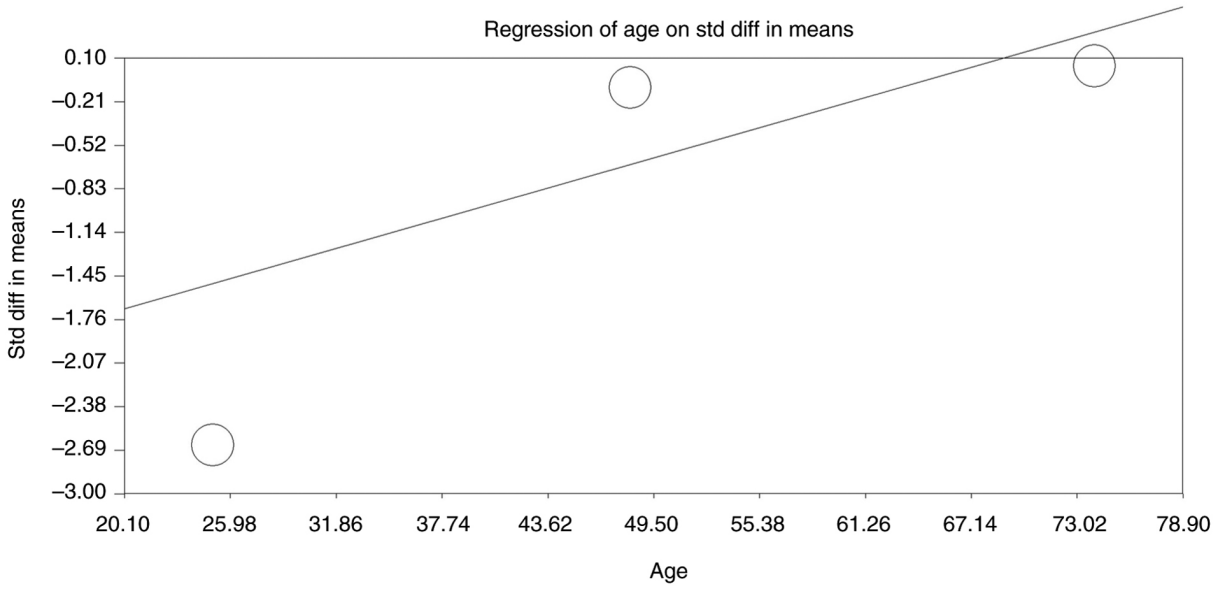


Figure 8. Moderator analysis: Regression of age on standardized mean differences. The regression plot shows the relationship between mean participant age and cognitive effect sizes. The positive slope indicates that younger participants experience greater cognitive impairments compared with older individuals.

of memory, executive function and attention-though the overall effect using a random-effects model did not reach statistical significance. This discussion contextualizes these findings within the broader literature, highlights potential explanations for the heterogeneous outcomes, and proposes clinical implications and future directions.

A key observation from the pooled results is the modest, albeit statistically non-significant, negative overall impact of anticholinergics on cognitive performance (SMD=-0.33; 95% CI: -0.72 to 0.06; P=0.10). Although the fixed-effects model produced a statistically significant SMD of -0.178 (P=0.011), the random-effects model was prioritized, which yielded a non-significant SMD of -0.33 (P=0.10). This choice was made because the random-effects model incorporates between-study heterogeneity, combining both within-study and between-study variance into the pooled estimate-an approach that is most appropriate given the observed high heterogeneity (Q=162.25, P<0.001; τ^2=0.738) (15). By contrast, the fixed-effects model assumes all studies estimate the same true effect. While it offers greater statistical power, it may underestimate uncertainty when substantial between-study variability exists (15). Therefore, to provide a more conservative and realistic estimate that reflects clinical diversity, the random-effects model was deemed more appropriate.

Our findings align with existing evidence indicating that anticholinergic medications can impair central cholinergic pathways involved in cognition (1,2). In particular, the cholinergic deficit hypothesis has been well-documented in several neurocognitive disorders, including Alzheimer's disease, emphasizing the importance of central acetylcholine in learning, memory, and attention (16). Given that anticholinergics block muscarinic receptors, a reduction in central cholinergic signaling can manifest as deficits in processing speed, executive functioning, and memory formation (17). While the lack of significance in the present meta-analysis calls for caution in interpreting the data, the consistency with theoretical mechanisms and other clinical trials warrants continued scrutiny of anticholinergic-induced cognitive decline.

A striking feature of the present meta-analysis is the substantial heterogeneity (Q-value of 162.25, P<0.001; τ^2=0.738). The wide prediction interval (-2.17 to 1.51) highlights significant between-study variability and reflects instability in the overall effect. This contrasts with the narrower CI, which estimates the precision of the mean effect (18). The breadth of the interval indicates that findings should be interpreted cautiously (19), and highlights the need for future large-scale and standardized trials to reduce uncertainty and improve

estimation of the true cognitive impact of anticholinergics. Several factors might underlie this variability in effect sizes. First, differences in sample characteristics, such as underlying etiologies (for example, MS, SCI and OAB) and disease progression, could contribute to varying baseline vulnerability to cognitive dysfunction. Individuals with MS or SCI often exhibit pre-existing cognitive deficits due to demyelination or traumatic central nervous system injury (20,21). The incremental burden of anticholinergic medications may, therefore, differ depending on neurological reserve and the severity of baseline impairments. Second, the use of various anticholinergic agents (for example, oxybutynin, tolterodine, solifenacin and imidafenacin) with diverse pharmacokinetic profiles likely influenced cognitive outcomes. Older-generation medications such as oxybutynin and tolterodine are known to cross the blood-brain barrier more readily, thereby increasing the likelihood of central side effects (22). Conversely, newer or more selective agents (for example, solifenacin and imidafenacin) may exert a lesser central anticholinergic burden, resulting in lower cognitive risk (22). It is thus plausible that differences in agent selectivity, dosing schedules, and treatment durations contributed to the heterogeneity detected in this review. Third, variations in outcome measures across the included studies can also drive heterogeneity. Some studies relied on global cognitive measures (for example, MMSE, ADAS-cog, FAB), which may lack sensitivity to subtle cognitive changes. More comprehensive or domain-specific instruments (for example, the SDMT or detailed memory tasks) might detect more nuanced impairments. This meta-analysis found stronger associations in targeted domains such as memory, executive function, and attention, suggesting that future research should prioritize sensitive, domain-specific assessments to capture the full extent of cognitive changes induced by anticholinergics.

Despite the non-significant pooled effect, the subgroup analyses offered valuable insights. Attention, executive function, and memory domains emerged as particularly vulnerable to the effects of anticholinergics. These domains are heavily reliant on adequate cholinergic transmission (23). Studies utilizing tests such as the Stroop Test, the SDMT, and word-list learning tasks have repeatedly demonstrated that blocking cholinergic receptors impairs selective attention, mental flexibility, and the encoding of new memories (24,25). In NLUTD populations where patients may already contend with the cognitive burden from neurological disorders, even minor reductions in performance can have profound practical consequences, affecting daily living activities, adherence to rehabilitation protocols, and overall quality of life.

The moderator analyses underscore the complexity of factors influencing cognitive vulnerability. Intriguingly, a higher proportion of females in a study's cohort correlated with smaller negative cognitive effects ($P<0.001$). Although evidence is mixed, some literature suggests that sex-related hormonal and genetic factors could modulate pharmacodynamic and pharmacokinetic responses to medications (26). Similarly, older age was associated with reduced severity of cognitive decline, suggesting that younger individuals with NLUTD may be more susceptible ($P<0.001$). While this finding appears counterintuitive-given that older adults are generally considered at elevated risk of anticholinergic-induced delirium or cognitive impairment-certain explanations may apply. Younger cohorts might exhibit higher baseline functioning, making any decrement from baseline more pronounced. Additionally, older adults with significant frailty or comorbidities might be preferentially prescribed lower doses or more selective anticholinergics, thereby moderating their cognitive risks.

Clinical implications from these findings revolve around two major points. First, prescribers must balance therapeutic goals in managing NLUTD with the potential for adverse cognitive events. Urinary incontinence, frequency, and urgency negatively affect patient well-being, but the costs of therapy include potential detrimental effects on higher-order brain function. In populations with existing neurologic compromise, vigilance is paramount. Clinicians could consider minimizing exposure to highly lipophilic or non-selective anticholinergics and employing the lowest efficacious dose. Second, alternative therapies such as β3-adrenergic agonists (for example, mirabegron) have shown promise in providing symptomatic relief with less central cholinergic interference (27). Transitioning or combining these agents with other interventions-for example, pelvic floor rehabilitation and neuromodulation therapies-may be a viable strategy for individuals with significant cognitive vulnerability (28).

While the publication bias analysis and trim-and-fill adjustments indicate only a minor impact of potential unpublished negative or null studies, the slight asymmetry in the funnel plot underscores the need for continued, transparent reporting of cognitive outcomes in NLUTD populations. Researchers must publish all relevant data, including neutral or equivocal results, to ensure that meta-analytic estimates accurately reflect true effects. Although Begg's test indicated possible small-study effects, the non-significant Egger's result and minimal change after applying trim-and-fill (only two studies imputed, with little effect on the pooled SMD) suggest that publication bias likely does not materially alter our overall conclusions (29).

The present meta-analytic systematic review has several limitations. First, the overall number of included studies was small (N=3), limiting the power to detect modest but clinically relevant cognitive changes. Moreover, the short treatment durations and heterogeneous follow-up periods (ranging from a few weeks to months) may not fully capture the long-term cognitive trajectory of patients receiving anticholinergics. Second, the included studies employed various cognitive tests, ranging from global measures (for example, MMSE) to domain-specific tools, making direct comparisons challenging and introducing potential measurement bias. Third, while the meta-analysis attempted to evaluate publication bias, the limited number of studies constrains the reliability of these statistical tests. Fourth, confounding variables-such as concomitant medication use, overall anticholinergic burden from multiple sources, and comorbid psychiatric or neurological conditions-were not consistently reported or controlled for across studies. Fifth, most studies had relatively small sample sizes and did not stratify participants based on the severity of NLUTD or baseline cognitive function, precluding more nuanced subgroup analyses. Sixth, although the subgroup analyses revealed statistically significant SMDs for attention (0.752), executive function (-0.948), and memory (-0.645), it was emphasized that these results are preliminary. With only three studies and small

subgroup samples, estimates may be unstable, and type I error is possible (30). These findings should be considered hypothesis-generating rather than confirmatory, aligned with broader trends observed in anticholinergic research that highlight domain-specific vulnerabilities but await validation in larger, adequately powered studies. Seventh, the moderator findings-suggesting less cognitive impact in studies with more female participants and greater declines in younger cohorts-should be interpreted cautiously. With only three contributing studies, the estimates are statistically underpowered and potentially confounded, in line with methodological cautions against overinterpreting such results. As such, these results remain hypothesis-generating and should be confirmed in larger, more robustly powered analyses. Eights, the subgroup and moderator analyses were performed post hoc and not pre-specified in a formal protocol. As such, these findings should be interpreted with caution, recognizing their exploratory nature. Finally, the observed high heterogeneity ($Q=162.25$, $\tau^2=0.738$) likely reflects not only clinical diversity but also methodological variability-notably, differences in cognitive testing instruments and anticholinergic pharmacodynamics. For instance, more sensitive domain-specific tools (for example, SDMT, FAB) may detect subtle deficits missed by global measures such as MMSE. Additionally, drug-specific factors-such as muscarinic receptor subtype selectivity and central nervous system penetration-might explain variability, as older agents (for example, oxybutynin) pose higher cognitive risks than newer, more selective agents (for example, imidafenacin) (31,32). Future meta-regression or individual participant data analyses are needed to more precisely quantify these structural sources of heterogeneity.

In conclusion, the present meta-analysis suggests that anticholinergic medications may exert a negative, though variably expressed, impact on cognition in patients with NLUTD, particularly in memory, executive function, and attention. While the pooled effect did not reach statistical significance using a random-effects model, considerable heterogeneity points to the influence of patient characteristics, drug choice, and methodological differences in outcome assessment. These findings underscore the need for carefully weighing therapeutic benefits against potential cognitive risks, especially in populations already burdened by neurological compromise. Future large-scale, longitudinal studies with standardized cognitive measures, detailed patient stratification, and attention to confounding factors are essential to refine our understanding of anticholinergic-related cognitive changes and guide safer prescribing practices.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HZ and YW conceptualized the study, designed the search strategy, and drafted the initial manuscript. HZ performed data extraction, contributed to data analysis, and assisted with manuscript revisions. HZ conducted the quality assessment, contributed to statistical analysis and finalized the manuscript. HZ and YW confirm the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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