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# ANTICHOLINERGIC BURDEN AND ITS EFFECTS ON ELDERLY POPULATION: A SYSTEMATIC REVIEW & META-ANALYSIS


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**ABSTRACT** Anticholinergic medications are widely used in older adults but may be associated with adverse effects. This meta-analysis aimed to evaluate the impact of anticholinergic burden on cognitive function, falls, grip strength, and other adverse events in the elderly population. A systematic review and meta-analysis were conducted following PRISMA guidelines. PubMed, EMBASE and Cochrane Library were searched for relevant studies. Random-effects meta-analyses were performed to calculate pooled risk ratios (RR) with 95% confidence intervals (CI). Sixteen studies with 631,110 older adults were included. Anticholinergic drug use was associated with significantly increased risks of cognitive decline (RR 1.83, 95% CI 0.84-3.99), falls (RR 2.75, 95% CI 0.54-13.93), and loss of grip strength (RR 2.37, 95% CI 0.56-10.08) compared to controls. There was no significant association with overall adverse events. High heterogeneity was observed for most outcomes. Conclusion: This meta-analysis found anticholinergic medication use in older adults is associated with increased risks of cognitive decline, injurious falls, and loss of grip strength. Clinicians should carefully consider the risks and benefits when prescribing anticholinergic drugs to elderly patients. Regular medication reviews may help reduce the anticholinergic burden in this vulnerable population.

KEYWORDS :

## BACKGROUND

With the increasing healthcare advancements, the geriatric population (> 65 years) has been increasing rapidly and is expected to grow up to 70 million by 2030 [1]. The rapid rise in the elderly population demands more medical care facilities as these patients are dependent on polypharmacy (multiple drug users) and at higher risk of comorbidities [2, 3]. Among older adults (> 65 years), the mean number of medications is 6 [4]. Various treatment guidelines such as Beers and STOPP/START criteria help in identifying the inappropriate medications whose long-term use is associated with more complications and more adverse events among adults older than 65 years [5].

The anticholinergic drugs are widely used for treatment of allergies, depression, overactive bladder, chronic obstructive pulmonary disease (COPD), and Parkinson's disease [6, 7]. These drugs act on the peripheral and central nervous system by blocking the neuro-transmitter acetylcholine. Even while anticholinergic drugs have therapeutic advantages, using those in older persons poses several serious risks because of age-related physiological changes [8]. Anticholinergic drugs have been frequently associated with a rapid increase in adverse events, as reported by previous studies [9]. These medications induce pharmacodynamics and pharmacokinetic changes, leading to a risk of adverse events including decreased renal clearance, increased sensitivity of the cholinergic system, and reduced hepatic metabolism among older adults [10]. Prolonged use of these drugs can lead to a high risk of injurious falls, loss of grip strength, impulsive behaviors, cognitive decline, and loss of independence [11].

"Anticholinergic Burden" is defined as the combined effects of two or more medications with anticholinergic properties. While the Anticholinergic Risk Scale (ARS) is a measure for assessing a patient's potential risk of anticholinergic side effects that can cause delirium and cognitive impairment, was developed in response to this. A three-point rating system (0, no, or low risk; 3, significant anticholinergic potential) has been adopted by the ARS to rank drugs for anticholinergic potential [12].

A greater anticholinergic drug burden is associated with higher rates of delirium or dementia, risk of falls, constipation, and cognitive dysfunction among older patients. The effect on cognitive function is particularly concerning because a higher anticholinergic burden has been associated with a higher risk of dementia and an earlier rate of cognitive decline. Given that dementia and cognitive decline are already significant public health issues due to older people, this is particularly alarming. Thus, various types of comorbidities linked with anticholinergic medications can be reversed by reducing the burden of anticholinergic drugs. The elderly are more likely to suffer from the negative consequences of anticholinergic burden [13, 14].

Due to the increasing use of anticholinergic medications and growing harmful effects, it is crucial to evaluate the adverse effects of the anticholinergic burden on the elderly population. Previous studies have evaluated the association of anticholinergic drugs with adverse effects among elderly populations [2, 3, 15]. The findings of these studies reported that anticholinergic drugs are associated with higher risks of cognitive impairments, falls, and all-cause mortalities. However, these studies either lack appropriate pooled analysis or the number of studies is limited to conclude. Therefore, this study aimed to evaluate the adverse events caused by anticholinergic burden among the elderly population by adopting a meta-analysis research approach.

## Methods

### Search Design

The "Reporting Items for Systematic Review and Meta-Analysis (PRISMA)" guidelines [16] were followed to perform this meta-analysis evaluating the adverse effects of anticholinergic burden on the elderly population. This study was a meta-analysis of already published randomized controlled trials, so there is no need for additional ethical review.

### PICO Framework

The PICO model was used to design research questions [17]. For meta-analysis, the model provided PICO questions according to above

mentioned research aims, as follows:
**Population:** Elder patients receiving any type of anticholinergic drug Intervention (effects): Anticholinergic drugs.

**Comparison:** Placebo or control or receiving any other type of drugs

**Outcomes:** Cognitive Functional decline, Risk of falls, Grip strength, adverse events (dementia or delirium).

### Search Strategy
The PRISMA guidelines assisted in the selection and screening of research articles related to the study aims. Three Electronic databases such as PubMed, EMBASE, and Cochrane Library were searched for data extraction by using MeSH search terms from inception to November 2024. These MeSH terms were ("anticholinergic drugs" OR "Antimuscarinic Agents" OR "Cholinergic Antagonists") AND ("elder population" OR "older adults" OR "geriatric population") AND ("risk of falls" OR "cognitive decline" OR "incidence of dementia" OR "Grip strength" OR "delirium"). We carefully examined the reference lists of all the previous systematic reviews and Meta-analysis-based articles to seek further research articles.

### Inclusion and Exclusion Criteria
The eligibility criteria assisted in selecting and screening research articles after searching research articles from electronic databases. Only those studies were included, meeting the following inclusion criteria; Studies analyzed the older adults or geriatric population, Studies analyzing the effects of anticholinergic drugs, Studies tracking the outcomes such as cognitive functional decline, risk of falls, grip strength, and adverse events (dementia or delirium), Studies based on randomized controlled trials (RCT's), cohort studies and observational studies, and the Studies published in English language and full text available.

Those studies excluded those discussing non-human samples or animals or young populations, those involving the impacts of other drugs rather than anticholinergic drugs, those discussing other outcomes rather than above mentioned, those based on a systematic review, meta-analysis, comprehensive reviews, narrative reviews, and editorials those studies published in other languages rather than English and non-full text papers.

### Data Extraction & Study Outcomes
Two independent reviewers extracted the data to put in the pre-specified table. The data related to demographic information such as authors, year of study, country, study population, sample size, study design, study follow-up, and primary outcomes of Cognitive Functional decline, Risk of falls, Grip strength, adverse events (dementia or delirium) were extracted (Table 1). Discrepancies were resolved by consulting a third reviewer.

### Quality Assessment
Two reviewers independently examined the quality of each included study based on criteria as designed by the Critical Appraisal Skills Program (CASP) tool [18]. Each question or parameter in the CASP checklist was allocated a numerical value: Yes=1, No=0, and Unclear=0. Each included study's overall score was determined, with a maximum score of nine. Articles that scored seven points or higher were categorized as high quality, whereas research that fell short of this standard was categorized as low quality.

### Statistical Analysis
All statistical analysis was conducted by using Review Manager Software (Cochrane Collaboration: version 5.4.0) [19]. A p-value of $<0.05$ was considered statistically significant. The pooled analysis of data was performed for studies with potential heterogeneity by using random-effects models. The effect sizes were shown as HR or OR ratios for outcomes such as Cognitive Functional decline, Risk of falls, Grip strength, and adverse events (dementia or delirium). Heterogeneity was evaluated using the $I^2$ statistic; $I^2$ values above 50% indicated significant heterogeneity.

## RESULTS
### Included Studies
In this meta-analysis, the selection and screening of research articles related to the study aim "Anticholinergic burden and its effects on elderly Population" was completed by following PRISMA guidelines. About 29,700 research articles were obtained through MeSH keywords from three prescribed electronic databases. About 3491 research articles were extracted after the implication of the search strategy. The eligibility criteria were applied to 569 articles and seven studies were included in the final pooled analysis, as mentioned in Figure 1

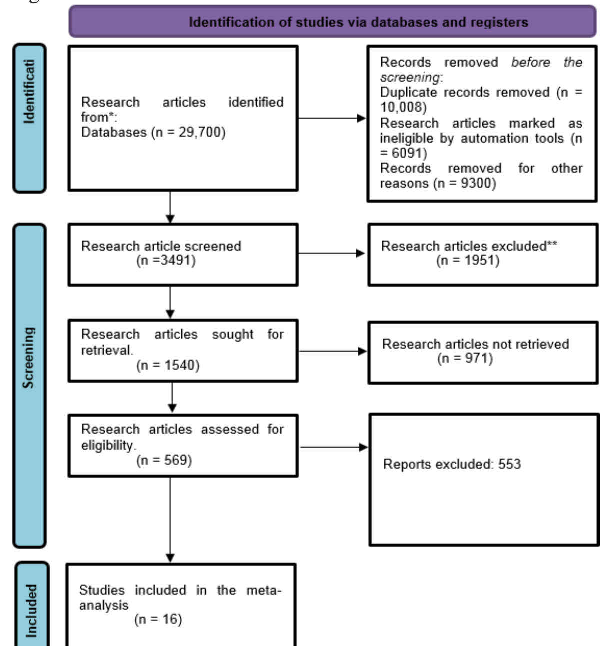


**Figure 1:** Flow Chart Of Screening And Selection Of Research Articles By PRISMA Guidelines

**Table 1: Characteristics Of Included Studies**

| Author, year | Country | Study Population (mean age) | Study groups | Study Design | Study follow up | Cognitive Functional decline (MMSE) | Risk of falls | Grip strength | Adverse events (dementia or delirium) |
|---|---|---|---|---|---|---|---|---|---|
| Landi et al., 2014 [20] | Italy | 1490 patients (73.4 years) | T: 769<br>P: 721 | Prospective observational study | 12 months | T: 1.13 (1.03-1.23) | T: 1.26 (1.13-1.41) | | T: 1.16 (1.02 -1.32) |
| Rudolph et al., 2008 [8] | USA | 117 patients (>65 years) | T; 62<br>P: 70 | Prospective cohort study | 1 year | N/A | N/A | N/A | N/A |
| Cao et al., 2008 [21] | USA | 932 patients (78 years) | T; 447<br>P: 484 | Prospective cohort study | 2.5 years | T: 2.6 (1.3–5.1 | T: 2.7 (1.2–5.8) | N/A | N/A |
| Gnjidic et al., 2016 [22] | Canada | 1793 patients (74.4 years) | T: 591<br>P; 1202 | Prospective cohort study | 1 year | T: -0.53 (-0.73 to -0.33) | N/A | N/A | N/A |
| Cossette et al., 2017 [23] | Finland | 1793 patients (73 years) | T: 1022<br>P: 770 | Prospective cohort study | 1 year | N/A | T: –0.98 (–2.05, 0.08) | T: –0.13 (–0.19, –0.08 | N/A |
| Gnjidic et al., 2012 [24] | Australia | 115 participants | T: 27<br>P; 65 | Prospective cohort study | 1 year | N/A | N/A | T: 0.10 (-2.54, 2.74) | N/A |
| Landi et al., 2007 [25] | Italy | 364 patients (85.5 years) | T; 144<br>P; 220 | Prospective cohort study | 1 year | T; 1.68 ± 0.15 | N/A | T; 3.5 (0.8-1.0) | N/A |

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|---|---|---|---|---|---|---|---|---|---|
| Sato et al., 2017 [26] | Japan | 306 participants | T; 176<br>P; 130 | cross-sectional study | 3 years | T: -0.21 (-1.78, 1.35) | N/A | T: -6.31 (-11.61, -1.01) | N/A |
| Wilson et al., 2011 [27] | Australia | 602 patients (85.5 years) | T: 158<br>P; 444 | Observational study | 1 year | T; 1.37 (1.06–1.76) | N/A | N/A | T; 1.10 (0.77–1.56) |
| Attoh-Mensah et al., 2020 —[28] | France | 177 (64.04 years) | T: 63<br>P: 114 | Cross-sectional study | 2 years | N/A | T: 1.17 (0.58–2.34) | 0.92 (0.82–1.03) | T: 1.74 (1.10–2.74) |
| Squires et al., 2020 [29] | USA | 1635 participants (78.8 years) | T: 986<br>P: 664 | Cohort study | 2.6 years | N/A | 1.60 [1.10–2.32] | N/A | N/A |
| Hsu et al., 2021 [30] | Taiwan | 116,043 people (74.8 years) | | Cross-sectional study | 10 years | N/A | N/A | N/A | 3.30 (2.84–3.84) |
| Krüger et al., 2021 [31] | Germany | 2750 patients | T;1475<br>P; 1274 | longitudinal cohort study | 3 years | T: −0.24 | N/A | N/A | N/A |
| Hanlon et al., 2020 [32] | United Kingdom | 502,538 participants (60 years) | T: 135,321<br>P; 367,319 | Longitudinal study | 6.2 years | N/A | N/A | N/A | T: 1.45 (1.3-1.61) |
| Kersten et al., 2013 [33] | Norway | 87 patients (47 years) | T: 47<br>P; 40 | Randomized controlled trial | 8 weeks | T: 0.39 (−0.96, 1.75) | N/A | N/A | N/A |
| Zia et al., 2016 [34] | Malaysia | 428 participants | T: 263<br>P; 165 | Case-control study | 12 months | N/A | T: 1.4; (0.89–2.4) | N/A | N/A |

(Legends: MMSE: Mini-Mental State Examination, T; treatment & P: placebo)

**Quality Assessment of Included Studies**

All 16 included studies were assessed by CASP due to the inclusion of cohort, cross-sectional, and observational studies. All studies were of high quality except one [33] which was of moderate quality, as mentioned in Table 2.

**Table 2: CASP Critical Appraisal Skills Program www.casp-uk.net**

| Author and year | Clear Statement of research aims | Appropriate qualitative methodology | Appropriate study design for research aims | Appropriate recruitment strategy | Data collection | Adequate relationship between participant and research | Ethical considerations | Rigorous data analysis | Clear Statement of Findings | Overall score |
|---|---|---|---|---|---|---|---|---|---|---|
| Landi et al., 2014 [20] | Y | Y | Y | N | Y | Y | N | Y | Y | 7 |
| Rudolph et al., 2008 [8] | Y | Y | Y | Y | Y | Y | N | Y | Y | 8 |
| Cao et al., 2008 [21] | Y | Y | N | Y | Y | Y | Y | UN | Y | 7 |
| Gnjidic et al., 2016 [22] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Cossette et al., 2017 [23] | Y | Y | UN | Y | Y | Y | Y | N | Y | 7 |
| Gnjidic et al., 2012 [24] | Y | Y | Y | Y | Y | Y | Y | N | Y | 8 |
| Landi et al., 2007 [25] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Sato et al., 2017 [26] | Y | Y | Y | Y | Y | Y | Y | UN | Y | 8 |
| Wilson et al., 2011 [27] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Attoh-Mensah et al., 2020 [28] | Y | Y | Y | N | N | Y | Y | Y | Y | 7 |
| Squires et al., 2020 [29] | Y | Y | N | Y | Y | Y | Y | Y | Y | 8 |
| Hsu et al., 2021 [30] | Y | Y | Y | Y | Y | Y | Y | Y | Y | 9 |
| Krüger et al., 2021 [31] | Y | Y | Y | Y | Y | Y | Y | UN | Y | 8 |
| Hanlon et al., 2020 [32] | Y | N | Y | Y | Y | Y | Y | Y | Y | 8 |
| Kersten et al., 2013 [33] | Y | Y | N | Y | Y | Y | N | Y | N | 6 |
| Zia et al., 2016 [34] | Y | N | Y | Y | Y | Y | Y | Y | Y | 8 |

(Legends: Y: yes, N: no, UN: unclear)

**Primary Outcomes**

**1. Cognitive Functional Decline (MMSE)**

Among 16 included studies, eight research articles reported a cognitive functional decline as an outcome among the elder population receiving anticholinergic drugs as compared to control. The pooled analysis reported that the risk of cognitive function decline was significantly higher in older adults receiving anticholinergic drugs than in the control group [RR: 1.83 (95% CI: 0.84 to 3.99) $p<0.00001$] and heterogeneity reported (df=7, $I^2$= 92%), as mentioned in Figure 2. The asymmetrical distribution of included studies on funnel plots shows high publication bias, as mentioned in Figure 3.

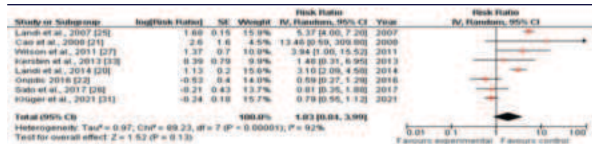

**Figure 2:** Forest Plot Of The Risk Ratio Of Cognitive Function Decline Among The Experimental Group As Compared To Control

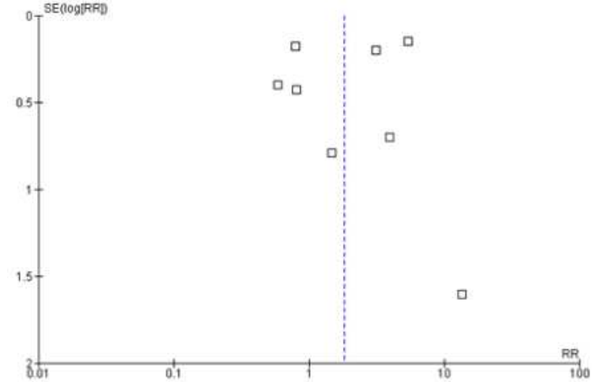

**Figure 3:** Funnel Plot Of The Risk Ratio Of Cognitive Function Decline Among The Experimental Group As Compared To Control

**2. Risk Of Falls**

Among 16 included studies, five research articles reported the risk of falls as an outcome among the elderly population receiving anticholinergic drugs as compared to control. The pooled analysis reported that the risk of injurious falls was significantly higher in older adults receiving anticholinergic drugs than in the control group [RR: 2.75 (95% CI: 0.54 to 13.93) p<0.00001] and heterogeneity reported (df=4, $I^2$ = 89%), as mentioned in Figure 4. The asymmetrical distribution of included studies on funnel plots shows high publication bias, as mentioned in Figure 5.

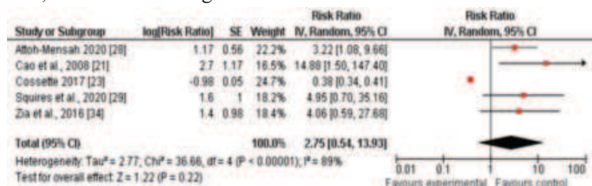

**Figure 4:** Forest Plot Of The Risk Ratio Of The Risk Of Falls Among The Experimental Group As Compared To The Control

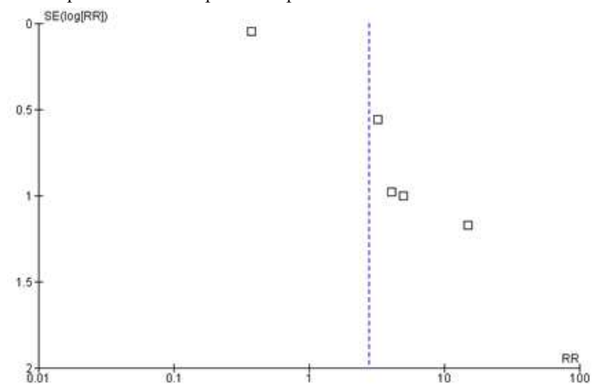

**Figure 5:** Funnel Plot Of The Risk Ratio Of The Risk Of Falls Among The Experimental Group As Compared To The Control

**3. Loss of Grip strength**

Among 16 included studies, five research articles reported a loss of grip strength as an outcome among the elderly population receiving anticholinergic drugs as compared to control. The pooled analysis reported that loss of grip strength was significantly higher in older adults receiving anticholinergic drugs than the control group [RR: 2.37 (95% CI: 0.56 to 10.08) p<0.00001] and heterogeneity reported (df=4, $I^2$ = 98%), as mentioned in Figure 6. The asymmetrical distribution of included studies on funnel plots shows high publication bias, as mentioned in Figure 7.

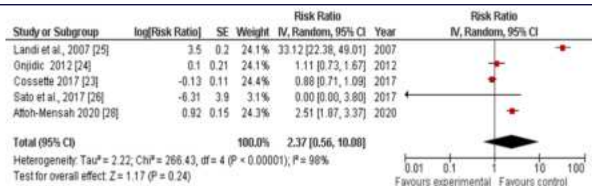

**Figure 6:** Forest Plot Of The Risk Ratio Of Grip Strength Among The Experimental Group As Compared To Control

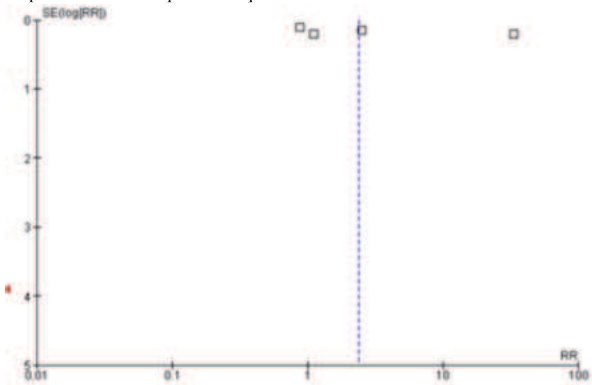

**Figure 7:** Funnel Plot Of The Risk Ratio Of Grip Strength Among The Experimental Group As Compared To Control

**4. Adverse Events (Dementia Or Delirium)**

Among 16 included studies, five research articles reported adverse events as outcomes among the elderly population receiving anticholinergic drugs as compared to control. The pooled analysis reported that adverse events were not associated with anticholinergic drugs among older adults receiving anticholinergic drugs than the control group [RR: 4.07 (95% CI: 2.60 to 6.36) p<0.35] and heterogeneity reported (df= 4, $I^2$ = 9%), as mentioned in Figure 8. The asymmetrical distribution of included studies on funnel plots shows high publication bias, as mentioned in Figure 9.

**Figure 8:** Forest Plot Of The Risk Ratio Of Adverse Events Among The Experimental Group As Compared To Control

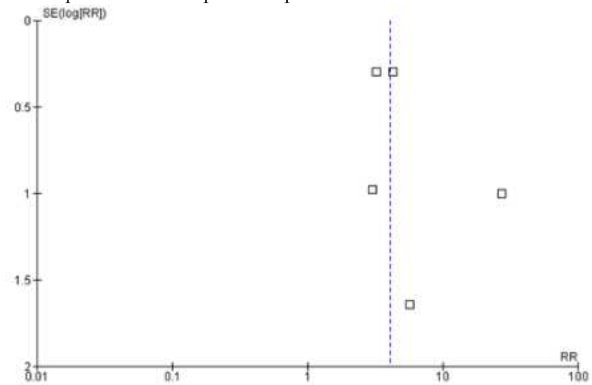

**Figure 9:** Funnel Plot Of The Risk Ratio Of Adverse Events Among The Experimental Group As Compared To Control

**DISCUSSION**

This study aimed to evaluate the adverse effects of anticholinergic burden on the elderly population by adopting a meta-analysis research approach. All 16 included studies were cross-sectional, cohort, and longitudinal studies. The mean age of the included patient population was 74.5 years. The median follow-up of anticholinergic drugs was 8 weeks to 10 years. Through 16 included studies and 631,110 older adults (>65 years), the findings reported that risk rates of cognitive

functional decline, injurious falls, and loss of grip strength were higher among older adults receiving anticholinergic drugs as compared to control. However, the risk of adverse events was not associated with the use of anticholinergic drugs. The pooled analysis reported that risk of cognitive function decline [RR: 1.83 (95% CI: 0.84 to 3.99) $p<0.00001$], injurious falls [RR: 2.75 (95% CI: 0.54 to 13.93) $p<0.00001$], and loss of grip strength [RR: 2.37 (95% CI: 0.56 to 10.08) $p<0.00001$] was significantly higher in older adults receiving anticholinergic drugs than control group. The funnel plots showed the asymmetrical distribution of included studies, representing high publication bias among included studies. The heterogeneity ranges from 89% to 98% (significant) for all outcomes except the adverse events having 9% heterogeneity (non-significant). All 16 included studies were assessed by CASP due to the inclusion of cohort, cross-sectional, and observational studies. All studies were of high quality except one [33] which was of moderate quality.

Anticholinergic medications are known to affect neurotransmitter systems essential for memory and cognition and may worsen age-related cognitive decline, according to the increased risk of cognitive decline. The findings are consistent with previous research that shows anticholinergic medications increase the risk of dementia and cognitive impairment in older persons [35]. Given that falls are a major source of disease and death among the elderly and frequently result in fractures, loss of independence, and higher healthcare expenses, the increased risk of harmful falls is also significant. The influence of anticholinergic medications on physical performance is further highlighted by the increased risk of losing grip strength, which may lead to frailty and a lower quality of life [36].

Previous studies have shown a correlation between anticholinergic medications and cognitive decline, and several reasons have been put out to explain this relationship. Apart from their direct impact on acetylcholine transmission, anticholinergic medications may also cause additional physiological modifications, like changes in cerebral blood flow or interference with neuroprotective pathways, which may hasten the progression of neurodegenerative diseases. Given the high rate of anticholinergic drug use in the elderly, our results highlight how crucial it is to periodically review and optimize prescription schedules to reduce cognitive hazards, particularly for patients who already have cognitive deficits or are at high risk of developing dementia [37, 38].

Several strengths are reported from the findings of this study. Firstly, the larger sample size, which includes 631,110 older adults from 16 researches, is one of its main advantages. This increases the findings' generalizability to the aged population and offers strong statistical power. Furthermore, a thorough assessment of the effects of anticholinergic medications throughout short and long periods—from 8 weeks to 10 years—is made possible by the inclusion of multiple study designs, including cohort, cross-sectional, and longitudinal studies. The validity of the conclusions reached is further supported by the study's thorough evaluation of study quality using the CASP method, which determined that the majority of the included studies were of good quality.

However, with enormous advantages, there are a few limitations of the study. High heterogeneity (ranging from 89% to 98%) was observed for key outcomes like cognitive decline, injurious falls, and loss of grip strength, indicating considerable variability across the studies in terms of patient populations, anticholinergic drug types, and follow-up durations. This variation could reduce the pooled estimates' accuracy. Further, the existence of publication bias, as shown by asymmetrical funnel plots, implies that studies with noteworthy findings might have had a higher chance of being published, which could have resulted in an exaggerated assessment of the negative consequences. The observational nature of all the included studies is another drawback, which makes it more difficult to prove a link between the use of anticholinergic drugs and unfavorable results. Lastly, there was no significant correlation between the use of anticholinergic drugs and general adverse events, although this may have been due to differences in how these events were measured or reported in the included trials. Despite these drawbacks, the results point to crucial factors for the treatment of anticholinergic medication use in geriatric populations.

## CONCLUSION

This meta-analysis reveals that anticholinergic drug use in older persons poses serious risks, especially in cognitive decline, falls resulting in injury, and loss of grip strength. To reduce the anticholinergic load in this exposed group, these findings have significant clinical management implications, highlighting the need for frequent medication review and the evaluation of alternative therapies. To lessen the negative effects of anticholinergic medications on cognitive and physical function, more study is required to examine ways to reduce their use in elderly people as well as possible therapies.

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