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The Effect of Anticholinergic Medications on People living with Dementia: A Systematic Literature Review.

Author: Israt Jahan Dowel

Supervisor: Sanjib Saha
Associate Researcher,
Assistant researcher, Health Economics

Abstract:

Background:

Dementia is a global public health concern as it causes high dependency of the patients with Dementia (PwD) on their families and the community. Dementia is an irreversible neurodegenerative disorder for the elderly often associated with many comorbidities such as hypertension, diabetes, kidney diseases, etc. which require different medications for treatment. The use of Anticholinergic (AC) medication is common among People living with Dementia (PwD). The current Systematic Literature review aims to compile the evidence on the worst outcome of AC medication's adverse effects on PwD.

Method:

A systematic literature search was performed in PubMed, Web of Science, and Google scholar from January 1, 2000, to January 31, 2022. "The Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guideline and population, exposure, control, outcomes, and setting (PECOS) inclusion and exclusion criteria have been followed to include studies for full-text review. EndNote and Covidence software were used for the selection of studies and extraction of data from the selected studies. The Newcastle-Ottawa Scale (NOS) was followed to judge the quality of the included studies.

Result:

The primary database search identified 532 articles, and after removing duplicates, 377 articles have been included for screening. After screening and full-text review, 15 articles have been included for data extraction. The mortality rate due to adverse effects of AC medication was found to be higher; the adjusted Hazard Ratio (aHR) ranges from 1.09 to 1.23. Additionally, the outcome of hospitalization was increased with simultaneous use of more than one AC medication. Other outcomes such as Mortality, Hospitalization, and Cognitive impairments showed the negative contribution of the AC. However, eleven out of fifteen studies meet the high-quality study criteria of The Newcastle Ottawa Scale (NOS).

Conclusion: AC medication is associated with an increased rate of mortality, cognitive impairment, and hospitalization among PwD. Therefore, health care professionals need to be cautious while prescribing AC for PWD.

Contents:

1. Introduction:

1.1. Background:

In the 21st Century, Dementia has become a prime concern in global public health issues, especially for the aged population (1). Dementia is a syndrome that causes progressive deterioration of brain function (2). It is characterized by cognitive, behavioral, and psychological impairments due to progressive neuronal loss and is the most prevalent degenerative neurological condition (2). People experience dysfunction in thought and memory processes, orientation, judgment, calculation, language, or learning capacities (3). It makes people dependable on others for their daily activities and is globally ranked seventh top cause of mortality (1). The people living with Dementia (PwD) are estimated globally at over 44 million, which may reach about 131 million by 2050 – indicating a significantly increasing global burden of the disease (2). The World Alzheimer's report predicted that the prevalence of Dementia in low and middle-income countries will increase by more than 70 percent of the older population by 2050 (4). With this estimation, we can correlate those millions of primary caregivers, and the whole community will experience mental stress, physical workload, and financial hardship (5).

The negative impact of the caregiver's physical and emotional health, social status, and financial state during caring for a patient is described as the Caregivers burden (6). Previous studies claim that caregivers of PwD experience more depression or extreme burden compared with caregivers of general older people (5). The duty or involvement of caregivers also increases with the progression of Dementia or the increasing disease burden of PwD (7). This situation also causes deterioration of caregivers' psychological and physical health, limits their time for rest or having leisure time, and impairs caregiver's personal life, marital or family life, and economic condition, including loss of employment and social relationships or involvements (5).

Furthermore, maintaining healthcare expenditures of PwD is higher than other patients like heart disease, kidney disease, or cancer patients, specifically for the last five years of life (8). In 2015 in the USA, the overall cost of Dementia was USD 818 billion (8). Moreover, most of the complications associated with Dementia lead to hospitalization and increased disease and financial burden (8). However, ensuring a skilled nursing facility at home for long term care is considered an attributable cost (8, 9). This reflects the family of PwD financially struggles more than a family of general older people.

Additionally, prescribing medication appropriately on PwD is essential. Previous studies presented that inappropriate prescribing or polypharmacy is strongly associated with impaired cognition or functional impairment or reverse Dementia among PwD (10, 11). However, older people generally suffer from comorbidities like Cardiovascular disease, hypertension, diabetes, and renal diseases; as a result, they

frequently receive multiple medications (10). Leelakanok described the concurrent use of five or more drugs in a patient as “Polypharmacy” (10). Alternatively, medicines prescribed without clear evidence-based indications, cost-ineffective or not well-tolerated, are termed “Inappropriate prescribing” (11). Thus, before prescribing any medication to PwD, the risk-benefit profile assessment is required to avoid “Polypharmacy” or “Inappropriate prescribing” (11). A systematic review has shown that polypharmacy and inappropriate medication use causes cognitive impairment and reverse Dementia among PwD and increases the risk of dementia among older people living without Dementia (10).

Anticholinergic (AC) medications are commonly used among PwD for various indications like urinary incontinence, parkinsonism, or respiratory illness though it has numerous side effects (12).

However, drugs having AC properties have been identified as “Inappropriate prescribing” among PwD as it increases the disease burden (6). The AC medication works by blocking Acetylcholine of neurotransmitters and interrupting neuronal function (13). Alternatively, Acetylcholinesterase inhibitors (AChEI) are routine medications for Alzheimer's or Dementia patients. It improves cognition by increasing acetylcholine concentration in the synapses of neuromuscular junctions (14). Therefore concurrent use of Acetylcholinesterase inhibitors (AChEI) and AC medications contradict action of each other (14).

Anticholinergic burden (ACB) means the adverse effects caused by one or more AC medications (6). PwD has a greater risk of adverse effects of AC medications or poor outcomes than older adults without Dementia (12, 14). A study described the significant adverse effect of AC drugs are - i) central effects- cognitive impairment, delirium, and ii) peripheral effects- dry mouth, blurred vision due to dry eye, constipation and iii) functional impairments- falls and hospitalization due to other complications like pneumonia or pneumonia stroke (15). However, the AC medications have a wide range of indications among older people; hence, many physicians commonly prescribe these drugs without considering the risk of cumulative burden (16). To evident the irrational prescribing of this medication and reduce the disease burden among PwD, a systematic literature review is indicated.

The systematic literature review is an evidence-based practice that estimates more reliable and effective intervention and, at the same time, identifies the risk factors for increasing disease burden or decreasing the prevalence of a particular disease (17). In research, a systematic literature review determines, selects, and critically appraises previously published articles to answer some precisely outlined questions (17). Although many PwD is suffering from the harmful impact of AC medications, any prescribing protocols were not adopted to date due to a lack of evidence. Few existing publications show the effects of AC medication on PwD. But establishing the burden over disease and determining association of AC medications with poor outcomes such as mortality, hospitalization, health related quality of life etc. among PwD should be proven through evidence-based study. Therefore, this systematic literature review aims to

categorize, evaluate, analyze, and critically appraise the existing literatures based on poor outcomes of ACB among PwD.

1.2. Existing literature review:

Several systematic literature reviews have been published regarding the use of AC medications among older people with or without dementia. A previous Systematic review by Cardwell et al. determined the appropriateness of ACB measuring tools and their quality among general older people (9). The authors explained the ACB on people over 80 years, where participants were not solely PwD (9). Finally, the Drug Burden Index (DBI) tool was identified as the most appropriate tool for measuring AC medication burden (9). Another systematic review by Zheng et al. identified the risk of developing Dementia after receiving medications with AC properties (18). The study solely mentioned the role of different drugs with AC properties and contributed to the prevention of Dementia but did not explore the health risks for PwD (18). Salahudeen et al. showed the variation in different ACB scales or tools, including their types and quality among general older people (16). In another review researchers identified poor outcomes, but the included participants were from a mixed population group (with or without Alzheimer's disease) (6). However, none of the studies have been conducted to estimate the disease burden or adverse outcome among PwD, as the participants with dementia get filtered out routinely from selection criteria, which determines the research gap among existing studies (18). In these circumstances, a systematic review of existing literature is compulsory to establish the evidence that the AC drug brings poor results and increases the disease burden among PwD.

1.3. Research questions:

To fill up the existing research gap and draw evidence in this field, the general objective of this review is to identify the adverse effects of anticholinergic (AC) medication for PwD. The specific t research questions are:

- Do AC medications increase the risk of mortality for PwD?
- Do AC medications increase the risk of hospitalization for PWD?
- Do AC medications increase the risk of other adverse outcome such as cognitive impairment, falls etc.
- What are the qualities of the studies in this field measured by a validated and well-used quality assessment tool?

2. Methodology:

This systematic review protocol has been performed following the "The Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guideline (19). The PRISMA flowchart of the study selection process has given below in Figure- 1.

2.1. Data source and search strategy:

A systematic literature search has been performed to identify the relevant studies and citation analysis. The effects of AC drugs on Dementia or Alzheimer's were performed in PubMed, Web of Science, and Google scholar. The time frame for the search was from January 1st, 2000 to January 31st, 2022. The search terms and MeSH (Medical Subject Heading) terms were developed, and keywords used related to Dementia and AC medications and its outcome to conduct the search strategy. The included publication's reference lists were also screened out, and a manual Google search was performed to prevent missing out of potential additional articles. Articles published in only the English language and studies on human has been investigated. The complete search strategy is included in Appendix 1.

2.2. Study Selection:

The studies found from search results were exported to the EndNote-20.0.1 web library database and attached full-text with all studies. Then all the selected studies were exported into COVIDENCE-systematic review management-2.0 software and screened out according to PECOS inclusion and exclusion criteria, presented in Table- 1.

Table-1: PECOS inclusion and exclusion criteria:

Criteria	Inclusion	Exclusion
Population	People living with dementia (PwD), ICD-10 code F00*, F00.0*, F00.1*, F00.2*, F00.9*, F01.9, F02*, F03, G30.	People with confusion, depression, age-related memory loss, and Parkinson's disease.
Exposure	Exposed to AC drug and measured as an ACB.	Studies where any standard scale has not been used to measure ACB.
Comparator	Nothing specified	Nothing specified.
Outcome	The adverse outcomes include disease progression, unwanted side effects, falls, decreased quality of life, hospitalizations, or death.	Nothing specified.
Settings	The study setting had no geographical boundary.	Nothing specified.

Others	Peer-reviewed quantitative papers, Articles in the English language with follow-up or retrospective studies.	Non-English, non-human, case reports, review papers, grey literature, and abstracts without full articles were excluded.

Abbreviation: ICD-10 code F00* = Dementia in Alzheimer disease (G30). F00.0* = Dementia in Alzheimer disease with early onset (G30.0). F00.1* = Dementia in Alzheimer disease with late onset (G30.1). F00.2* = Dementia in Alzheimer disease, atypical or mixed type (G30.8). F00.9* = Dementia in Alzheimer disease, unspecified (G30.9). F01.9 = Vascular dementia, unspecified. F02* = Dementia in other diseases classified elsewhere. F03 = Unspecified dementia. G30 = Alzheimer disease (20).

2.3. Data Extraction and Synthesis:

The assembled studies were assessed in two steps. First, according to PECOS criteria, the title and abstract were checked, then the full text of each article was reviewed, and data was exported into Microsoft Excel for data extraction (Appendix-2). Secondly, the information from publications, study characteristics, and significant findings related to the research question, the study are included in the standardized data extraction form (attached in the supplementary document – Appendix- 2). The recorded particulars are: - i) publication information (First author, title, year of publication), ii) Characteristics of study (target population group and sample size, study design and study duration, type of medications, exposure measurement, and statistical method), iii) Study results (analysis of study result, reference group, confounders).

2.4. Critical Appraisal of Studies:

The quality of the included studies has been assessed by The Newcastle-Ottawa Scale (NOS) (21). The Cohort studies have been scored according to the standard questionnaire and divided into three major categories, consisting of Category-1 is **Selection (maximum four stars)**, Category-2 is **Comparability (maximum two stars),** and Category-3 is **Outcome (maximum three stars)** (21). A total of 9 stars can be achieved by a study and studies with ≥7 stars are considered a high quality study, 5-6 stars indicate medium quality, and ≤4 stars are considered as low quality of the study (21). Moreover, the checklist of The Newcastle-Ottawa Scale has been used for case-control study and categorized for establishing validation (21). Additionally, Modified The Newcastle-Ottawa Scale (Modified NOS) has been validated cross-sectional studies, whereas the scale determined maximum 10 stars (21). The filled-out questionnaire of the Standard Newcastle-Ottawa Scale (NOS), and Modified Newcastle-Ottawa Scale (Modified NOS) have been shown in Appendix-3.

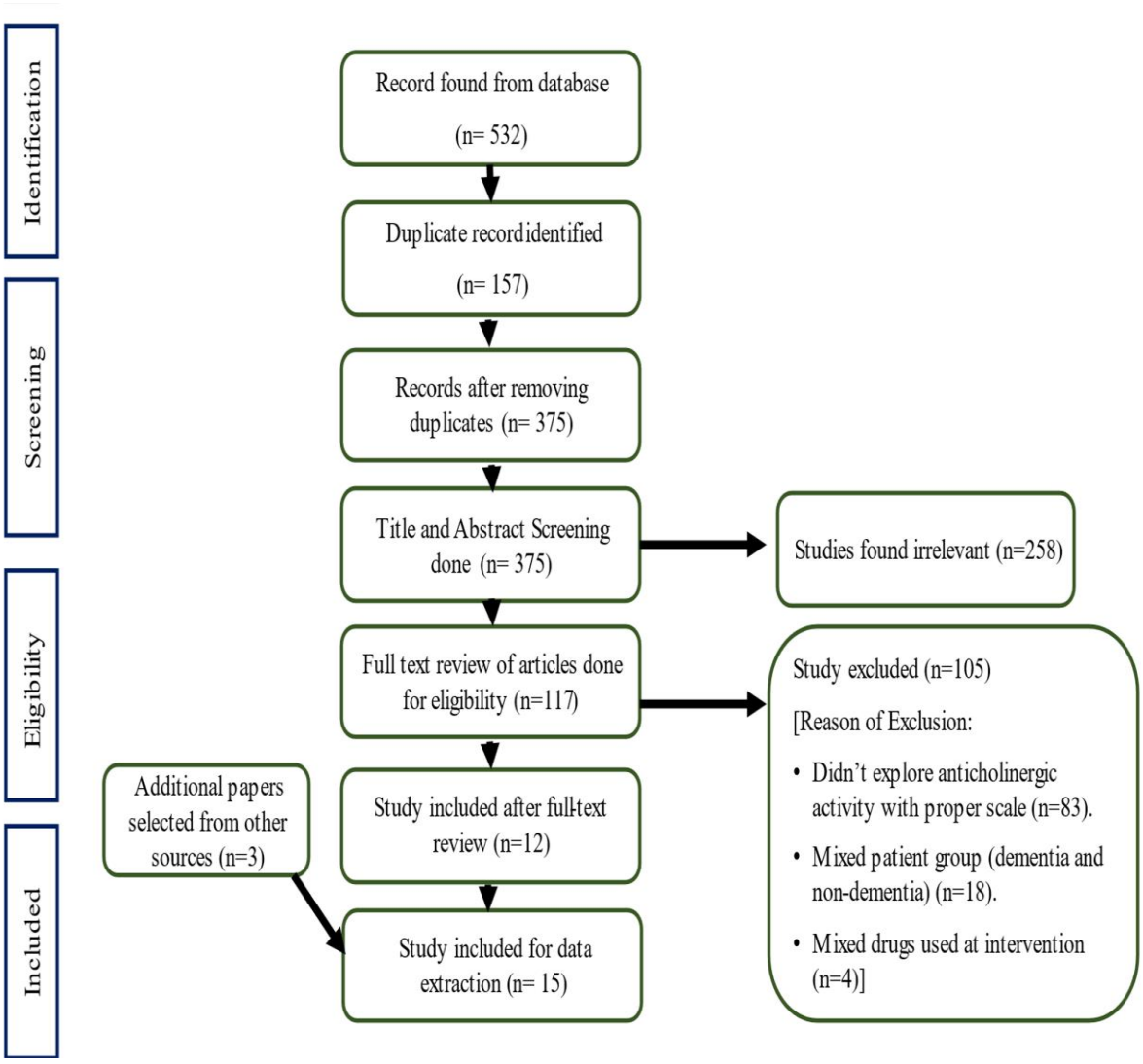
2.5. Ethical Consideration:

This is a systematic literature review of published articles and thus no ethical consideration is required. However, ethical approval was obtained by the primary researchers for the studies included in this review.

3. Result:

The primary database search identified 532 articles, and after removing duplicates, 375 articles were included for screening and review. From these articles, 117 papers have been screened, and 258 articles have been found irrelevant. After a full-text review, 105 articles did not meet inclusion criteria, and 3 articles were included from relevant articles cited papers. Finally, total of 15 articles have been included for data extraction [Figure-1].

Figure- 1: Prisma flowchart of the study selection process.



The study selection process shown in the PRISMA flowchart, which displays the initial search results, several studies after removing duplicate articles, steps of study selection (Title and abstract screening, then full-text review), also recorded prime reasons for excluded papers after reviewing full-text. During title and abstract screening, articles were excluded that were related to Dementia or Alzheimer's but not related to AC medication or consequences. Hence, during screening 258 articles identified irrelevant and excluded. The articles were mainly regarding Dementia disease and its overview, or cost-effectiveness, exploring incidence or prevalence and use of Acetylcholinesterase inhibitors or other medications. Which did not meet the PECOs inclusion criteria. Then a thorough reading of selected 117 articles was done and matched with PECOs inclusion/exclusion criteria. Only 12 articles exclusively met the selection criteria. During the full-text review the diagnosis of study population was matched with ICD-10 code F00*, F00.0*, F00.1*, F00.2*, F00.9*, F01.9, F02*, F03, G30 to identify correct articles with right participants and included the articles for review. In the step of full-text review, 105 articles were excluded, where 83 articles didn't estimate ACB using any measuring scale or examined pharmacokinetics of AC drugs, and 18 studies performed with mixed patient groups (dementia and non-dementia participants), and 4 articles intervention showed the use of AC medications combined with antipsychotics and sedatives, which does not have AC properties. Thus, determining the adverse outcome by AC medications were difficult from result presented with mixed drugs effects, ultimately studies excluded. However, related cited articles were explored during the full-text review, and (n=3) articles were included via Goggle scholar search, which met the eligibility. Finally, 15 articles were included for data extraction.

From the included articles, 12 cohort studies (12, 22-32), one case-control study (14), 1 cross-sectional study (33), and one study where data was taken from the control group of an ongoing Randomized clinical trial study (3). The overall outcomes and related studies, including their characteristics, are summarized in Table 1. The included studies were conducted in the United States (US) (n = 4) (3, 25, 28, 32), Japan (n=2) (31, 33), UK (n=2) (22, 24), Finland (n = 1) (14), France (n = 1) (26), Korea (n = 1) (12), Ireland (n = 1) (29), Sweden (n = 1) (30), Thailand (n = 1) (27) and European countries (n=1) (23). Participants included from different sources such as National data of community-dwelling older people diagnosed with Alzheimer's disease or Dementia, from hospital registries or nursing homes and rehabilitation centers. The included studies participant's ages started from 50 years and above. The selected sample size ranged from 61 to 39,107. The study duration and follow-up time ranged from 30 days to 6 years.

3.1. Outcomes:

After reviewing all the studies, total twelve outcomes were recorded which includes:- Mortality (n=4) (12, 22, 29, 30), Hospitalization (n=3) (3, 22, 31), Cognitive impairment/ Dementia severity (n=1) (23), Cognitive impairment (n=5) (3, 24, 27, 28, 33), Delirium (n=2) (3, 12), Stroke (n=1) (30), Pneumonia (n=1) (14), Fall or fall related injury (n=1) (25), Neuropsychiatric function (n=1) (26), Health-related quality of life (HRQoL) (n=1) (32), Impaired physical function (n=1) (3), Treatment modification within 1 year, due to non-responsive treatment or disease progression (n=1) (12).

3.1.1. Mortality:

There were 4 studies reported the same outcome mortality (12, 22, 29, 30) that is related to AC drug use and its adverse effect. From the national data registry, the association of AC drugs with mortality noticed for all causes among PwD showed consistent results. Among those articles, a Korean study showed increased mortality risk in people with ACB (>3) using Anticholinergic Cognitive Burden Scale (ACB scale) with aHR =1.23, 95% CI 1.06–1.41 (12). Another Swedish study identified a greater mortality risk among PwD with score-1 ACB (aHR=1.09, 95%CI 1.04–1.14) or with (Score-2 or more) ACB resulted (aHR=1.18, 95%CI 1.12–1.24) (30). Inversely, an Irish study explained the risk of mortality with different types of AC drugs and their doses; but the result was not statistically significant (29). Moreover, another study in the UK showed, increased mortality risk (all causes) due to ACB, adjusted hazard ratio = 1.10, 95%CI 1.03–1.18, recorded using AC Effect on Cognition (AEC) score (22). Finally, after analyzing the above studies, the outcome mortality due to adverse effects of AC medication estimated among PwD is higher; adjusted HR ranges from 1.09 to 1.23.

3.1.2. Hospitalization:

Three studies recorded the outcome of Hospitalization due to adverse conditions of Dementia or other symptoms because of ACB (3, 22, 31). A study from Japan showed the risk of hospitalization increases with one or more AC drugs used; the aHR was 4.54, 95%CI 1.03–20.0 (31). A USA study explored the length of hospital stay up to 30 days among patients admitted to a rehabilitation centers and showed- use of AC drugs causes length-of-stay (β=0.227 days, p-value = <0.05) (3). A UK study found that every one-point increase in AEC score was associated with the rate of emergency hospital admission had increased with every one-point increment of AEC score (aHR=1.03, 95%CI 1.01–1.04), although the non-significant result stated regarding the effect on total hospital days; aHR ratio=1.02, 95%CI 1.00–1.04) (22).

3.1.3. Cognitive Function:

A total of six articles identified the relationship between AC drugs and cognitive function (3, 23, 24, 27, 28, 33). The characteristics and quality of these studies contrasted impressively and conflicted. In a study, the author Lu expressed the result through t-tests, which represents the differences in Mini-Mental State Examination (MMSE) score between the two groups of AC medications (28). Where, the use of one or more AC drugs continuously decreased the MMSE score on follow-up at 24 months ($t=-2.24$, $p = 0.032$); however, it did not diminish on follow-up at 12 months ($t=-1.82$, $p = 0.073$) (28). Particularly, this study had some limitations, such as a small study sample, unclear study setting, gross assessment of cognitive function, and the result was not adjusted for confounders (28). Another study reported that the score on Thai Mental State Examination (TMSE), where cognitive function had reduced with every-one-point in ACB over 12 months period (adjusted $\beta=-2.52$, $p = 0.20$) (27). A study from the UK did not find a significant association between Severe Impairment Battery scores (SIB), Alzheimer's Disease Assessment Battery Scale-Cognitive (ADAS-Cog), Mini-Mental State Exam (MMSE) performance scoring (adjusted $\beta = 0.69$) on one or more AC drug use compared with the group of participants who did not receive any AC drugs (24). Another study conducted at 23 academic centers in Europe, assessed ACB on cognitive function or dementia severity, but no association was found on the ADAS-Cog scale throughout the study time (23). Alternatively, Dementia severity measured by Disability Assessment for Dementia (DAD) significantly increased on greater ACB, indicated worsening of Dementia (23). DAD scores increased over time in Model- 3: β Coef: -1.53 95% CI: -2.83 to -0.23, $p = .021$ (23). Furthermore, another study from a rehabilitation center USA, reported – no association between patient's cognition and ACB, where the participants are PwD associated with delirium (3). Except, the Digit Span Backward test revealed slight poor performance in patients who received AC drugs (3). Nonetheless, analyzing three studies which expressed MMSE score to evaluate cognitive impairment, the adjusted β score ranged from –2.52 to 0.69.

3.1.4. Other Outcomes:

A French study explored the neuropsychiatric function of admitted dementia patients from the hospital to assess the behavioral and psychological symptoms of Dementia (BPSDs) after reducing the ACB among PwD (26). The result showed a reduction (every 2 points) of the ACB assessed by the AC drug scale (ADS) among dementia patients with moderate BPSD improved the frequency x severity score, $\beta=6.34$, 95% CI 4.54–8.14 and $\beta=7.63$, 95%CI 6.08–9.19 respectively (26). Furthermore, dementia patients with moderate BPSD scored improvement on occupational disruptiveness ($\beta=4.26$, 95% CI 3.11–5.41), during a reduction in 3 points of ACB (26). Another study from Sweden examined categorizing ACB scores (0, 1, and ≥2). It results, incident stroke was not related with ACB scored 1; hence the aHR =0.97, 95%CI 0.86–1.08 or

incident ischemic stroke =1.01, 95%CI 0.89–1.15 (30). Moreover, the rate of incident stroke was raised to ACB scored two or more, aHR =1.13 and 95% CI 1.00-1.27, also, rate of incident ischemic stroke aHR = 1.15 and 95% CI 1.00–1.31 (30). Additionally, the score of composite result of stroke and death due to all causes aHR = 1.20 and 95% CI 1.14–1.26 (30).

Another study from Finland, identified the risk of pneumonia increases and leads to hospitalization or increased mortality among Alzheimer's disease patients with any ACB, with the adjusted odds ratio = 1.36, 95% CI 1.29–1.43 (14). However, incident use of AC drugs had the greater risk of pneumonia, adjusted odd ratio =2.68, 95% CI = 2.15–3.34 compared with prevalent users adjusted odd ratio= 1.48, 95% CI 1.40–1.57) (14). A Korean study recorded that the risk of delirium increases with high ACB (>3)-(aHR=1.52, 95%CI 1.17–1.96) and treatment modification was recorded within 1 year due to non-responsiveness of treatment or exacerbation of symptoms (aHR=1.12, 95%CI 1.02–1.24) (12). A US study noticed poor performance on physical function assessed by Barthel Index ($\beta = -5.761$, $p<0.05$) that was predicted with the moderate or higher ACB (3). Another outcome of health-related quality-of-life has been measured in another US study, which showed – incident use of AC drugs among patients with Dementia causes diminished health-related quality-of-life ($\beta = -7.48$, $p<0.01$) (32). Finally, a cohort study from the USA estimated fall or fall-related injuries among Emergency department patients with existing Alzheimer's disease (25). The result was significant for the level 2 group of ACB increases the risk of fall or fall-related injuries, the HR 1.05, CI 1.01–1.10 compared with level 2 and level 3 drugs (25).

Table-2: Outcome-Based Categorization of Study:

Outcome: Mortality

First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Ah, Y. M. 2018 Korea	patient with Dementia (age>60 years) N=25825	Retrospective Cohort, 2003-2011 max. 24 months observation for each patient.	Anticholinergic medications used for various indications, who is receiving Cholinesterase inhibitors-donepezil, galantamine and rivastigmine.	Within 1st 3 months of Anti-dementia drug treatment, average daily AB has been measured.	High ACB (> 3) indicates higher mortality risk for all causes: aHR: 1.23, CI: 1.06-1.41.	No or minimal AB (≤ 1) -vs- High AB >3 AB = 0 -vs- AB ≥ 1	Age, sex, baseline comorbid disease, baseline ACB score, baseline sedative load, ginkgo extract use
Bishara et al, 2020 South London	Patient with Dementia n = 14 093	Retrospective Cohort 1st January 2007 and 31st December 2015.	Anticholinergic medications	AB measured at diagnosis and 6 month after dementia. Multivariate cox regression	Increased mortality: aHR (1 or 2 Anticholinergic medication use, AEC=1)=1.10, 95% CI=1.03-1.17. aHR (at least 1 medication with AEC =≥2)= 1.10, 95% CI= 1.03-1.18. aHR (1 point increase in AEC score)=1.02, 95%CI=1.01-1.04.	AEC=0, patients taking 1 or 2 medications with AEC=1 (total AEC <3), patients taking medications with AEC ≥ 2 (total AEC ≥ 3)	Age, gender, ethnicity, marital status, baseline MMSE, neighbourhood deprivation score, HoNOS65+ symptoms scores (agitation, hallucinations/delusions, self-injury, substance use, depressed mood, physical illness), HoNOS65+ functional problem scores (ADL, living conditions, occupational/ recreational activities, social relationships), acetylcholinesterase inhibitor prescription.
McMichael, 2020. Ireland	General population of people prescribed ≥ 1 dementia. N= 25,418	Retrospective cohort. 6 years	AC	1. Overall AB use over the study duration. 2. AB score. 3. AB drug class. (ACB). Unadjusted and adjusted cox proportional hazard model,	Overall AB > 0 increased mortality risk (all cause): • aHR(1≥AB≤4) = 1.17 (1.11, 1.24) • aHR(5≥AB≤9) = 1.26 (1.18, 1.34) • aHR(10≥AB≤14) = 1.41 (1.26, 1.59) • aHR(AB≥15) = 1.57 (1.06, 2.34) Urological and respiratory AM increased mortality risk (all cause): • aHR(Antidepressant) = 1.12 (0.94, 1.33)	Overall AB (0, 1–4, 5–9, 10–14, ≥15) 0, 1, 2, 3 e.g. antipsychotics, urological, respiratory antihistamines, antidepressants (No/Yes)	Age, gender (in all models), marital status, urban/rural, area deprivation (in some models)

					• aHR(Antipsychotic) = 0.93 (0.77, 1.12) • aHR(Gastrointestinal) = 1.02 (0.93, 1.12) • aHR(Antiparkinson) = 1.17 (0.82, 1.69) • aHR(Respiratory) = 1.12 (1.03, 1.22) • aHR(Urological) = 1.18 (1.03, 1.36) • aHR(Antihistamine) = 0.75 (0.49, 1.15)		
Edwin C.K. Tan, 2018. Sweden	Dementia patient with no history of stroke. N = 39,107	Retrospective cohort. Since 2008, participants included from the diagnosis of dementia date to 31 December 2014.	ACD	AB measured prior outcome or end of study period.	Mortality: AB > 0 increased mortality risk (all cause): • aHR(AB=1) = 1.09 (1.04, 1.14) • aHR(AB≥2) = 1.18 (1.12, 1.24) AB > 0 increased the composite outcome of mortality (all cause) or first stroke:DE aHR(AB=1) = 1.09 (1.04, 1.14) • aHR(AB≥2) = 1.20 (1.14, 1.26)	1 AB as a continuous variable: effect of a 1-point unit increase 2 AB groups: 0, 1, and ≥ 2	Age, gender, Charlson Comorbidity Index, living situation, home care, dementia disorder, MMSE, use of antidementia drugs at baseline
Outcome: Hospitalization							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Bishara et al, 2020 South London	Patient with Dementia n = 14 093	Retrospective Cohort first January 2007 and 31st December 2015.	Anticholinergic medications	AB measured at diagnosis and 6 month after dementia. Multivariate cox regression	AEC increased emergency hospitalization: • aHR(1 or 2 medications with AEC=1) =1.12, 95%CI=1.05-1.18) • aHR(at least 1 medications with AEC≥2) =1.13, 95%CI=1.07-1.21) • aHR(1-point increase in AEC score) =1.03, 95%CI=1.01-1.04) AEC increased total hospital days: • aHR(1 or 2 medications with AEC=1) =1.14, 95%CI=1.04-1.25)	AEC=0, patients taking 1 or 2 medications with AEC=1 (total AEC <3), patients taking medications with AEC ≥ 2 (total AEC ≥ 3)	Age, gender, ethnicity, marital status, baseline MMSE, neighbourhood deprivation score, HoNOS65+ symptoms scores (agitation, hallucinations/delusions, self-injury, substance use, depressed mood, physical illness), HoNOS65+ functional problem scores (ADL, living conditions, occupational/ recreational activities, social

					• aHR(at least one medications with AEC≥2) =1.07, 95%CI=0.97, 1.19. • aHR(1-point increase in AEC score) =1.02, 95%CI= 1.00, 1.04.		relationships), acetylcholinesterase inhibitor prescription.
Ann Kolanowski, 2015 USA	inpatients (≥65 years) with dementia from rehabilitation center. N = 99	multi-centre RCT. Hospital stay 30 days or until discharge	Mild Anticholinergic Medications: Metoprolol Furosemide Warfarin Hydralazine Risperidone Isosorbide Alprazolam Digoxin Atenolol Prednisone Moderate/Severe Anticholinergic Medications: Quetiapine Dicycloverine Carbamazepine Paroxetine Amitriptyline Methocarbamol Olanzapine Diphenhydramine Hydroxyzine Meclizine	Delirium Cognitive function Physical function Hospitalization AB measured weekly during rehabilitation hospital stay (ACB). Multilevel models	Hospitalization : Moderate/severe AB predicted a longer inpatient LOS: • (AB=1) = 0.105 (p > 0.05) • (AB≥2) = 0.227 (p < 0.05)	Any mild AB use (AB = 1) No -vs- Yes Any moderate/ severe AB use (AB ≥ 2) No -vs- Yes	Age, gender, education level, ethnicity, Clinical Dementia Rating score, APOE allele status, Charlson Comorbidity Index score, previous week's cognitive and physical function performance, number of days in the facility on the outcome assessment week.
Shuichi WATANABE, 2018 Japan	Dementia patient , who received AC drugs and hospitalised during study time period. N = 61	Retrospective Chart-based study. Between 1 May 2013 and 31 December 2014, from outdoor visit date to end of study time.	Mirtazapine, Risperidone, Chlorpromazine hydrochloride, Olanzapine, Metoclopramide hydrochloride, Paroxetine hydrochloride, and Quetiapine fumarate.	AB at baseline through ARS score. Fisher's exact test for catagorical variables. Mann–Whitney U-test for continuous variables. regression model Kaplan–Meier survival curves	AB ≥ 1 increased the risk of a hospitalization: • aHR(AB≥1) = 4.54 (1.03, 20.0)	Non-users of medication with AB (ARS = 0)* -vs- Users of medication with AB ≥ 1	Age, gender, BMI, MMSE, total number of drugs, Charlson Comorbidity Index
Ann Kolanowski, 2015 USA	inpatients (≥65 years)	multi-centre RCT.	Mild Anticholinergic Medications:	Delirium Cognitive function	Hospitalization : Moderate/severe AB predicted a longer inpatient LOS:	Any mild AB use (AB = 1) No -vs- Yes	Age, gender, education level, ethnicity, Clinical Dementia Rating

	with dementia from rehabilitation center. N = 99	Hospital stay 30 days or until discharge	Metoprolol Furosemide Warfarin Hydralazine Risperidone Isosorbide Alprazolam Digoxin Atenolol Prednisone Moderate/Severe Anticholinergic Medications: Quetiapine Dicycloverine Carbamazepine Paroxetine Amitriptyline Methocarbamol Olanzapine Diphenhydramine Hydroxyzine Meclizine	Physical function Hospitalization AB measured weekly during rehabilitation hospital stay (ACB). Multilevel models	• (AB=1) = 0.105 (p > 0.05) • (AB≥2) = 0.227 (p < 0.05)	Any moderate/ severe AB use (AB ≥ 2) No -vs- Yes	score, APOE allele status, Charlson Comorbidity Index score, previous week's cognitive and physical function performance, number of days in the facility on the outcome assessment week.

Outcome: Cognitive Impairment/ Dementia Severity

First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Adam H. Dyer, 2019 23 academic centers in nine European countries (Ireland, United Kingdom, Italy, the Netherlands, France, Greece, Sweden, Germany, and Hungary).	aged 50 years or older, diagnosed with AD, who were included at NILVAD study. From 510 patient of total participants, 142 patients received AC drugs at baseline	Prospective cohort 18 months	The definite anticholinergics- Quetiapine, Oxybutynin, Paroxetine, Amitriptyline. The potential anticholinergics- Trazodone, Venlafaxine, Alprazolam, Furosemide, and Risperidone.	Over 18 Months, Anticholinergic Burden measured on ADAS-Cog Scores to assess cognitive impairment and CDR-sb scoring done for measuring dementia severity.	ACB on cognitive impairment: No association between ADAS-Cog and ACB scores (β Coef: 0.28; 95% CI −0.09 to 0.64, p = .144). ACB on dementia severity: DAD scores increased over time under all three models Model 1: β Coef: −1.52, 95% CI: −2.83 to −0.21, p = .023. Model 2: β Coef: −1.51, 95% CI: −2.83 to −0.21, p = .023. MOdel 3: β Coef: −1.53 95% CI: −2.83 to −0.23, p = .021.	Baseline ADAS-Cog Score on any anticholinergics, mean (SD) =36.08 (10.41), p-value= 0.009* Baseline CDR-Sb Score of any anticholinergics, mean (SD)= 5.53 (2.76), p-value= 0.105. Baseline DAD Score of any anticholinergics, mean (SD)= 28.22 (8.26), p-value= 0.113.	Model 1 consisted of adjustment for age, gender, BMI, years of education, baseline CDR-sb/DAD score, diagnosis duration, study group, and cholinesterase inhibitor. Model 2 further adjusted for total number of medications/comorbidities in addition to a known history of mood/anxiety disorder or behavioral and psychological symptoms of dementia (BPSD). Model 3 adjusted for history of behavioral and psychological symptoms of dementia, history of urinary incontinence, mood/anxiety disorder, and ongoing benzodiazepine use.

Outcome: Cognitive impairment							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Fox et al. 2011 UK	General population (age >55 years) of people with Alzheimer's Disease. n=224	longitudinal cohort study. July 2002 to January 2003, measured at 6 month and 18 months	Anticholinergic drugs	AB at baseline. (ACB)	At 6 months: aβ(ADAS-COG / AB=0) = − 1.59 (− 1.14, 1.03) aβ(MMSE=0/ AB=0) = 0.53 (− 0.47, 1.53) aβ(SIB=0/ AB=0) = 1.75 (− 2.28, 5.77) At 18 months : aβ(ADAS-COG / AB=0) = − 1.49 (− 1.96, 1.06) aβ(MMSE=0/ AB=0) = 0.69 (− 0.84, 2.21) aβ(SIB=0/ AB=0) = 6.23 (− 0.26, 12.73)	AB = 0 -vs- AB ≥ 1	Baseline cognition, age, gender, use of a cholinesterase inhibitor
Jenraumjit, 2020 Thailand	Older outpatients (≥60 years) with Alzheimer's Disease receiving AChEI. N = 133	Retrospective cohort study. From 2015 to 2016.	ACs, benzodiazepines (BZDs) and AChEIs. Anticholinergic drugs have been catagorised according to its property- ACB score 1 was diazepam, score 2 was cyproheptadine and score 3 was amitriptyline.	AB measured every four months (± 3 to 4 weeks) over a period of 12 months. (ACB). Chi-square test	Every one-point increase in AB reduced (worsened) the TMSE score: • aβ = − 2.52 (− 0.40, − 4.64)	AB as a continuous variable: effect of a 1- point unit increase	Age, gender, benzodiazepine use, time
Ann Kolanowski, 2015 USA	inpatients (≥65 years) with dementia from rehabilitation center. N = 99	multi-centre RCT. Hospital stay 30 days or until discharge	Mild Anticholinergic Medications: Metoprolol Furosemide Warfarin Hydralazine Risperidone Isosorbide Alprazolam Digoxin Atenolol Prednisone Moderate/Severe Anticholinergic Medications: Quetiapine Dicycloverine Carbamazepine Paroxetine	Delirium Cognitive function Physical function Hospitalization AB measured weekly during rehabilitation hospital stay (ACB). Multilevel models	Cognitive function: Moderate/severe AB (≥ 2) predicted poorer performance on the Digit span backwards task (attention and working memory): • (AB=1 / Orientation) = − 0.178 (p>0.05) • (AB≥2 / Orientation) = − 0.195 (p>0.05) • (AB=1 / Digit forward) = 0.327 (p>0.05) • (AB≥2 / Digit forward) = 0.235 (p>0.05)	Any mild AB use (AB = 1) No -vs- Yes Any moderate/ severe AB use (AB ≥ 2) No -vs- Yes	Age, gender, education level, ethnicity, Clinical Dementia Rating score, APOE allele status, Charlson Comorbidity Index score, previous week's cognitive and physical function performance, number of days in the facility on the outcome assessment week.

			Amitriptyline Methocarbamol Olanzapine Diphenhydramine Hydroxyzine Meclizine		• (AB=1 / Digit backward) = 0.327 (p>0.05) • (AB≥2 / Digit backward) = − 0.575 (p<0.05) • (AB=1 / Memory) = − 0.212 (p>0.05) • (AB≥2 / Digit forward) = − 0.008 (p>0.05) • (AB=1 / CLOX1) = 0.024 (p>0.05) • (AB≥2 / CLOX1) = 0.502 (p>0.05)		
Konishi, 2010 Japan	AD patinet who regularly visited National Shimofusa Hospital due to behavioural symptoms. N=76	Cross-sectional?? Enrolled from 1 May 2003 to 31 March 2005	Atropine	SAA measured	The mean SAA value in the SAA (+) group was 4.14 1 2.70 nmol. Total MMSE, SAA (+) = p-value= 0.0367	p value= <0.05.	
Lu, 2003 USA	People with Alzheimer's Disease receiving AChEI (10 mg/day donepezil hydrochloride). N=69	Retrospective cohort. 2 years	one or more AC drugs along with cholinesterase inhibitor donepezil hydrochloride at a dose of10 mg/day.	Author's scale has been used to measure anticholinergic effects after continuous use of ≥ 1 ACD. t-test	Continuous use of ≥ 1 medication with significant AB showed no worsening in MMSE score: • t = − 1.82 (p = 0.073)	No medication with AC effects -vsContinuous use of ≥ 1 medication with significant AC effects	None

Other Outcomes:

Outcome: Delirium

First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Ah, Y. M. 2018 Korea	patient with Dementia (age>60 years) N=25825	Retrospective Cohort, 2003-2011	Anticholinergic medications used for various indications, who is receiving Cholinesterase inhibitors-donepezil, galantamine and rivastigmine.	Within 1st 3 month of Anti-dementia drugs treatment, average daily AB has been measured.	High ACB (> 3) indicates higher delirium risk: aHR: 1.23, CI: 1.06-1.41.	No or minimal AB (≤ 1) -vs- High AB >3 AB = 0 -vs- AB ≥ 1	Age, sex, baseline comorbid disease, baseline ACB score, baseline sedative load, ginkgo extract use

Ann Kolanowski, 2015 USA	inpatients (≥65 years) with dementia from rehabilitation center. N = 99	multi-centre RCT. Hospital stay 30 days or until discharge	Mild Anticholinergic Medications: Metoprolol Furosemide Warfarin Hydralazine Risperidone Isosorbide Alprazolam Digoxin Atenolol Prednisone Moderate/Severe Anticholinergic Medications: Quetiapine Dicycloverine Carbamazepine Paroxetine Amitriptyline Methocarbamol Olanzapine Diphenhydramine Hydroxyzine Meclizine	Delirium Cognitive function Physical function Hospitalization AB measured weekly during rehabilitation hospital stay (ACB). Multilevel models	Delirium: No effect of moderate/severe AB on delirium severity: (AB≥2) = 0.160 (p>0.05).	Any mild AB use (AB = 1) No -vs- Yes Any moderate/ severe AB use (AB ≥ 2) No -vs- Yes	Age, gender, education level, ethnicity, Clinical Dementia Rating score, APOE allele status, Charlson Comorbidity Index score, previous week's cognitive and physical function performance, number of days in the facility on the outcome assessment week.

Outcome: Stroke

First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Edwin C.K. Tan, 2018. Sweden	Dementia patient with no history of stroke. N = 39,107	Retrospective cohort. Since 2008, participants included from the diagnosis of dementia date to 31 December 2014.	ACD	AB measured prior outcome or end of study period.	Stroke: Increased risks of any incident stroke, AB ≥ 2: • aHR(AB=1) = 0.97 (0.86, 1.08) • aHR(AB≥2) = 1.13 (1.00, 1.27) Increased risk of incident Ischemic stroke, AB ≥ 2: • aHR(AB=1) = 1.01 (0.89, 1.15) • aHR(AB≥2) = 1.15 (1.00, 1.31) Increased the composite outcome of mortality (all cause) or first stroke, AB > 0: • aHR(AB=1) = 1.09 (1.04, 1.14) • aHR(AB≥2) = 1.20 (1.14, 1.26)	1 AB as a continuous variable: effect of a 1-point unit increase 2 AB groups: 0, 1, and ≥ 2	Age, gender, Charlson Comorbidity Index, living situation, home care, dementia disorder, MMSE, use of antidementia drugs at baseline

Outcome: Pneumonia							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Lampela, 2017 Finland	Community-dwelling people with Alzheimer's Disease. N= 36,791(12,442 cases, 24,349 controls)	Nested Case control. 12 months	ACD	Any AM use in the 14 days prior to the index event (pneumonia case or control matching date). Logistic regression models.	People with any AB were at increased risk of pneumonia: • aOR(Any AB): 1.36 (1.29–1.43) Highest risk of pneumonia was amongst people with level 2 AB, followed by level 1 AB and no significant effect for Level 3 AB: • aOR(Level1): 1.37 (1.30, 1.44) • aOR(Level2): 1.40 (1.17, 1.68) • aOR(Level3): 1.03 (0.87, 1.23) Incident anticholinergic users had the highest risk of pneumonia, followed by past and prevalent use: • aOR(Incident): 2.68 (2.15, 3.34) • aOR(Past): 1.51 (1.38, 1.65) • aOR(Prevalent): 1.48(1.40, 1.57) Non-chronic anticholinergic users (< 274 days) had the highest risk of pneumonia followed by chronic users (≥ 274 days): • aOR(Non-chronic): 1.63 (1.51, 1.75) • aOR(Chronic): 1.35 (1.28, 1.43) Increased risk of pneumonia for all durations of AB use, with the highest risk for the lowest and highest AB quartiles: • aOR(1–273): 1.62 (1.50, 1.74) • aOR(274–472): 1.21 (1.14, 1.30) • aOR(473–817): 1.44 (1.34, 1.54)	Non-use of any AC -vs- Any use of AC	Gender, age group, a list of comorbidities, a list of other drug use

					• aOR(≥818): 1.58 (1.47, 1.71)		
Outcome: Fall or Fall Related Injury							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
A. R. Green, 2019 USA	Age >65 years with MCI, Alzheimer's disease or dementia. N=6992	Retrospective cohort. 12 months (since 1st Nov 2015 to 31 Oct 2016)	Anticholinergic drugs	ACB leveled as 1, 2 and 3, then outcome measured among target group. Multivariate cox regression	ACB level =1, aHR= 1.05, 95% CI=1.01-1.10, p-value= 0.02. ACB level=2, aHR=1.56, 95%CI=1.16 - 2.10, p-value= <0.01. ACB level=3, aHR=1.08, 95%CI= 0.97 - 1.20, p-value= 0.17.	p value= <0.05.	a condition had to at least be partially associated with the outcome in the absence or presence of the ACB exposure or both, and a comorbid condition had to be at least partially associated with the average ACB score, in the group who had falls, in the group that was censored without falls, or both.
Outcome: Neuropsychiatric Function							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Y. Jaïdi, 2019 France	Deemntia patients age (≥65 years) with BPSD. specialising in dementia management. N = 147	Prospective cohort at Reims University Hospital, France (single center). Since July 15, 2015, to October 31, 2017.	Anticholinergic drugs	AB at baseline and during discharge from hospital. (ADS, ACB, ARS). NPI-NH frequency x severity score (F x S) – NPI-NH occupational disruptiveness score (OD). Multiple linear regression	Clinically significant reduction (improvement) in F x S score of subjects with moderately intense BPSD when AB was reduced by onepoint increments (using the ADS): • (AB reduction=1 / Mild BPSD) = 1.17 (− 0.28, 2.62) • (AB reduction=2 / Mild BPSD) = 1.09 (− 0.86, 3.04) • (AB reduction=3 / Mild BPSD) = − 0.24 (− 3.20, 2.72) •(AB reduction=1 / Moderate BPSD) = 3.79 (1.76, 5.83) • (AB reduction=2 / Moderate BPSD) = 6.34 (4.54, 8.14) • (AB reduction=3 / Moderate BPSD) = 7.63 (6.08, 9.19) • (AB reduction=1 / Severe BPSD) = 0.70 (− 1.23, 2.63) • (AB reduction=2 / Severe BPSD) = 0.16	AB reduction groups: 0 reduction, 1- point reduction, 2-point reduction, 3- point reduction	Age, gender, ADL, type of dementia, stage of dementia, likelihood of depression, comorbidity, nutritional status

					(− 1.64, 1.95) • (AB reduction=3 / Severe BPSD) = − 1.64 (− 3.83, 0.54) Clinically significant reduction (improvement) in the OD score of subjects with moderately intense BPSDs symptoms when AB was reduced by one-point increments (Assessed using the ADS):H • (AB reduction=1 / Mild BPSD) = 1.27, 2.44) • (AB reduction=2 / Mild BPSD) = 1.91 (0.62, 3.2) • (AB reduction=3 / Mild BPSD) = 1.92 (0.20, 3.63) • (AB reduction=1 / Moderate BPSD) = 2.05 (1.01, 3.09) • (AB reduction=2 / Moderate BPSD) = 3.47 (2.41, 4.54) • (AB reduction=3 / Moderate BPSD) = 4.26 (3.11, 5.41) • (AB reduction=1 / Severe BPSD) = 0.26 (− 0.98, 1.51) • (AB reduction=2 / Severe BPSD) = − 0.10 (− 1.23, 1.02) • (AB reduction=3 / Severe BPSD) = − 1.10 (− 2.28, 0.07)		
Y. Jaïdi, 2019 France	Deemntia patients age (≥65 years) with BPSD. specialising in dementia management. N = 147	Prospective cohort at Reims University Hospital, France (single-center). Since July 15, 2015 to October 31, 2017.	Anticholinergic drugs	AB at baseline and during discharge from hospital. (ADS, ACB, ARS). NPI-NH frequency x severity score (F x S) – NPI-NH occupational disruptiveness score (OD). Multiple linear regression	Clinically significant reduction (improvement) in F x S score of subjects with moderately intense BPSD when AB was reduced by one point increments (using the ADS): • (AB reduction=1 / Mild BPSD) = 1.17 (− 0.28, 2.62) • (AB reduction=2 / Mild BPSD) = 1.09 (− 0.86, 3.04) • (AB reduction=3 / Mild BPSD) =	AB reduction groups: 0 reduction, 1- point reduction, 2-point reduction, 3- point reduction	Age, gender, ADL, type of dementia, stage of dementia, likelihood of depression, comorbidity, nutritional status

					− 0.24 (− 3.20, 2.72) •(AB reduction=1 / Moderate BPSD) = 3.79 (1.76, 5.83) • (AB reduction=2 / Moderate BPSD) = 6.34 (4.54, 8.14) • (AB reduction=3 / Moderate BPSD) = 7.63 (6.08, 9.19) • (AB reduction=1 / Severe BPSD) = 0.70 (− 1.23, 2.63) • (AB reduction=2 / Severe BPSD) = 0.16 (− 1.64, 1.95) • (AB reduction=3 / Severe BPSD) = − 1.64 (− 3.83, 0.54) Clinically significant reduction (improvement) in the OD score of subjects with moderately intense BPSDs symptoms when AB was reduced by one-point increments (assessed using the ADS):H • (AB reduction=1 / Mild BPSD) = 1.27, 2.44) • (AB reduction=2 / Mild BPSD) = 1.91 (0.62, 3.2) • (AB reduction=3 / Mild BPSD) = 1.92 (0.20, 3.63) • (AB reduction=1 / Moderate BPSD) = 2.05 (1.01, 3.09) • (AB reduction=2 / Moderate BPSD) = 3.47 (2.41, 4.54) • (AB reduction=3 / Moderate BPSD) = 4.26 (3.11, 5.41) • (AB reduction=1 / Severe BPSD) = 0.26 (− 0.98, 1.51) • (AB reduction=2 / Severe BPSD) = − 0.10 (− 1.23, 1.02) • (AB reduction=3 / Severe BPSD) = − 1.10 (− 2.28, 0.07)		

Outcome: Impaired Physical Function							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Ann Kolanowski, 2015 USA	inpatients (≥65 years) with dementia from rehabilitation center. N = 99	multi-center RCT. Hospital stays 30 days or until discharge	Mild Anticholinergic Medications: Metoprolol Furosemide Warfarin Hydralazine Risperidone Isosorbide Alprazolam Digoxin Atenolol Prednisone Moderate/Severe Anticholinergic Medications: Quetiapine Dicycloverine Carbamazepine Paroxetine Amitriptyline Methocarbamol Olanzapine Diphenhydramine Hydroxyzine Meclizine	Delirium Cognitive function Physical function Hospitalization AB measured weekly during rehabilitation hospital stay (ACB). Multilevel models	Physical function: Moderate/severe AB (≥ 2) predicted poorer physical performance on the Barthel Index: • (AB=1) = − 3.411 ($p > 0.05$) • (AB≥2) = − 5.761 ($p < 0.05$)	Any mild AB use (AB = 1) No -vs- Yes Any moderate/ severe AB use (AB ≥ 2) No -vs- Yes	Age, gender, education level, ethnicity, Clinical Dementia Rating score, APOE allele status, Charlson Comorbidity Index score, previous week's cognitive and physical function performance, number of days in the facility on the outcome assessment week.
Outcome: Health-Related Quality of Life (HRQoL)							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Sura et al., 2015 USA	dementia patients (age >65 years) who are receiving AChEI or memantine. N=112	retrospective, longitudinal, cohort study. 2 years, Between 2005 to 2009	Anticholinergic drugs	Incident use of Anticholinergic medication with marked AB in rounds 3 or 4 of the panel survey. (ADS). Multiple linear regression.	Incident use of anticholinergic medication (≥ 2) reduced (worsened) the HRQoL PCS: • β(PCS) = − 7.48 ($p < 0.01$) • β(MCS) = − 2.27 ($p = 0.43$)	Nonusers of AC medication* -vs- Incident users of AC medication with an AB ≥ 2	Baseline HRQoL (PCS and MCS), age, gender, race/ethnicity, marital status, education, family income, region, health insurance coverage, metropolitan area, ADLs, IADLs, general health status, mental health status, use of cholinesterase inhibitors

Outcome: Treatment modification within 1 year, due to non-responsive treatment or disease progression							
First author, year, and country	Target population group and sample size.	Study design and duration	Type of medications	Exposure measure and statistical method	Result	Reference group/compared with	Confounders
Ah, Y. M. 2018 Korea	patient with Dementia (age>60 years) N=25825	Retrospective Cohort, 2003-2011	Anticholinergic medications used for various indications, who is receiving Cholinesterase inhibitors-donepezil, galantamine and rivastigmine.	Within 1st 3 month of Anti-dementia drugs treatment, average daily AB has been measured.	High AB (> 3)-vs- no or minimal ACB (≤ 1): • aHR = 1.12 (1.02, 1.24).	No or minimal AB (≤ 1) -vs- High AB >3 AB = 0 -vs- AB ≥ 1	Age, sex, baseline comorbid disease, baseline ACB score, baseline sedative load, ginkgo extract use

Abbreviations: AB = Anticholinergic burden. ADAS-COG = Alzheimer's Disease Assessment Score, Cognitive subscale. ADL = Activities of daily living. AEC: Anticholinergic Effect on Cognition scale. AM = Anticholinergic medication. aOR = Adjusted odds ratio. aHR = Adjusted hazard ratio. β Coef. = Adjusted effect of a 1-point unit increase in AB (as a continuous variable). BMI = Body Mass Index. BPSD = Behavioral and psychological symptoms of dementia. CLOX1 = A quantitative clock-drawing test in two parts, where part 1 measures executive function deficits. DAD = Disability Assessment for Dementia scale. IADL = Instrumental activities of daily living aIRR = Adjusted incidence rate ratio. LOS = Length of stay. MCS = Mental Component Score of the SF12. MMSE = Mini-mental State Exam. TMSE = Thai Mental State Exam. NPI-NH = Neuropsychiatric Inventory-Nursing Home scale (e.g. delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety). PCS = Physical Component Score of the SF12. SD = Standard deviation. SF12 = Short Form Survey. SIB= Severe Impairment Battery.

3.2. Quality of selected studies:

In this systematic review, the quality assessment was done by the Newcastle-Ottawa Scale (NOS). After using the questionnaire (Appendix-3) among twelve cohort studies, three studies were scored 9 stars (25, 29, 32). Another three studies scored 8 stars (21-23), and two scored 7 stars (26, 30) evaluated high quality study. However, three cohort studies scored 6 stars (12, 27, 31) and only one cohort study scored 5 stars (28) indicated medium quality study. Additionally, the included one case-control study has been scored 8 stars (14), indicated a high quality study. The article cross-sectional study, where participants included from the control arm of randomized control trials, scored maximum 10 stars (3) and another cross-sectional study scored 7 stars (33), both considered as high quality studies.

In this review, from the included articles, four studies had high risk of bias (12, 27, 28, 31). Three studies had the moderate risk of bias (26, 30, 33). Rest of nine studies had low risk of bias (3, 14, 22-25, 29, 32) (Appendix-3). The risk of bias was determined by the lack of adjusting potential

confounders like age, gender or comorbidities, for example study did not use any confounders (28). Other studies have reasonably less risk of bias.

4. Discussion:

4.1. Discussion of results:

This is the first systematic literature review, where the linkage between AC medications and increasing disease burden or adverse outcome for PwD has been explored. In this review, four cohort studies has identified, AC medications are responsible for increasing the risk of mortality among PwD (12, 22, 29, 30). Six studies have been addressed, AC medications are responsible for cognitive impairment among PwD (3, 23, 24, 27, 28, 33), but few studies have lower quality. Hence, having a strong argeement with this opinion is challenging. However, there was a mixed result for cognitive function among PwD, as dementia itself causes cognitive impairment (2). Therefore, to assess baseline cognitive function and determining its worsening condition, differnet scales to measure cognitive status has been used in different studies. There is a high possibility of bias results due to variations in measuring scales. Another study showed cognitive impairment associated with chronic use of AC drugs but did not adjust for any potential confounders like age, gender, and comorbidities (28). There is a higher possibility of confounding bias, which means the outcome may result from the indication of AC medication use rather than the ACB.

This study supports the outcome of hospitalization and mortality related to AC medications in various ways. Watanabe et al. described in their research, that the main reason for hospitalization was not directly associated with AC drug use; rather, polypharmacy or higher comorbidity among PwD was contributing factor (31). Most of the patients are admitted to the hospital due to cardiac disease, gastrointestinal disease, fall or injury, respiratory infection, which might be expected in a dementia patient with multiple comorbid patients (31). In another study with a large sample size, Bishara et al. found AC medications increase both emergency hospitalization and length of hospital stay among PwD (22). This can be explained as dementia is a chronic illness that also makes people vulnerable; the AC drug causes acute disease, mostly respiratory and causes a slower healing process, leading to an extended hospital stay (14, 22).

However, the immune response in the brain is inhibited by AC medications among PwD; thus, worsening existing Dementia occurs (13). Lampela et al. showed that AC medicines are

responsible for developing pneumonia among PwD by depriving mucociliary transport in the bronchus, which favors bacterial growth in the lung (14). Another mechanism identified AC medications reduce the pressure of the esophageal sphincter, cause acid reflux from the stomach, and aspirate to the lung, causing aspiration pneumonia (14) which is a life-threatening condition. Tan et el. explained AC medications increases incident stroke among vascular dementia and mixed type dementia patients by inhibiting the immune response system (30). Nevertheless, this gives an impression, that before prescribing AC medication with PwD should exclude risk factors of stroke and respiratory illness to prevent stroke and pneumonia.

A study conducted in Korea showed that nearly half of the PwD who received AC medications before starting the Acetylcholinesterase inhibitors (AChEI) had experienced a greater ACB as a result of chronic exposure (12). Therefore, frequent treatment modification has been noticed due to the non-responsiveness of Dementia treatment and the worsening of symptoms occurred (12). Hence, before starting Acetylcholinesterase inhibitors (AChEI) among PwD, discontinuation of AC medications or using alternative medications would be helpful (12). Exposure to AC medications is usually assessed by the Anticholinergic burden scale (ACB scale), which also indicates other comorbidities and polypharmacy can be helpful in adjusting confounders (16).

Four studies have showed, ACB has a strong association with mortality, but study from Ireland did not have a statistically significant results, which indicates a further prospective cohort with follow-up study is required (29). However, one study showed that PwD with existing vascular component increases stroke and mortality, those who has an ACB score of two or more (30). However, the outcome of stroke is precisely contributed by ACB is questionable whereas, the Dementia itself can confound the outcome stroke.

Another study claimed that ACB is responsible for fall or fall-related injury among PwD (25). The risk of fall has been estimated by the ACB scale, and AC drugs have been categorized into 3 groups depending on drug potency (25). However, the study was not adjusted for existing sedative-hypnotic users, that may confound the result. Nevertheless, the systematic review findings indicate that the ACB was related to cognitive and physical impairment and hospitalization or mortality; however, stroke, risk of fall or fall-related injury, pneumonia, and neuropsychiatric dysfunction was uncertain. Further research is needed with higher quality articles to determine that the poor health outcomes of PwD is purely associated with the ACB. In this review, most of the studies used administrative data. As a result, making a comparison of disease conditions like delirium or

dementia severity was difficult. Additionally, none of the study could be certain that patients took all medications that had been prescribed for them. Therefore, there might be a gap between study results and real burden of AC medications on PwD.

4.2. Discussion of methodological consideration:

The validity of this systematic review can be determined by its methodological process. This systematic review was performed through a comprehensive literature search in the major database and explored all relevant studies, including their references. The search term included both the MeSH term and text words. During study selection, the pre-defined inclusion and exclusion criteria were followed, and to prevent missing out of any relevant articles all the references of selected papers was screened. Interestingly, three articles were found from selected papers reference list, which added manually on later step. This made this systematic review reliable and prevented selection bias. The significant study results were analyzed and assembled in table- 2. Overall, this study has strong validity which summarizes the study result and shows the evidence of worst outcome causes by using AC medications among PwD. However, the heterogenicity of study results prevented meta-analysis. For example, to assess cognitive impairment in PwD, the Alzheimer's Disease Assessment Battery Scale-Cognitive (ADAS-Cog) and Mini-Mental State Exam (MMSE) scale were used in two different articles; hence the different scale gives the different formatted result (23, 24). Nevertheless, there is a scope for future research to perform mini meta-analyses with similar results. A strength of this study is using the standard PRISMA guideline in this review process and critical appraisal has done by using The Newcastle-Ottawa Scale (NOS), which made the quality assessment of each study transparent. The Newcastle-Ottawa scale is recommended by the Cochrane collaboration which is best tool for assessing validity and reliability (34).

This systematic review paper has generalizability, as the study setting has no geographical boundary. Dementia is a global disease, the disease burden or suffering of patients and caregivers are more or less similar in all over the world (5). On the other hand, the generalizability has been compromised in this paper, as the study population was restricted only to PwD, not the general older people. However, AC medication use is frequent both in Dementia and non-dementia patients (9). Additionally, this study's strength is that the included articles intervention was restricted to AC medications, to estimate the actual result of adverse outcome among PwD. Another papers

which showed the result of mixed groups of drugs like antipsychotics or sedatives, along with AC medications were excluded (35).

Moreover, this study shows more generalizability in the perspective of the broad term Dementia was used here. The systematic review of determining adverse effects of AC medications on the patient with one of the subgroups of Dementia, could not be possible due to less available primary research, which is a limitation of this paper. Alternatively, the strength of this study is its validity, where the ICD-10 code F03. 90, and F03.91 have been used and matched with the included study population (20). This helped to get the correct articles with desired study population. However, the generalizability is also expressed during measuring intervention "use of AC medications." The AC medications are classified into two broad groups and have other subgroups (36). In one study, researchers found that 107 AC drugs are commonly used for elderly patients (37). But lack of primary research on specific AC medication and its effects on PwD prevented this systematic review from being precise.

Another methodological strength of this study is- it explored more than 20 years of publications and observed the trend of investigating consequences. For example, the study performed in 2003 and 2010 examined the "cognitive impairment" due to the use of AC medications among PwD (28, 33). Alternatively, in recent years, the researchers investigated- the "Treatment modification required within one year after starting AC drugs" or "Neuropsychiatric dysfunction" caused by AC medications among PwD (12, 26). With this understanding, further research can be conducted to identify the correct treatment protocol for PwD. Finally, the study was limited to select articles in the only English language. However, some Japanese and Chinese articles with similar interests were excluded during the study selection process, which is a limitation of this study. To overcome this limitation, further research may conduct without the language barrier.

4.3. Recommendations for physicians and policymakers and further scope of research:

This study was performed inspired by reading several articles that showed AC medications are responsible for increasing disease burden among PwD. But the evidence was insufficient. Eventually, the research questions were developed to investigate and outline the adverse outcomes caused by using AC medications among PwD. Also, to determine the association of increasing disease burden among PwD with the same drug. The findings of this systematic review already

demonstrated the adverse outcomes and their association with increasing disease burden and causing financial drain by hospitalization and excess requirement of care. The physicians can keep in mind the risk factors before prescribing, and policymakers need develop treatment protocols, and National guidelines of each country to adopt the implications. However, AC medications have some beneficial effects in elderly patients but it causes some adverse outcome in PwD (37, 38). Hence, this systematic review will help physicians to asess risk over benefits during prescribing AC medications among PwD.

Moreover, This systematic review will help conduct further research at Dementia care centers. Future research can be conducted in three major steps. First, to identify the accurate method to estimate ACB. Secondly, the adverse effects AC medications can be assessed among different subgroups of Dementia. Finally, to explore effects of different medications having AC properties among specific subgroup of Dementia. However, further research with a large number of samples is necessary to establish the AC medications responsible for physical function impairment, declining Health-related quality of life (HRQoL), and neuropsychiatric dysfunction. Nevertheless, primary data collection from relevant patients at Dementia care center and conducting prospective cohort studies, and recording sequential follow-ups may avoid bias on outcomes like Dementia severity or delirium (12). This Systematic review gives an understanding that AC medications are harmful to PwD. But it is possible to conduct further research with specific drugs and examine their adverse effects on PwD. The researchers can get an insight from this study to conduct further research to identify the Gold-standard ACB measuring scale. That would be helpful for policymakers to build research criteria and validate the research. Finally, the safety margin of using AC medication or threshold level of the duration of use among PwD can be determined by further research, and prescribing guidelines for Dementia should be developed to reduce the disease burden.

4.4. Limitations:

This review has investigated whether the existing literature suggests that the ACB is responsible for adverse health outcomes among PwD. This study's potential limitation is that it did not explore the ACB in different types of Dementia. Similarly, the study did not investigate the specific drug of the AC group responsible for causing adverse outcomes in PwD. Thus, there might have selection bias; different sorts of Dementia might not affect by all classes of AC medications.

Furthermore, among included articles, several indicators have been used to measure ACB, and each method could have strengths and weaknesses. In this study, articles included with no ideal evidence-based approach might bias the study result. Another limitation of this study is that it does not show the mean duration of AC medication use, to develop adverse effects. Though it has been observed that the different outcomes like prolonging hospital stay or hastening mortality among PwD occur due to the use of AC medications, the duration of use was not accounted for. This study could not identify the over-the-counter medication use having AC properties and could not exclude treatment non-compliance, as this review depended on primary researchers' data.

5. Conclusion:

The prevalence of dementia is rising tremendously, and it contributes to increasing the global burden of the disease (39). In this regard, this Systematic literature review identified using AC medications among PwD is a prime contributor to the rising disease burden. This systematic review showed that PwD who received AC drugs suffered more from complications like cognitive impairment, neuropsychiatric dysfunction, stroke, pneumonia, fall-related injury, increased hospitalization, and hastened mortality. This study gives physicians and policymakers insight into developing the Dementia treatment protocol and includes it in National guidelines. Physicians should consider risks and seek pharmacological alternatives before prescribing PwD. However, to achieve the SDG -3: Good health and well-being are directly related to reducing the AC medication burden among PwD, and SDG- 1: No poverty is also linked with this (40). Reducing the disease burden will reduce the treatment cost of PwD, the workload of caregivers, and their engagement with the patient. Ultimately, caregivers and family members would be able to work outside and reduce poverty. Finally, my motto was to highlight adverse outcomes due to AC medication use, which is a modifiable factor for reducing the disease burden of PwD, ultimately decreasing global disease and financial obligations. Nonetheless, future research is necessary with a large sample number to find specific AC medication, which brings adverse outcomes among PwD.

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7. Appendix:

7.1. Appendix-1:

Search strategy: The effect of Anticholinergic medications among PwD. Method of searching in PubMed and Web of Science. (Additional search done in Google scholar to explore cited articles.)

Database (Search conducted from 1st January 2000 to 31st January 2022)	Search terms	Number of studies searched
PubMed	#1a: "Dementia"[MeSH Terms] OR "Alzheimer Disease"[MeSH Terms] OR "Huntington Disease"[MeSH Terms] OR "Frontotemporal Dementia"[MeSH Terms] OR "Lewy Body Disease"[MeSH Terms].	187,581 hits.
PubMed	#1b: "dement*"[Title/Abstract] OR "huntington*"[Title/Abstract] OR "alzheimer*"[Title/Abstract] "lewy body*"[Title/Abstract] OR "lewy body*"[Title/Abstract] OR "lewybody*"[Title/Abstract] OR "severe cognitive impairment"[Title/Abstract]OR "frontotemporal diseas*"[Title/Abstract] OR	269,093 hits.
PubMed	#1a OR #1b	298,361 hits.
PubMed	#2: "anticholinergic agents"[Title/Abstract] OR "cholinergic receptor antagonist"[Title/Abstract] OR "cholinergic blocking agent"[Title/Abstract] OR "cholinergic blocking agent"[Title/Abstract] OR "Acetylcholine Antagonist"[Title/Abstract] OR "Cholinergic Antagonist"[Title/Abstract] OR "Anticholinergics"[Title/Abstract] OR "anti cholinergics"[Title/Abstract] OR "Anticholinergic"[Title/Abstract	14,199 hits.
PubMed	#3: (((((("outcome"[All Fields]) OR ("burden"[All Fields])) OR	2,952,307 hits

	("hospitalization"[MeSH Terms])) OR ("death"[MeSH Terms])) OR ("mortality"[MeSH Terms])) OR ("adverse effect"[All Fields])	
PubMed	#1 OR #2 OR #3	2,192,549 hits
PubMed	#1 AND #2 AND #3	204 hits.
Web of Science	#1a: TI=(dement* OR alzheimer* OR huntington* OR "frontotemporal diseas*" OR "lewy body*" OR lewy-body* OR lewybody*)	182,041 hits
Web of Science	#1b: (AB=(dement* OR alzheimer* OR huntington* OR "frontotemporal diseas*" OR "lewy body*" OR lewy-body* OR lewybody*))	20,559 hits
Web of Science	#1c: TS=(Dementia OR Alzheimer disease OR huntington disease OR frontotemporal disease OR frontotemporal dementia OR lewy body disease)	327,309 hits
Web of Science	#1a OR #1b OR #1c	190,452 hits
Web of Science	#3a: AB=("anticholinergic*" OR "anticholinergic agent*" OR "cholinergic receptor antagonist" OR "cholinergic blocking agent*" OR "acetylcholine antagonist*" OR "cholinergic antagonist" OR "anti cholinergics")	8,021 hits
Web of Science	TS=("anticholinergics" OR "anticholinergic agent*" OR "cholinergic receptor antagonist" OR "cholinergic blocking agent*" OR "acetylcholine antagonist*" OR "cholinergic antagonist" OR "anti cholinergics")	4,613 results.
Web of Science	TI=("anticholinergic agent" OR "cholinergic receptor antagonist" OR "acetylcholine antagonist*" OR "cholinergic antagonist")	185 results

7.2. Appendix- 2: Data extraction format excel link:

Microsoft Excel Worksheet

7.3. Appendix- 3.1:

Quality assessment of included fifteen studies using Newcastle-Ottawa scale for quality assessment assessing anticholinergic burden among Dementia or Alzheimer's disease patients (each star mark represents the fulfillment of the criterion within the subsection)

	Selection (max. 4 stars)				**Comparability (max. 2 stars)**	**Outcome (max. 3 stars)**			
Study ID	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of	Comparability of cohorts based on the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality score (max. 9 stars)
Ah, Y. M. et al.	-	*	-	-	**	*	*	*	******(6)
Bishara et al.	*	*	*	-	**	*	*	*	********(8)
Dyer et al.	-	*	*	*	**	*	*	*	********(8)
Fox et al.	*	*	*	-	**	**	*	*	********(8)
Green et al	*	*	*	*	**	*	*	*	*********(9)
Jaïdi et al.	*	*	*	*	**	*	-	-	*******(7)
Jenraumjit et al.	*	*	*	-	**	*	-	-	******(6)
Lu et al.	-	*	*	*	-	*	*	-	******(5)
Tan et al.	*	*	-	-	**	*	*	*	*******(7)
McMichael et al.	*	*	*	*	**	*	*	*	*********(9)
Watanabe et al.	-	*	*	*	**	*	-	-	******(6)
Sura et al	*	*	*	*	**	*	*	*	********(9)

For cross-sectional study

	Selection (Max. 5 stars)				Comparability (max. 2 stars)	Outcome (Max. 3 stars)		
Study ID	Representativeness of the sample (*)	Samples size (*)	Non-respondents (*)	Ascertainment of the exposure (**)	Confounding factors controlled (**)	Assessment of outcome (**)	Statistical test (*)	Total quality score (Max. 10 stars)
Konishi et. al	-	*	*	**	-	**	*	*******(7)
Kolanowski et al	*	*	*	**	*	**	*	********** (10)

Appendix-3.2: For Case-control study:

Quality assessment criteria	Acceptable (*)	Lampela et. al.
Selection		
Is the case definition adequate?	Yes, with independent validation	*
	yes, eg record linkage or based on self-reports	-
Representativeness of the cases	consecutive or obviously representative series of cases	*
Selection of Controls	community controls	*
	hospital controls	-
Definition of Controls	no history of disease (endpoint)	*
Comparability		
Comparability of cohorts based on the design or analysis controlled for confounders	The study controls for age and BMI	*
	Study controls for other factors	*
Exposure		
Ascertainment of exposure	secure record	*
	structured interview	-
Same method of ascertainment for cases and controls	yes	*
Non-Response rate	same rate for both groups	-
Overall Quality Score (Maximum = 10)		********(8)

8. Popular Science Summary:

The prevalence of Dementia is increasing among the elderly population. Generally, while people age, they start suffering from various comorbidities and become vulnerable. Physicians commonly prescribe medication to control symptoms like respiratory illness, urinary incontinence, or parkinsonism. Most of the medications are with anticholinergic properties. Those medications are beneficial for general older people. However, patients with dementia (PwD) experience physical, behavioral, and psychological impairments; ultimately become dependent on families or caregivers. The standard treatment of Dementia is Acetylcholinesterase Inhibitors (AchEI), which work oppositely with Anticholinergic medications. Thus, if a dementia patient receives AchEI to treat dementia and Anticholinergic drugs to control other symptoms, the complications arise. The patient requires frequent hospitalization, increases cognitive impairment, incidence of stroke, pneumonia, and delirium, and increases the rate of mortality.

This study aims to establish adverse outcomes caused by using anticholinergic medications among PwD. This literature review will provide prescribers insight into using these medications among PwD cautiously and monitoring closely to avoid unwanted effects. Finally, this would be helpful to adopt prescribing guidelines for policymakers, which would reduce the disease burden, caregivers' burden, and financial burden among PwD and their families. Researchers have a scope to explore the effects of Anticholinergic medications among different types of Dementia.

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