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Cholinergic Antagonist use and the risk of Developing Dementia in persons aged 65 years and olders

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CHOLINERGIC ANTAGONIST USE AND THE RISK OF DEVELOPING DEMENTIA IN PERSONS AGED 65 YEARS AND OLDER

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Abstract

Anticholinergic medications cause a therapeutic or negative effect in the human body by blocking neuronal cholinergic receptors, thereby inhibiting the binding of acetylcholine in the central nervous system and the peripheral nervous system. These medications have short-term side effects including dry mouth, constipation, visual impairments, or delirium; however, research regarding the long-term side effects is limited. The purpose of this systemic literature review is to determine the correlation between prolonged exposure to anticholinergic medications and the development of dementia. The literature databases PubMed, Cochrane Review, Science Direct (Elsevier), and DynaMed were utilized in this review. Journal articles published within the years 2010-2020 were considered in the literature search. Only 11 journal articles qualified for this study by eliminating articles that did not specifically address a population aged ≥65 years, use of anticholinergic medications, and symptoms including dementia, impaired cognition, or Alzheimer's disease. The results of this review concluded the Anticholinergic Cognitive Burden and Anticholinergic Drug Scale were superior at quantifying the anticholinergic burden of anticholinergic medication exposure compared to other scales. Employing these anticholinergic scales, it was determined that individuals using a medication with a higher anticholinergic activity of 2 or 3 have been found to be at greater risk for developing dementia compared to those who are not taking them. An increased anticholinergic burden was also associated with a risk for fall. Further research needs to be conducted regarding the rating system of anticholinergic medications by medical professionals and how to accurately measure the cumulative effects of anticholinergic medications.

Keywords: anticholinergic medications, cholinergic antagonists, anticholinergic mechanism, cholinergic system, dementia, Alzheimer's disease, cognition, cognitive impairment, cohort study, aged, drug safety, anticholinergic burden

Introduction

In recent studies it has been estimated that close to 50% of individuals over the age of 65 are taking a medication with anticholinergic activity. Cholinergic antagonists, also referred to as anticholinergic medications, cause a therapeutic or negative effect in the human body by blocking neuronal cholinergic receptors, which inhibits the binding of acetylcholine in both the central nervous system (CNS) and the peripheral nervous system (PNS). This mechanism of action leads to inhibition of the smooth muscle of the gut, exocrine glands, and the heart. There is also a high density of cholinergic synapses found in the thalamus, striatum, limbic system, and neocortex of the CNS that are thought to play a vital role in functions such as memory, learning, and attention. Cholinergic antagonists may also block these routes of cholinergic transmission in the CNS, which could lead to cognitive impairment or dementia in patients that utilize them long term.

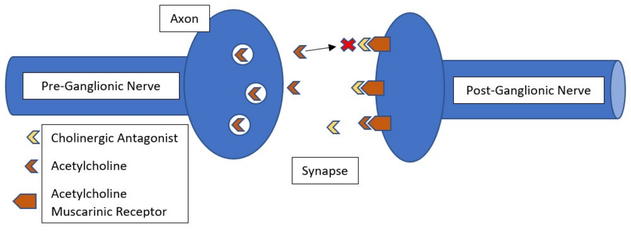

Image 1. Anticholinergic Medication Mechanism of Action

Statement of the Problem

•Cholinergic antagonists are commonly prescribed medications in primary care medicine and other various medical specialties. They are utilized for conditions regarding overactive bladder, gastrointestinal conditions, Parkinson's disease, chronic obstructive pulmonary disorder, depression, along with many other diseases. Often these conditions present in patients over the age of 65 years old, so it is valuable for providers to understand if there is a correlation between the use of anticholinergic medications and an increased risk of developing dementia. In an aging population that is already at increased risk for developing dementia, it is important to take a closer look at the adverse effects of medications that these individuals are taking as they may contribute to memory decline.

Research Question

❖Does the use of cholinergic antagonists increase the risk for dementia in patients 65 years and older who take them long term compared to patients who do not take them long term?

Literature Review

- Hampel et al. (2018) stated that due to its critical role in the thalamus, striatum, limbic system, neocortex, and forebrain, the human cholinergic system is thought to be important in cognitive decline, and more specifically Alzheimer's disease (AD). There is a cholinergic hypothesis of Alzheimer's disease that believes the disease occurs due to cholinergic innervation in the limbic system and the neocortex and that dysfunction of the forebrain is caused by loss of cholinergic neurons due to the break down of neurofibrillary tangles.
- Hampel et al. (2018) also suggests that the cholinergic system can increase vasodilation and blood flow to various cortical areas of the brain, which has been tested in multiple studies with cholinesterase inhibitors.
- Grossi et al. (2019) found the incidence of developing dementia between years Y2 to Y10 was 9.3% with the incident rate ratios (95% CI) measuring 1.06 for benzodiazepines, 1.28 for ACB_3, and 0.89 for ABC_{12} for ever users. IRR's increased with recurrent use.
- Lozana-Ortega et al. (2019) concluded that the Anticholinergic Cognitive Burden (ACB) and Anticholinergic Drug Scale (ADS) were the best-suited scales because they have been tested on older populations, easy to use in the clinical setting, included the greatest number of medications, and were found to have the highest inter-scale agreement at 0.82 using Spearman's correlation of scores
- Salahudeen, Duffull, & Nishtala (2015) found the Anticholinergic Cognitive Burden Scale (ACB) to be validated most by experts for determining the cumulative effects of anticholinergic medications.
- Green, Reifler, Bayliss, Weffald, and Boyd (2019) concluded that ACB Level 2 drug exposure caused the greatest individual increase in risk for falls or fall-related injuries, but the greatest risk came from a combination of Level 2 and Level 3 medication use.
- Cai, Campbell, Khan, Callahan, and Boustani (2013) discovered a larger anticholinergic burden (ACB=1), along with ≥ 3 medications and increased exposure of >90 days led to an increase in cognitive impairment (P=0.02) compared to an exposure period of <90 days.
- Campbell, Lane, Gao, Boustani, and Unverzagt (2018) concluded that participants that were diagnosed with stable MCI at baseline, strong anticholinergics were not found to have a significant effect on reversing the diagnosis back to normal cognition (p = 0.3266).
- Campbell et al. (2016) discovered the risk for cognitive impairment increased by 13% with every 1-point increase in mean total daily ACB score (p=0.043). Inpatient admissions also increased with every 1-point increase.
- Fox et al. (2011) found there was a 0.33 decrease in MMSE score in those that used an ACB Level 2-3 medication (P=0.03). Use of an ACB Level 1 medication was not associated with a decline in cognitive impairment (P= 0.79).
- Gray et al. (2015) found 23.2% of participants were diagnosed with dementia at the average follow up time of 7.3 years. Subjects that had Total Standardized Daily Doses >1095, had an increased risk for dementia (adjusted Hazard Ratio, 1.54).
- Heath et al. (2018) concluded that both high dose exposure to paroxetine and low dose exposure to paroxetine for the treatment of depression were associated with an increased risk for development of dementia compared with participants with no exposure (aHR=1.69).

Discussion

Class of Anticholinergic Cognitive Burden	Associated Negative Outcome	Study
ACB Score 1	Increased Mortality Rate	Fox et al (2011)
ACB Score 2	Increased Mortality Rate	Fox et al. (2011)
	Increased Risk of Dementia	Fox et al. (2011)
	Increased Risk for Falls	Green et al. (2019)
ACB Score 3	Increased Mortality Rate	Fox et al. (2011)
	Increased Risk of Dementia	Grossi et al. (2019) Fox et al. (2011) Heath et al. (2018)
	Increased Risk for Falls	Green et al. (2019)

Figure 1. Risks Associated with Anticholinergic Burden of Anticholinergic Medications

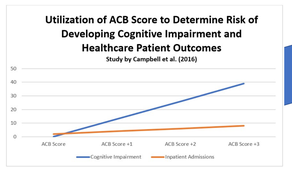

Figure 3. Development of Cognitive Impairment and Healthcare Outcomes with Anticholinergic Use

ACB Score 1	ACB Score 2	ACB Score 3
Atenolol	Baclofen	Amitriptyline
Codeine	Cetirizine	Atropine
Furosemide	Cyclobenzaprine	Diphenhydramine
Prednisone	Loperamide	Oxybutynin
Trazadone	Pseudoephedrine	Paroxetine

Image 2. Anticholinergic Cognitive Burden Scale Medication Ratings

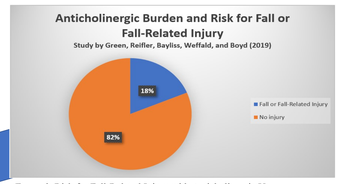

Figure 2: Risk for Fall-Related Injury with Anticholinergic Use

Further Considerations	Study
Increased risk for the development of dementia with increased exposure time to anticholinergic medications	Gray et al. 2015 Cai et al. (2013)
Factors that increase risk for development of dementia: -older, non-white, male, history of stroke, greater number of comorbidities -increase in age, inverse relationship with level of education	Cai et al. (2013) Campbell et al. (2018)
Use of cholinesterase inhibitors, such as donepezil or galantamine, for the treatment of Alzheimer's disease	Hampel et al. (2018)

Figure 4: Further Research Considerations for Discussion

Applicability to Clinical Practice

Caution needs to be taken by providers in the clinical setting when prescribing medications with a high cholinergic activity as it may lead to the development of cognitive impairment in patients who need to take them long term.

Administration of an anticholinergic medication in the clinic:

- Assign anticholinergic burden score to medication
- Evaluate other medications for anticholinergic activity
- Administer Mini-Mental Status Exam or similar test
- Re-evaluate yearly for changes in cognitive function

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