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Anticholinergic Medications and Risk of Developing Dementia

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Cholinergic Antagonist Use and the Risk of Developing Dementia in Persons Aged 65 Years and Older

By

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Abstract (to Come)

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Introduction

The population of the United States (US), along with many other countries around the world, continues to age which has a great impact on resources within the healthcare system. This increase in life expectancy is mainly due to advances in medicine, which has led to better preventative practices and greater treatments to improve and prolong the lives of chronically ill people. As the size of the aging population grows, the number of individuals requiring some form of prescription medication to manage their chronic illnesses will also grow. The US National Health and Nutrition Examination Survey revealed that of persons over the age of 65 years, 90% of them were on at least one prescription medication and 39% were taking five or more (Lozano-Ortega et al., 2019).

In a separate study, it was discovered that 47% of patients 65 years and older were taking a medication with anticholinergic activity. Cholinergic antagonists, also referred to as anticholinergic medications or anticholinergic drugs, 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 (Lozano-Ortega et al., 2019). 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 (Hampel et al., 2018).

Statement of 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?

Methodology

For this literature review, an extensive search of the current literature regarding anticholinergic medications and their correlation to dementia. I utilized literature databases such as Pubmed, Cochrane Review, Science Direct (Elsevier), and Dynamed. The MeSH words I used in my literature search included: anticholinergic medications, cholinergic antagonists, anticholinergic mechanism, cholinergic system, dementia, Alzheimer's disease, cognition,

cognitive impairment, cohort study, aged, drug safety, and anticholinergic burden. Only journal articles from the years 2010-2020 were considered in my literature search. The primary search resulted in 168 studies. Of these, only 11 journal articles qualified for this study by eliminating journal articles that did not specifically address a population greater than the age of 65, use of anticholinergic medications, and symptoms including dementia, impaired cognition, or Alzheimer's disease.

Literature Review

A review of the current literature demonstrates that anticholinergic medications have been a popular research topic, especially in recent years. Overall, research regarding mild and reversible side effects of anticholinergic medications is well established and includes symptoms such as dry mouth, constipation, visual impairments, and delirium. However, research regarding the cumulative and long-term effects of prolonged anticholinergic medication exposure is more limited and of great interest, as many patients are prescribed these medications for many years or for a lifetime.

Theme 1: Role of the Cholinergic System in Cognition

Hampel et al. (2018) conducted an extensive review of the current literature regarding the pathophysiology of the cholinergic system and its correlation to the pathophysiology of Alzheimer's disease. It also discusses the therapeutic management of Alzheimer's disease using cholinergic therapy. The methods utilized in this extensive review were not specifically stated in the article. Keywords used in the database search included acetylcholine, Alzheimer's disease, cholinergic system, cholinesterase inhibitors, and cognition. The literature databases used to

identify the included research articles were not included in the methods. Over 100 research articles were referenced throughout the course of the review.

The results of the review concluded that the cholinergic system is vital for central nervous functions such as memory, learning, and attention and is a large component in overall neural connectivity, coordination, and plasticity. 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). The Nucleus Basalis of Meynert (NBM) of the forebrain is known to provide the majority of cholinergic innervation to the cerebral cortex, limbic system, hippocampus, and entorhinal cortex. Loss of cholinergic innervation of the NBM, due to neurofibrillary tangles, has been identified in not only patient's with AD, but also in individuals with normal cognitive function and mild cognitive impairment that struggle with memory tasks. 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 breakdown of neurofibrillary tangles. Because of the hypothesis of Alzheimer's disease, cholinesterase inhibitors have been utilized in the therapeutic management of this disease which has demonstrated clinically significant results (Hampel et al., 2018).

The review by Hampel et al. 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, such as donepezil or galantamine, on subjects with dementia or Alzheimer's disease. These studies have also shown promising results but require further testing with more conclusive results. Furthermore, Alzheimer's disease is characterized by amyloid-β plaques, neurofibril tangles, neuroinflammation, changes in insulin

resistance, oxidative stress, and vascular insufficiencies. Researchers have created multiple hypotheses regarding the relationship between the characteristics of AD and the cholinergic system, but most are not yet well understood and require further investigation. The use of MRI with cholinesterase inhibitors has also been utilized in recent studies in attempts to track disease progress but was not found to be a beneficial diagnostic tool on its own. Ultimately, it is thought that the treatment of Alzheimer's Disease will include personalized treatment regimens based on genetic risks, brain imaging, and biomarkers in to offer the greatest therapeutic management for patients.

Theme 2: Anticholinergic Burden Scale Classification

Grossi et al. (2019) conducted a cohort study in the United Kingdom to test the relationship between the use of anticholinergic medications and benzodiazepines with an increased risk for developing dementia. This integrative study offers an in-depth analysis on the burden of anticholinergic medications from various potency categories and their relationship to cognitive impairment. The methods utilized in this study included data used from the Medical Research Council Cognitive Function and Aging Study (MRC CFAS), which was a cohort study that was conducted to predict the risk factors associated with dementia and the prevalence in the population, along with the course of the disease in participants over the age of 65. 13,004 subjects were interviewed at baseline (Y0), which included questions regarding mental health, physical health, lifestyle factors, sociodemographic variables, cognitive function, and medication use. Subjects, if still living, were re-interviewed with the same set of questions at year 2 (Y2) and year 10 (Y10). Medications were separated into three categories based on the Anticholinergic Cognitive Burden Scale: benzodiazepines, anticholinergics score 3 (ACB_3), anticholinergics score 1 or 2 (ACB_{12}). They were then coded by use including, "ever

used (use at Y0 or Y2), recurrent use (Y0 or Y2), new use (Y2, but no Y0), or discontinued used (Y0, but not Y2)" (paragraph 2). Outcomes of dementia that occurred by Y10 were calculated with univariable Poisson regression models to estimate incident rate ratios with a 95% confidence interval. Multivariable analyses were carried out testing 'ever use' of medication, year of birth, sex, and Mini-Mental State Examination (MMSE) using a logistic regression model. These analyses assessed changes from Y2 to Y10 regarding side effects, variables, and interactions between exposures of cumulative medication exposure (BZD, ACB_{12}, ACB_3), sex, and MMSE scores.

The results of the Medical Research Council Cognitive Function and Aging Study based on 13,004 participants at baseline, found 220 with incident dementia by Y10 and 2,825 without incident dementia. By year two (Y2), only 8,216 of the 13,004 participants had an unknown dementia status or no dementia. Between years Y2 to Y10, 3,136 subjects died, 1,990 did not follow up, and other participants were excluded for other various reasons. The incidence of 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. Incidence Rate Ratios (IRRs) for recurrent users were 1.30 for benzodiazepines, 1.68 for ACB_3, and 0.95 for ABC_{12}. Furthermore, participants who ever used an ACB_3 medication and had an MMSE score of >25 at Y2 evaluation were found to have an IRR of 2.28 compared to participants with a MMSE <25 at Y2 and IRR of 0.94 (Grossi et al., 2019).

One of the limitations of this study was that medication use was self-reported and adherence was not measured, as this would have been difficult to calculate. Between interview periods, for example Y2 to Y10, medication use was not measured; it was only measured during

the current interview period. Also, some participants that may have developed dementia between the assessment periods were not included in the finals results as there was no follow-up with patients that died during the study or that dropped out. The strengths of the study included measurement of dementia with a validated algorithm that eliminated bias. Furthermore, a large population was used in this study and followed for 8-10 years, using two baselines (Y0 and Y2), which helped determine any long-term effects of exposure to various medication patterns.

A review published by Lozana-Ortega et al. (2019) analyzed and compared various anticholinergic scales with the purpose of identifying the best scale to conduct retrospective database analyses. Anticholinergic scales were previously created to quantify the anticholinergic burden of anticholinergic exposure in medications. Anticholinergic medications vary in their level of activity and are categorized in these scales based on their potency which can help predict the risk of adverse effects in individuals that are using them long-term.

The methods of this review included an extensive search using Medline and EMBASE to identify any reviews or analyses which categorized the extent of the anticholinergic burden of medications. The various scales and measures that were identified were then analyzed for their ability to be used in backdated data analyses. All the scales underwent a preliminary review to see which ones would qualify for the final review. Preliminary review qualifications included, “sufficient data provided by authors to allow calculation of summary scores, some grading of anticholinergic potency, and inclusion of high potency medications” (paragraph 7). The full and final review of the selected anticholinergic scales included a full analysis of each scale, which was evaluated based on fourteen different categories. The categories included in the criteria were methods of development, year developed, country of development, the population excluded from

the analysis, clinical settings in which the scale has been applied, a ranking mechanism for anticholinergic medication, potential threshold, number of most common medications considered, the population in which the scale was validated, optimal target populations, a method by which the scale was designed to be administered, derivation of a summary score, percentage of high potency medications considered, and percentage of prescription medications considered. Anticholinergic measures were also evaluated based on eight different categories. Those criteria included: disease context for which measurement was developed, consideration of medication dose, whether the development was based on a specific anticholinergic scale, mathematical properties, consideration of anticholinergic potency of medications, capability for use with all anticholinergic scales, and considerations for categorization of resulting scores (Lozana-Ortega et al., 2019).

The results of the review published by Lozana-Ortega et al. concluded that the Anticholinergic Cognitive Burden (ACB) and Anticholinergic Drug Scale (ADS) were the best-suited scales for the purpose of conducting retrospective observational studies. A total of sixteen scales were analyzed, with six scales being eligible for the full and final review. When reviewing the results, it was discovered that all the scales did not include all the available anticholinergic medications in the U.S. They also varied greatly in the number of medications they were measuring, ranging from 27-520 medications, with the ADS having the most. Only two scales, the ADS and Anticholinergic Risk Scale (ARS), considered the dosing of the medication in their measurements and the Anticholinergic Activity Scale (AAS) targeted patients with Parkinson's Disease instead of a specific age group. Furthermore, there was a disagreement between the scales based on the potency of the anticholinergic medication being analyzed. The commonly prescribed medication paroxetine was found to have potency scores of 1, 2, or 3, depending on

the scale, with 3 being higher on the potency scale. The ACB and ADS scales were found to be best suited for this review 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) published a comprehensive systemic review to evaluate and compare which anticholinergic grading scale is superior in determining the cumulative effects of anticholinergic medications. It sought to determine negative effects on cognitive function, physical function, and mortality risk based on the anticholinergic burden. It discussed the four different potency classes of anticholinergic medications ranging from 0 or no anticholinergic activity all the way to a 3, which signifies high anticholinergic activity. The methods utilized in the study included a detailed literature search for anticholinergic risk scales in Ovid MEDLINE, EMBASE, and PsycINFO databases. A citation analysis was also conducted using Web of Science and Google Scholar to identify potential individual studies that discussed a specific anticholinergic risk scale that quantified the burden of anticholinergic use and its associated adverse effects. A total of 1,250 studies were identified in the primary search and after the removal of duplicates and non-eligible studies by two reviewers, a total of seven studies were included in the final review after meeting the pre-defined inclusion criteria. The data from the final seven studies was extracted and analyzed.

The results of this systemic review discovered a total of seven expert based anticholinergic risk scales: Anticholinergic Drug Scale (ADS), Anticholinergic Burden Classification (ABC), Clinician-rated Anticholinergic Score (CrAS), Anticholinergic Risk Scale (ARS), Anticholinergic Cognitive Burden Scale (ACB), Anticholinergic Activity Scale (AAS),

Anticholinergic Loading Scale (ACL), in which considerable inconsistencies were identified between them. Anticholinergic potency rating was found to be the greatest inconsistency between all anticholinergic risk scales. For example, a common medication such as quetiapine was designated scores or 1, 2, or 3, depending on what scale it was ranked, which leads to inconsistencies in scoring and decreased accuracy in predicting adverse outcomes. Furthermore, the citation analysis discovered the Anticholinergic Cognitive Burden Scale (ACB) to be validated most by experts for determining adverse effects (Salahudeen, Duffull, & Nishtala, 2015).

Theme 3: Risks of Anticholinergic Medications in Patients Aged ≥65

Green, Reifler, Bayliss, Weffald, and Boyd (2019) conducted a retrospective cohort study in adults with either dementia or impaired cognition, age ≥65, to assess their anticholinergic burden and associated risk of falls or similar injuries. Common side effects of anticholinergic medications include dry mouth, constipation, and delirium; however, the relationship between fall risk and the use of anticholinergics has not been clearly identified. Research is also lacking in knowledge regarding the cumulative effects of anticholinergic medications, also known as anticholinergic burden.

The methods utilized in the cohort study by Green, Reifler, Bayliss, Weffald, and Boyd (2019) included 10,698 participants that were members of Kaiser Permanente Colorado (KPCO), a nonprofit organization. The members considered for this study had to be aged ≥65 years, have a diagnosis of dementia or mild cognitive impairment (MCI), ≥2 comorbid conditions, and a two-year enrollment plan with the KPCO which covered pharmacy benefits. The Anticholinergic Cognitive Burden Scale (ACB) was utilized in this study to measure anticholinergic medication use and fall-related events, which was accessed through KPCO Virtual Data Warehouse, a

secondary database that allows access to electronic health records, pharmacy fills, and diagnosis claims. ACB scores were calculated during each participants' risk for fall which included an average ACB score and individual scores related to classes of medications based on their anticholinergic rating, either 1, 2, or 3. Participants were no longer followed after a fall or similar injury occurred, death, disenrollment from the 2-year plan, or the end of the study. Participants that had a fall-related event prior to the start of the study were excluded from the analysis. The first fall-related injury was used as the dependent variable using the Cox proportional hazards method for data analyses.

Results of the study revealed that 6,692 (63%) of participants were taking ≥1 ACB drug and around 2,015 (18%) of them experienced some type of fall-related injury over the course of 366 days. Participants that were using a combination of higher potency anticholinergic medications, Level 2 or 3, and had a >5 ACB score, were found to have a greater risk for fall or similar injury (Hazards Ratio (HR) 2.06, CI 1.51, 2.83). Anticholinergic burden, due to exposure to multiple Level 1 drugs, caused an increase in fall risk (HR 1.16, CI 1.03, 1.32). It was also discovered that there was a greater risk of injury associated with the use of ACB Level 2 medications than drugs in the other three categories (HR 1.56, CI 1.16, 2.10; P<0.01). In addition, there was a 5% increase in risk when a Level 1 drug was added to a participant's medication list (HR 1.05, CI 1.01–1.10; P 0.02). An 8% increase was noted with the addition of a Level 3 drug (HR 1.08, CI 0.97–1.20; P 0.17), which was not found to be statistically significant; however, the risk for falls or related injuries increased by 56% with the addition of one Level 2 drug (HR 1.56, CI 1.16–2.10; P<0.01). Furthermore, other interaction models were carried out which 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 (Green, Reifler, Bayliss, Weffald, and Boyd, 2019).

The limitations of this cohort study include possible inconsistencies in the hazard ratios which were utilized to calculate the fall risk of Level 2 medications. Adjustments were made because Level 2 medications are commonly prescribed for diseases that increase the risk of falls. Similar adjustments were also unable to be made for "incident versus prevalent drug use and related clinician judgment" (paragraph 23). Other limitations include medication dosage, which was not taken into consideration when accounting for ACB exposure. Lastly, the participants of the study were from the Denver metropolitan area and may not be an accurate representation of other populations.

Theme 4: Anticholinergics Use and the Risk for Increased Cognitive Impairment or Dementia

Cai, Campbell, Khan, Callahan, and Boustani (2013) conducted a retrospective cohort study with 3,690 participants, aged 65 and older, that investigated the relationship between anticholinergic use and cognitive impairment. With over nine million people in the United States taking at least one prescribed anticholinergic medication, Cai et al. carried out this retrospective study using information from the Indianapolis Dementia Screening and Diagnosis (IDSD) study to determine if increased anticholinergic medication use led to an increase in cognitive impairment in participants.

Methods utilized in the study by Cai, Campbell, Khan, Callahan, and Boustani (2013) included 4,197 participants who were part of the Indianapolis Dementia Screening and Diagnosis (IDSD) study in 2002-2004 and chosen based on their cognitive function test and their pharmacy fill history the year prior. Due to a lack of pharmacy dispensing records in the Regenstrief Medical Record System, 507 of the 4,197 subjects were excluded from the study. A multi-step

dementia screening assessment was performed on all the participants, which included the six-item screener and the Community Screening Instrument for Dementia (CSI-D). Further cognitive assessments were conducted on willing participants that tested positive for cognitive impairment during the primary screening. Roughly half of the participants denied further cognitive testing and it was discovered that those who pursued further testing were more likely to be younger (73.8 vs. 75.4; P = 0.01) and scored lower on the CSI-D (18.3 vs. 19.2; P = 0.07). 277 participants were excluded from the study after the primary screening because they denied further cognitive testing after testing positive. Cognitive outcomes resulted in 562 participants testing positive during the primary screening, of which only 285 underwent a full diagnostic assessment. One hundred twenty-nine subjects were diagnosed with dementia, while 93 were diagnosed with mild cognitive impairment (MCI). Upon the official diagnosis of dementia or mild cognitive impairment MCI by medical professionals, data was taken from the IDSD and the participants' electronic medical record, and the results were analyzed. The Anticholinergic Cognitive Burden Scale was utilized to calculate the anticholinergic burden in the study. Three categories of anticholinergic medication exposure were taken into consideration including, anticholinergic burden, total time of anticholinergic medication use, and amount of anticholinergic medication use at one time. Comorbidities were also taken into consideration for multivariate analyses.

The results of this cohort study revealed that participants that were older, non-white, male gender, and had a greater number of comorbidities, were more likely to develop dementia or MCI. Odds ratios were calculated, with adjustments made for age, race, gender, and comorbidities, which identified a chance of 2.73 for developing MCI (95% confidence interval, CI; 1.27, 5.87) and 0.43 for developing dementia (95% CI; 0.10, 1.81) with exposure to three

anticholinergic medications for a period of 90 days. 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. The comorbidity of greatest concern for a diagnosis of cognitive impairment is stroke. Roughly twenty-seven percent (27.8%) of participants with a history of stroke screened negative for cognitive impairment, while 40.9% of them screen positive for MCI and 48.8% tested positive for dementia (p<0.001). Hypertension, coronary heart failure, and coronary artery disease were not found to be statistically significant for a diagnosis of cognitive impairment or dementia with values of p=0.65, p=0.63, and p=0.73 respectively (Cai, Campbell, Khan, Callahan, and Boustani, 2013).

The limitations of this study included possible cases of cognitive impairment that were undiagnosed during the primary cognitive assessment due to a sensitivity of 98% for the six-item screener test and sensitivity of 87% for the CSI-D. Another limitation is that medication adherence was not considered. The pharmacy fill of medications were measured, and adherence was assumed, which may overestimate the participants' exposure to anticholinergic medications. Also, OTC medications may not be administered by the pharmacy, thus were not considered. Lastly, it is unknown whether participants who developed adverse cognitive outcomes continued to take their anticholinergic medications which would skew the association.

A prospective observational cohort study by Campbell, Lane, Gao, Boustani, and Unverzagt (2018) was conducted over the course of four years to assess the progression of cognitive impairment in participants over the age of 65 using anticholinergic medications. In order to prevent or reduce the risk of developing mild cognitive impairment or dementia, Campbell et al. set out to gain a better understanding of the cognitive outcomes associated with anticholinergic use and the reversibility of these effects. The methods of this study included a

sample size of 350 participants, who were all primary care patients of the Eskenazi Healthcare system, 65 years or older with no prior diagnosis of dementia. These patients all had to undergo a baseline cognitive screen using either the Mini-Mental Status Examination (MMSE) or the Telephone Interview for Cognitive Status (TICS). Once participants were accepted into the study, they had to complete a cognitive assessment every twelve months by an expert panel. This also involved a health history, depression screening (Geriatric Depression Scale), functional status screening, psychiatric status screening, neurologic exam, physical exam, and medication review, along with ten other cognitive assessment tests. The anticholinergic standard daily dose was measured with the help of the Indiana Network for Patient Care (INPC) to collect relevant medication and clinical data. Anticholinergic medications taken over the ten years prior to the baseline assessment were extracted to create a historical exposure variable. A time-varying variable was created using anticholinergic medication exposure over the course of twelve months between each assessment period. The Anticholinergic Cognitive Burden (ACB) scale was also utilized to classify the potency of each anticholinergic medication. Patient demographics, including comorbidities, were also taken into consideration in the analysis (Campbell, Lane, Gao, Boustani, and Unverzagt, 2018).

The results of the study were based on a total of 978 diagnostic assessments conducted on 350 participants over the course of four years. It was discovered at baseline that 70.6 % of participants had been exposed to at least one ACB medication, with 30.6% having taken a high potency ACB medication. Participants that had no diagnosis of cognitive impairment at baseline, were more likely to develop MCI with the use of strong anticholinergics compared to those with stable cognition (odds ratio [OR] 1.15, 95% confidence interval [CI] 1.01–1.31, p = 0.0342). The transition to MCI was also greatly influenced by the participants' age (OR 1.07, 95% CI

1.01–1.12, p = 0.0117); however, an increase in education had an inverse effect on the transition to MCI from normal cognition (OR 0.78, 95% CI 0.69–0.88, p < 0.001). In 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 (OR 0.95, 95% CI 0.86–1.05, p = 0.3266). The total standard daily dose was utilized to calculate the odds ratios which is defined by Campbell, Lane, Gao, Boustani, and Unverzagt (2018), as "a cumulative measure of anticholinergic exposure for all anticholinergics identified in the ACB scale (scores 1, 2, and 3) as well as for strong anticholinergics only" (paragraph 12).

Campbell et al. (2016) conducted a retrospective cohort study analyzing anticholinergic medication use and clinical data of 3,344 participants, all of which were adults 65 years and older. The objective of the study was to determine the relationship between impaired cognitive function and Anticholinergic Cognitive Burden (ACB) score and ACB score and utilization in healthcare.

Methods in this study included 3,344 community-dwelling participants, aged 65 years or older, that were all patients with Eskenazi Healthcare system, and were previously part of a dementia screening study between 2001 and 2004. Participants were chosen based on their age, ≥65 years, if they had one appointment with their primary care provider and had one prescription filled, both in the past year, and had one trip to an inpatient, outpatient, or emergency department in the first twelve months after acceptance into the study. Comorbidities and patient demographics were also considered in the analysis of this study which utilized the Regenstrief Medical Record System (RMRS) to collect data. The comorbidities considered in this study included congestive heart failure, coronary artery disease, stroke, arthritis, diabetes mellitus, liver disease, kidney disease, chronic obstructive pulmonary disease, and cancer. A two-phase

cognitive assessment was conducted on patients to diagnose cognitive impairment. Phase 1: Stage 1 included the 6-Item Screening Instrument, in which patients had to score 100% to skip stage 2. Participants that answered 1 or more of the questions incorrectly were asked to complete Phase 1: Stage 2, which included the Community Screening Interview for Dementia (CSI-D). Participants that tested positive for cognitive impairment in phase 1 were asked to participate in Phase 2, which involved an interview, a neuropsychological evaluation, and a review of medical records by a panel of experts. Diagnoses of either mild cognitive impairment or dementia were assigned upon the completion of phase 2 for participants that tested positive. Measurement of anticholinergic exposure was done using the RMRS, and the Anticholinergic Cognitive Burden Scale was utilized to assign the activity to anticholinergic medications. A mean total ACB score equation was created to determine each patient's additive anticholinergic exposure (Campbell et al., 2016).

The results of the study by Campbell et al. (2016) based on 3,344 participants, included population demographics as follows: mean age of 71.5, 71% female, and 58% African American. The risk for cognitive impairment was found to rise by 13% with every 1-point increase in mean total daily ACB score (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.004–1.27, p=0.043). There was also an increase in inpatient admissions for every 1-point increase in mean total daily ACB score (OR 1.11, 95% CI 1.02–1.29, p=0.014). Once demographic corrections were made, there was also a significant increase in outpatient visits (estimate 0.382, standard error [SE] 0.113; p=0.001) and emergency department visits (estimate 0.046, SE 0.023, p=0.043) with increases in mean total daily ACB score. Overall, it was concluded that increased mean total daily ACB scores were associated with greater risk for cognitive impairment and greater utilization of health care.

A longitudinal study by Fox et al. (2011) was conducted over the course of two years to try and identify if anticholinergic medications increased the risk of cognitive impairment and mortality in people 65 years or older. They were also trying to determine if there is a cumulative relationship between risk and anticholinergic use. The methods utilized in this study included 13,004 community-dwelling and institutionalized participants, ≥65 years of age, who were enrolled in the Medical Research Council Cognitive Function and Ageing Study. Participants completed an interview process that gathered information regarding sociodemographic factors, medications, activities of daily living, and cognitive measures, including a Mini-Mental Status Examination (MMSE). The MMSE was given for baseline screening to measure cognitive function and again at a two-year follow-up assessment. Anticholinergic medication exposure was measured using the Anticholinergic Cognitive Burden Scale (ACB). Prescribed and over-the-counter medication information, including name, dose, frequency, and quantity, was recorded by interviewers, along with other patient covariates (age, sex, educational level, social class, number of nonanticholinergic medications, number of comorbid health conditions, and baseline cognitive function).

Results of the study by Fox et al. (2011) discovered that 47% of participants were taking an ACB Level 1 (possible anticholinergic properties), medication, whereas only 4% were using an anticholinergic ACB Level 2-3 (definite anticholinergic properties) medication. Adjustments were made for participant covariates at baseline and it was found there was a 0.33 decrease in MMSE score in those that used an ACB Level 2-3 medication (95% confidence interval (CI) = 0.03–0.64, P=0.03). Use of an ACB Level 1 medication was not associated with a decline in cognitive impairment (0.02, 95% CI=- 0.14–0.11, P= 0.79). At the two year follow up

assessment, mortality rate was increased by both ACB Level 2-3 drugs (OR=1.68; 95% CI=1.30–2.16; P<.001) and ACB Level 1 drugs (OR= 1.56; 95% CI = 1.36–1.79; P<.001).

A limitation of this study involves unknown anticholinergic medication adherence over the course of the two-year study, which may not accurately represent the anticholinergic burden. Other considerations for possible limitations include compliance, duration, dosage variation, and interruption of use with regards to anticholinergic medications.

Gray et al. (2015) conducted a prospective cohort study to assess if greater anticholinergic exposure is associated with an increased risk of dementia. The methods utilized in this study included 3,434 participants, aged 65 years or older, that were all enrolled in the Adult Changes in Thought (ACT) study conducted by Group Health. Participants had no diagnosis of dementia at the start of the study which was measured using the Cognitive Abilities Screening Instrument (CASI). A baseline assessment was performed at study entry which included a cognitive function test, along with an interview collecting patient demographics, current health status, medical history, and health behaviors. Reassessments were conducted biennially. The initial cognitive evaluation utilized the Cognitive Abilities Screening Instrument (CASI), which has a sensitivity of 96.5% and a specificity of 92.0%. Participants that tested positive for cognitive impairment with the CASI, had to undergo a secondary diagnostic evaluation and examinations by medical experts, at which point a final diagnosis would be assigned. Total anticholinergic exposure in participants was measured for ten years prior to the onset of the study using electronic pharmacy fill records; medications used during the prior twelve months were not included in the study due to possible associated adverse symptoms and concern for bias. Exposure was measured using the Total Standardized Daily Doses (TSDD), which is stated by Gray et al. (2015), “to allow for standardized conversion of doses of different

anticholinergics into a single exposure measure so that we are able to capture overall anticholinergic burden" (paragraph 9). Categories for TSDD were created and are as follows: 1-90 = no use, 91-365 = 1 year, 366-1095=2 years, and >1095 = 3 years, which is considered heavy level exposure. Covariate data, such as age, sex, education, BMI, smoking status, etc. was taken from the GH electronic health records and considered in the association of anticholinergic exposure and dementia (Gray et al., 2015).

The outcomes of the study by Gray et al. (2015) found that 90% of anticholinergics used by participants were from the antihistamine, antidepressant, and bladder antimuscarinic classes. Of the sample size, 78.3% had used an anticholinergic medication in the ten years prior to the beginning of the study. Of the 3,434 participants, 797 (23.2%) were diagnosed with dementia at the average follow up time of 7.3 years. Alzheimer's Disease (AD) was considered likely in 637 of the 797 participants diagnosed with dementia. Compared to participants that had no anticholinergic exposure, those that had TSDD's >1095, had an increased risk for dementia (adjusted Hazard Ratio, 1.54 [95% CI, 1.21-1.96]) or Alzheimer's Disease (adjusted Hazard Ratio, 1.63 [95% CI, 1.24-2.14]), while participants with TSDD's 366-1095, had only a mild risk for developing dementia (adjusted HR, 1.23 [95% CI, 0.94-1.62]) and AD (adjusted HR, 1.30 [95% CI, 0.96-1.76]). All other secondary and multivariate analyses, including age, sex, APO3 e4 genotype, and exposure measures, were found insignificant with all statistics measuring $P>0.5$.

Limitations of this study include the measure of anticholinergic medication exposure, which was performed by collecting pharmacy dispensing data. Medication adherence was not measured, and some medications could have been missed if filled with another healthcare system. Another limitation included the time period for follow up which may have been too short

to allow pathophysiological changes to develop. Lastly, measurement of anticholinergic exposure lacked data on dosage and duration of use which could have impacted the outcome of dementia or AD.

Heath et al. (2018) conducted a prospective cohort study to explore the relationship between the use of antidepressants with anticholinergic activity and the risk of developing dementia. Commonly prescribed antidepressants that are discussed in the study include Selective Serotonin Reuptake Inhibitors (SSRI's), specifically paroxetine, and Tricyclic Antidepressants (TCA's) which have known anticholinergic activity, thus are not recommended in the elderly population.

The methods used in this study included 3, 059 community-dwelling participants, ≥65 years, that were members of the Kaiser Permanente Washington (KPWA) health care system and were enrolled in the Adult Changes in Thought (ACT) study. The inclusion criteria for this analysis included a ten-year membership history with KPWA, continued membership throughout the study, and one required follow-up assessment. Cognitive function was assessed using the Cognitive Abilities Screening Instrument (CASI) and was administered at study entry and every two years over the course of the study. Participants that tested positive for cognitive impairment with the CASI were required to undergo a secondary diagnostic evaluation, along with examinations by clinical experts to receive a diagnosis of dementia or Alzheimer's Disease. Antidepressant medication exposure was measured using electronic pharmacy fill data from the KPWA healthcare system. The three classes of antidepressant medications analyzed in this study were SSRI's, TCA's, and serotonin antagonist and reuptake inhibitors (SARI's), but were grouped into three different categories: 1) Paroxetine (SSRI) 2) other SSRI's, and 3) all other antidepressants. Cumulative exposure to these medications over a ten-year time period was

measured using the Total Standard Daily Dose (TSDD). A TSDD of 1-90=no use, 90-365=1 year, 365-1095=2 years, and >1095 = 3 years of daily use (Heath et al., 2018).

The results of the study by Heath et al. (2018) concluded that in the ten years prior to the start of the study, 34% of the participants had used an antidepressant, whereas 49% had used an antidepressant by the end of the study. Of the 3,059 participants, 775 were diagnosed with dementia at the average follow-up time of the study was 7.7 years (+/-5.1 years), 659 of the 775 likely having a diagnosis of AD. Participants that were exposed to non-paroxetine SSRI's and TCA's had no increased risk for developing dementia compared to nonusers, whereas there was a decrease in dementia risk for participants exposed to low dose SARI's (TSDD 1–90: adjusted HR (aHR)=0.65, 95% CI=0.46–0.92). Both high dose exposure to paroxetine and low dose exposure to paroxetine were associated with an increased risk for dementia development compared with participants with no exposure (aHR=1.69, 95% CI=1.18–2.42).

Discussion

Role of the Cholinergic System in Cognition

The study by Hampel et al. (2018) found that the cholinergic system not only plays a vital role in central nervous functions such as memory, learning, and attention, but also in overall neural connectivity, coordination, and plasticity of the brain. The cholinergic system has been discovered in numerous areas of the brain, so when the loss of cholinergic innervation occurs, memory impairment has been found to occur, including mild cognitive impairment and Alzheimer's disease. One of the hypotheses of Alzheimer's disease follows this cholinergic system theory, which is why cholinesterase inhibitors have been utilized in the therapeutic management of Alzheimer's disease. It's also been suggested cholinesterase inhibitors, such as donepezil or galantamine, can influence the vasodilation and blood flow to various cortical areas

of the brain. Treatment with these types of cholinergic medications has yielded clinically significant results, which helps us to believe scientists are advancing towards a reliable treatment option and preventative measure to cure dementia.

Anticholinergic Burden Scale Classification

A cohort study conducted by Grossi et al. (2019), offered an in-depth analysis on the burden of anticholinergic medications, also benzodiazepines, of varying potency categories and their relationship to the incidence of developing dementia in patient's over the age of 65. The results concluded that individuals over the age of 65 that had ever used an anticholinergic medication score 3 (ACB_3) were more likely to develop dementia than those who had never used them or used an anticholinergic medication score 1 or score 2. Results also showed that individuals who were recurrent anticholinergic score 3 medication users, were more likely to develop dementia then all other participants. It was also discovered that participants who ever used an ACB_3 medication and had an MMSE score of >25 were over two times more likely to develop dementia (Grossi et al., 2019). This information provides consistent results that show a positive correlation between the use of anticholinergic medications with a burden score of three and the risk of developing dementia. Risks and benefits to a patient should be considered before prescribing an ACB_3 medication.

A review published by Lozana-Ortega et al. (2019) compared various anticholinergic scales to identify which scale was best at quantifying the anticholinergic burden of anticholinergic exposure in medications. It is known that anticholinergic medications vary in their level of activity and overall potency and these scales try to sort these medications into categories to help predict the risk of adverse effects in individuals who are using them long-term. The results concluded that the Anticholinergic Cognitive Burden (ACB) and Anticholinergic

Drug Scale (ADS) were the best-suited scale for the purpose of the study because they had been tested on older populations, they were easy to use in the clinical setting, and they included the greatest number of medications. A comprehensive systemic review performed by Salahudeen, Duffull, & Nishtala (2015) also evaluated and compared the various anticholinergic grading scales to determine which is superior in determining the cumulative effects of anticholinergic medications. This study specifically sought to determine negative effects on cognitive function, physical function, and mortality risk based on the anticholinergic burden. Researchers concluded the Anticholinergic Cognitive Burden Scale (ACB) to be validated most by experts for determining adverse effects. In addition to these two studies, the ACB scale is utilized in many of the other journal articles cited in this literature review, which signifies its stamp of approval by many researchers in the field.

Risks of Anticholinergic Medications in Patients Aged ≥65

The retrospective cohort study conducted by Green, Reifler, Bayliss, Weffald, and Boyd (2019) sought to determine the anticholinergic burden and associated risk of falls or fall-related injuries in individuals age ≥65 with dementia or impaired cognition. The side effect profile of anticholinergic medications includes dry mouth, constipation, and delirium; however, the relationship between fall risk and the use of anticholinergics is not well-understood. Results of the study showed that 18% of participants experienced some type of fall related injury throughout the coursed of the study. A greater risk of injury was associated with the use of an ACB score 2 medication over no use, ACB score 1 use, or ACB score 2 use. Furthermore, the results concluded that the combined use of ACB score 2 and ACB score 3 anticholinergic medications caused the greatest individual increase in risk for fall or fall-related injury. This information was somewhat surprising considering ACB score 3 medications are classified to

have the greatest level of activity and strongest potency, which would typically correlate with a greater number or more severe case of adverse effects. Further studies need to be carried out to validate these specific findings.

Anticholinergic Use and the Risk for Increased Cognitive Impairment or Dementia

In 2013, over nine million people in the United States alone were taking at least one prescribed anticholinergic mediation according to a study by Cai, Campbell, Khan, Callahan, and Boustani (2013). This retrospective cohort study was performed to determine the relationship between anticholinergic medication use and cognitive impairment. The results of this study found that participants were more likely to develop dementia or mild cognitive impairment (MCI) if they were older, non-white, male gender, and had a greater number of comorbidities. Stroke was the comorbidity associated with the greatest risk for the diagnosis of cognitive impairment. Comorbidities such as hypertension, coronary heart failure, and coronary artery disease weren't significant for a diagnosis of MCI or dementia. Other results of the study included increased risk of dementia or MCI for individuals with a larger anticholinergic burden, ≥ 3 medications, and increased exposure of >90 days, compared to an exposure of <90 days.

In the prospective observational cohort study conducted by Campbell, Lane, Gao, Boustani, and Unverzagt (2018), researchers found that >70% of participants had been exposed to at least one ACB medication at baseline and 30% had already taken a high potency ACB medication. This study was performed to assess the progression of cognitive impairment over the course of four years. Participants over the age of 65 were more likely to develop MCI with the use of strong anticholinergics. This was also influenced by an increase in the participants' age. The greater the participants' education level, the less likely they were to develop MCI. Lastly, participants that were diagnosed with MCI at baseline were found to have no significant effect

on reversing the diagnosis back to normal cognition. Many of the results concluded in this study follow trends we see and already know regarding cognition. For example, an increase in a person's age is more likely to result in impaired cognitive function. Another example would be increased intelligence is often associated with a decreased diagnosis for cognitive impairment.

The retrospective cohort study performed by Campbell et al. (2016) also analyzed anticholinergic medication use in adults age 65 years and older to determine the relationship between impaired cognitive function and ACB score. The ACB score was also utilized in healthcare to determine patient outcomes. The results of this study found that the risk for cognitive impairment rose by 13% with every 1-point increase in mean total daily ACB score. Inpatient admissions also increased for every 1-point increase. Furthermore, a significant increase in outpatient and emergency department visits was found with an ACB score increase. Overall, the study concluded that an increased mean total daily ACB score was correlated with a greater risk for the development of cognitive impairment and an increase in healthcare utilization. The results of this study by Campbell et al. may be associated with the increase in the risk of fall/fall-related injuries founded by the study of Green, Reifler, Bayliss, Weffald, and Boyd (2019). An increase in ACB score results in a greater risk of injury, which in turn increases the need for healthcare by patients using these medications.

The risk of developing cognitive impairment and the incidence of mortality in people 65 years and older was analyzed in a longitudinal study by Fox et al. (2011). This study also sought to determine a cumulative relationship between anticholinergic use and an increase in risk. The study found that 4% of participants were using an ACB level 2-3 medication which resulted in a 0.33 decrease in their Mini-Mental Status Exam (MMSE). The 47% of participants taking an ACB level 1 mediation had no association with a decline in cognitive function. However, results

did conclude at a two year follow up that mortality rate was increased in individuals taking both ACB level 2-3 drugs and ACB level 1 drugs, compared to those not taking any ACB medications. Although ACB level 1 medications may not be contributing to cognitive impairment, it is alarming that they may be contributing to overall mortality outcomes.

Gray et al. (2015) conducted a prospective cohort study to determine if greater anticholinergic exposure is associated with an increased risk of dementia. Outcomes of the study were roughly 23% of participants were diagnosed with dementia by the average follow-up time of 7.3 years. Those that had a greater Total Standardized Daily Dose (TSDD) exposure were at an increased risk for developing dementia compared to non-users. Lower TSDD levels were associated with only a mild risk of developing dementia. A similar prospective cohort study was performed by Heath et al. specifically exploring the relationship between antidepressants that have anticholinergic activity and the risk of developing dementia. Approximately 25% of participants in the study by Heath et al. were diagnosed with dementia by the average follow-up time of 7.7 years. There was no increased risk for developing dementia in participants exposed to non-paroxetine Selective Serotonin Reuptake Inhibitors (SSRI's) and Tricyclic Antidepressants (TCA's) compared to non-users. Use of Serotonin antagonist and reuptake inhibitors (SARI's) actually showed a decrease in dementia risk. Lastly, both low dose and high dose exposure to paroxetine, an SSRI, were associated with increased risk for dementia development. TCA's are not recommended in the elderly population due to common anticholinergic adverse effects, which should still be taken into consideration even though they have shown no correlation to the development of dementia in this study.

Conclusion

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. There has been a large amount of research carried out regarding the mild and reversible side effects of anticholinergic medications that includes symptoms such as dry mouth, constipation, visual impairments, and delirium; however, there is very limited research regarding the cumulative and long-term effects of prolonged anticholinergic medication exposure. Recent studies on anticholinergic medications have shown that long-term use of these medications may contribute to mild cognitive impairment (MCI) or dementia. There are many medications that have been ranked by medical professionals for their anticholinergic activity and given a rating from 0 (no anticholinergic activity) to 3 (most anticholinergic activity). Individuals taking a medication with a higher anticholinergic activity of 2 or 3 have been found to be at greater risk for developing cognitive impairment compared to those who are not taking them.

Awareness of the cumulative and long-term effects of anticholinergic medications is important moving forward in the medical field as prior research has shown a strong correlation between the development of cognitive impairment and long-term use of anticholinergic medications. Based on the finding of this review, further research needs to be conducted to support the research that has already been conducted; specifically, regarding the rating system of anticholinergic medications by medical professionals, how to accurately measure the cumulative effects of anticholinergic medication use, and the impact of anticholinergic medication use in younger populations.

Applicability to Clinical Practice

As the size of the aging population in the US continues to grow, so will the demand for prescription medications for individuals over the age of 65 to manage their chronic illnesses. 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. As always, the risks and benefits associated with each medication need to be taken into consideration prior to starting treatment, but the risk of developing MCI or dementia should be included in the conversation regarding anticholinergic medications. If patients choose to take an anticholinergic medication long-term or take numerous anticholinergic medications at one time, clinical providers might consider performing a yearly memory examination, such as the mini-mental status exam. A yearly examination would allow providers to more closely monitor their patients for any changes in memory that they may have developed over the past year while taking an anticholinergic medication. If memory decline has been appreciated in patients, providers may be able to stop or slow the progression of cognitive impairment by discontinuing any medications with a higher anticholinergic activity that may be contributing to the disease process.

References

Cai, X., Campbell, N., Khan, B., Callahan, C., & Boustani, M. (2013). Long-term anticholinergic use and the aging brain. *Alzheimer's & dementia: the journal of the Alzheimer's Association*, *9*(4), 377–385. https://doi.org/10.1016/j.jalz.2012.02.005

Campbell, N., Lane, K., Gao, S., Boustani, M., & Unverzagt, F. (2018). Anticholinergics influence transition from normal cognition to mild cognitive impairment in older adults in primary care. *Pharmacotherapy*, *38*(5), 511–519. https://doi.org/10.1002/phar.2106

Campbell, N., Perkins, A., Bradt, P., Perk, S., Wielage, R., Boustani, M., & Ng, D. (2016). Association of anticholinergic burden with cognitive impairment and health care utilization among a diverse ambulatory older adult population. *Pharmacotherapy*, *36*(11), 1123–1131. https://doi.org/10.1002/phar.1843

Fox, C., Richardson, K., Maidment, I. D., Savva, G. M., Matthews, F. E., Smithard, D., Coulton, S., Katona, C., Boustani, M. A., & Brayne, C. (2011). Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *Journal of the American Geriatrics Society*, *59*(8), 1477–1483. https://doi.org/10.1111/j.1532-5415.2011.03491.x

Gray, S. L., Anderson, M. L., Dublin, S., Hanlon, J. T., Hubbard, R., Walker, R., Yu, O., Crane, P. K., & Larson, E. B. (2015). Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA internal medicine*, *175*(3), 401–407. https://doi.org/10.1001/jamainternmed.2014.7663

Green, A., Reifler, L., Bayliss, E., Weffald, L., & Boyd, C. (2019). Drugs contributing to anticholinergic burden and risk of fall or fall-related injury among older adults with mild

cognitive impairment, dementia and multiple chronic conditions: a retrospective cohort study. *Drugs & aging*, *36*(3), 289–297. https://doi.org/10.1007/s40266-018-00630-z

Grossi, C., Richardson, K., Fox, C., Maidment, I., Steel, N., Loke, Y., Arthur, A., Myint, P., Campbell, N., Boustani, M., Robinson, L., Brayne, C., Matthews, F., & Savva, G. (2019). Anticholinergic and benzodiazepine medication use and risk of incident dementia: a UK cohort study. *BMC geriatrics*, *19*(1), 276. https://doi.org/10.1186/s12877-019-1280-2

Hampel, H., Mesulam, M., Cuello, A., Farlow, M., Giacobini, E., Grossberg, G., Khachaturian, A., Vergallo, A., Cavedo, E., Snyder, P., & Khachaturian, Z. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain: a journal of neurology*, *141*(7), 1917–1933. https://doi.org/10.1093/brain/awy132

Heath, L., Gray, S., Boudreau, D., Thummel, K., Edwards, K., Fullerton, S., Crane, P., & Larson, E. (2018). Cumulative antidepressant use and risk of dementia in a prospective cohort study. *Journal of the American Geriatrics Society*, *66*(10), 1948–1955. https://doi.org/10.1111/jgs.15508

Lozano-Ortega, G., Johnston, K., Cheung, A., Wagg, A., Campbell, N., Dmochowski, R., & Ng, D. (2019). A review of published anticholinergic scales and measures and their applicability in database analyses. *Archives of Gerontology and Geriatrics, 87.* [Online Edition]. Retrieved from https://www.sciencedirect.com/journal

Salahudeen, M., Duffull, S., & Nishtala, P. (2015). Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC geriatrics*, *15*, 31. https://doi.org/10.1186/s12877-015-0029-9