The Link Between Anticholinergic Drug Use and Cognitive Impairment in Older Adults

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The goal of this paper is to examine the association between anticholinergic drug use and cognitive functioning in older adults, including the increased risk of dementia. I was persuaded to pursue this topic after experiencing what appeared to be challenges with cognition after taking the over-the-counter (OTC) allergy medication, diphenhydramine, on a consistent basis for close to six months. After conducting some research, I discovered medical literature that revealed an association between the use of anticholinergic agents and cognitive decline, including increased risk of dementia in older adults. Included among these anticholinergic agents are prescription therapies that treat various conditions and OTC products such as first-generation antihistamines, including diphenhydramine, doxylamine, and dimenhydrinate, and OTC proton pump inhibitors (PPIs) for the treatment of acid reflux. Some OTC PPIs that exhibit anticholinergic effects include lansoprazole (Prevacid 24HR), esomeprazole (Nexium 24HR), omeprazole magnesium (Prilosec OTC), and omeprazole and sodium bicarbonate (Zegerid OTC). However, these OTC PPIs are only recommended for 14-day use up to three times a year. Problematically, older adults in the United States may be more likely to use OTC cholinergic antagonists for long periods of time to treat allergies, sleepiness, cold symptoms, motion sickness, and other acute or chronic diseases (Holden et al., 2019). Furthermore, older adults are more likely to be subject to polypharmacy, which increases their risk for exposure to inappropriate and unsafe medication prescribing practices (Rochon et al., 2021). They are also commonly exposed to medications that have anticholinergic properties, which increases the anticholinergic burden (Okudur et al., 2021).

Due to the ease of accessibility to anticholinergic therapies, and because these agents tend to be commonly and even inappropriately prescribed by clinicians, it is important to understand

the possible implications that these agents have on the cognitive functioning and the health of patients (Cooksey et al., 2020; Holden et al., 2019; Rochon et al., 2021).

Anticholinergic Drugs and Their Impact on Cognitive Functioning

Anticholinergic drugs represent a wide range of therapeutic agents whose mechanism of action involves blocking muscarinic receptors from the neurotransmitter acetylcholine. Acetylcholine is a chemical found in the central nervous system (CNS) and the peripheral nervous system (PNS) and is released from cholinergic nerve endings in the airways (Ghezzi et al., 2021). It exhibits a highly protective role in mammals. The chemical is involved in many functions of the brain and other organ systems, including the control of nerve and muscle communication at neuromuscular junctions, and the regulation of critical bodily functions such as heart rate, digestion, muscle tone, and endocrine activity. However, acetylcholine is most notably recognized for its role in cognitive functioning, including attention and the facilitation of learning (Mineur & Picciotto, 2019).

Anticholinergic drugs are routinely prescribed to treat various conditions including, depression, vertigo, asthma, chronic obstructive pulmonary disease (COPD), cardiac arrhythmias, acid reflux, and incontinence. However, increasing amounts of evidence suggest a link between the use of anticholinergic agents and a higher risk of incident cognitive impairment and dementia in older adults (Angevaare et al., 2021; Ghezzi et al., 2021; Grossi et al., 2020; Holden et al., 2019). In fact, 93% of all human studies that have examined anticholinergic activity and adverse cognitive results have revealed an association between the use of anticholinergic drugs and brain atrophy, cognitive reduction, hospitalizations, incidence of delirium or dementia, and death. Yet, while The American Geriatrics Society includes anticholinergic drugs on its 2015 Beers list of medications that may be inappropriate for older

adults, as many as one in every two older Americans takes an anticholinergic medication (Holden et al., 2019).

Cognitive impairment generally encompasses problems with cognitive abilities such as memory, problem solving, learning, perception, and language (Pieper et al., 2020). According to Ghezzi et al., 2021, high potency anticholinergic medications appear to have the most critical influence on cognition in older adults when compared to low potency anticholinergic agents. Moreover, the extent of cognitive decline in late-life has also been shown to be determined by the class of anticholinergic medication a patient is taking. Accordingly, anti-depressants such as amitriptyline, dosulepin, paroxetine, urological drugs (oxybutynin, tolerodine), and antiparkinsonian medications have demonstrated the strongest associations with incident dementia (Ghezzi et al., 2021; Ziad et al., 2018).

A hallmark of neurodegenerative conditions that lead to dementia is the deterioration of cholinergic neurons. Hence, it is probable that the dysregulation of acetylcholine signaling is the primary issue fueling a large part of the cognitive challenges associated with neurodegenerative diseases. In fact, recent imaging studies have suggested that cholinergic status could serve as a significant marker for diagnosis, to trace disease development, and to evaluate the precognitive impact of cholinergic agents (Kumar et al., 2020; Mineur & Picciotto, 2019; Risacher et al., 2016). As such, the majority of pharmaceutical agents used to enhance cognitive health and memory in patients experiencing neurodegeneration are pro-cholinergic compounds that work by increasing the level of acetylcholine concentration or signaling in the brain (Mineur & Picciotto, 2019).

Numerous studies show evidence of an association between the use of anticholinergic drugs and declines in cognitive functioning and an increased risk of dementia (Ghezzi et al.,

2021). Studies that involved scopolamine hydrobromide, a cholinergic antagonist used for the treatment of nausea and vomiting caused by motion sickness, revealed short-term cognitive impairment in young and older adults. Another recent study demonstrated an association between anticholinergic drugs and the modulation of brain volume and cognition (Risacher et al., 2016). Risacher et al., 2016 conducted a cohort study to assess the effects of the use of anticholinergic medications in cognitively normal older adults and evaluate whether an association exist between cognitive performance, brain glucose hypometabolism, structural brain atrophy, and clinical progression to mild cognitive impairment and/or Alzheimer disease (AD). The study results revealed that the use of drugs with medium or high anticholinergic effects were linked to poorer cognition. Specifically, participants exhibited poorer immediate memory recall and executive functioning. Participants who received medium to high anticholinergic medications also demonstrated reductions in their ability to metabolize glucose, whole-brain atrophy as well as atrophy of the temporal lobe, and clinical decline. The study investigators concluded that the effects seemed to be additive, with an increased burden of anticholinergic medications being associated with an increase in brain atrophy and poorer executive functioning. Thus, the authors suggested that based on study findings, medications with anticholinergic effects may have critical influence on brain structure, function, and cognition. The observed findings were supportive of outcomes from previous studies that demonstrate an association between anticholinergic agent use and cognitive deficits, including a consequential effect on executive and immediate memory. A link between the use of anticholinergic medication and the progression from cognitively normal functioning to mild cognitive impairment and/or AD was also evidenced (Risacher et al., 2016). These findings are also further supported by outcomes from multiple pharmacoepidemiological studies that have reported an association between

prolonged and accumulative exposure to medications with anticholinergic effects and the development of clinical symptoms similar to dementia, and an increase in the actual incidence of dementia (Kumar et al., 2020).

Multiple studies have revealed the capacity of PPIs to significantly increase the risk of dementia (Bishara et al., 2022; Ghezzi et al., 2021). However, some findings have been conflicting, and an association between PPI use and dementia development were unable to be determined in all studies. A recent study found a 44% increased risk of developing dementia associated with PPI use. Another study suggested that using PPIs does not increase the risk of dementia or cognitive impairment. To the contrary, the study suggested that PPI use was associated with a nearly 20% reduced risk of dementia. Although a recent study conducted by Cooksey et al., 2020 revealed a relationship between PPI use and dementia, the underlying mechanisms of how this happens are not fully understood. However, study results showed that PPIs inhibit choline-acetyltransferase (ChAT), which is the core-cholinergic enzyme responsible for the biosynthesis of acetylcholine (Cooksey et al., 2020; Kumar et al., 2020).

Conclusions

Due to the concerning nature of numerous study findings, it is recommended that PPIs be prescribed for the least amount of time possible. This is especially important for older patients and individuals suffering from dementia (Kumar et al., 2020). Education for older consumers regarding decision-making in the selection of anticholinergic OTC drugs and the use of anticholinergic prescription medications is also recommended (Dauphinot et al., 2017; Grossi et al., 2020; Holden et al., 2019). Further, I believe that different therapeutic pathways need to be considered in the delivery of therapy for common conditions treated with anticholinergic agents.

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