

Long-term anticholinergic use and the aging brain

Xueya Cai^a, Noll Campbell^{b,c,d,e}, Babar Khan^f, Christopher Callahan^{b,c,f}, Malaz Boustan^{b,c,f,*}

^aDepartment of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA

^bRegenstrief Institute, Inc., Indianapolis, IN, USA

^cIndiana University Center for Aging Research, Indianapolis, IN, USA

^dDepartment of Pharmacy Practice, Purdue University College of Pharmacy, West Lafayette, IN, USA

^eWishard Health Services, Indianapolis, IN, USA

^fDepartment of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Abstract

Background: Older Americans are facing an epidemic of chronic diseases and are thus exposed to anticholinergics (ACs) that might negatively affect their risk of developing mild cognitive impairment (MCI) or dementia.

Objective: To investigate the association between impairment in cognitive function and previous AC exposure.

Design: A retrospective cohort study.

Setting: Primary care clinics in Indianapolis, Indiana.

Participants: A total of 3690 older adults who have undergone cognitive assessment and had a 1-year medication-dispensing record.

Outcome: Cognitive function was measured in two sequential steps: a two-step screening process followed by a formal diagnostic process for participants with positive screening results.

Exposure: Three patterns of AC exposure were defined by the duration of AC exposure, the number of AC medications dispensed at the same time, and the severity of AC effects as determined by the Anticholinergic Cognitive Burden list.

Results: Compared with older adults with no AC exposure and after adjusting for age, race, gender, and underlying comorbidity, the odds ratio for having a diagnosis of MCI was 2.73 (95% confidence interval, 1.27–5.87) among older adults who were exposed to at least three possible ACs for at least 90 days; the odds ratio for having dementia was 0.43 (95% confidence interval, 0.10–1.81).

Conclusion: Exposure to medications with severe AC cognitive burden may be a risk factor for developing MCI.

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Keywords:

Anticholinergics; Cognitive impairment; Dementia; Mild cognitive impairment; Elderly

1. Introduction

More than seven million Americans are suffering from dementia or mild cognitive impairment (MCI), and half of them are coping with at least two additional chronic diseases that require treatment with more than five medications [1–4]. The elderly population is sensitive to experiencing drug-related adverse effects that negatively impact their cognitive function, such as exposure to anticholinergics (ACs) [5–10]. It is estimated that more than nine million older Americans,

including those with cognitive impairment, are prescribed at least one AC with negative cognitive effects [5,7].

The negative cognitive effects of ACs have been known for decades and were assumed to be reversible and transient [5,8–10]. More recently, a new hypothesis has been emerging that connects the effects of AC exposure to the pathogenesis of Alzheimer's disease (AD) [11–14]. The basis for this connection between ACs and AD pathology was primarily investigated in Parkinson disease [11]. Perry et al found that the continuous use of ACs for at least 2 years doubled the prevalence of both amyloid plaque and neurofibrillary tangle densities in Parkinson disease patients [11]. This hypothesis was further supported by recent animal

*Corresponding author. Tel.: 317-423-5633; Fax: 317-423-5695.

E-mail address: mboustan@iupui.edu

studies [12,13]. Caccamo et al studied the effects of ACs on the development of β -amyloid peptides in transgenic mice that express several features similar to the human AD brain and found that a long-term blockade of the M_1 receptor with the use of ACs increased the presence of A β peptides in the cortex, hippocampus, and amygdala [12].

We recently completed a systematic evidence review (SER) of the literature, which confirmed that ACs have an acute negative effect on cognition (delirium) but found only few longitudinal studies that evaluated the long-term exposure to ACs as a risk factor for developing chronic cognitive impairment [7,15]. Our SER found several gaps in the literature. First, few studies evaluated the long-term effects of ACs on cognition in the elderly population, and their results are conflicting [6–11,16]. One recent study reported a potentially reversible association between AC use and cognitive decline [16]. Second, the measurement of drug exposure in the longitudinal studies was not based on actual medication-dispensing records, including the recent study that found a reversible association between AC exposure and cognitive deficit [7,15,16]. Third, the only study that had access to dispensing data did not have access to a comprehensive cognitive assessment [9], thus most likely not recognizing half of the cognitively impaired patients among their control group [4–14,17,18].

As a first step in enhancing prescribing patterns for older adults with chronic diseases and reducing their risk for developing MCI or dementia, we are presenting the findings of a 1-year retrospective cohort study of primary care patients aged ≥ 65 years to better understand the relationship between cognitive function, comorbidity, and AC use. The data of the proposed study were generated by merging the cognitive assessment results of >4000 older patients enrolled in the 2002–2004 Indianapolis Dementia Screening and Diagnosis (IDSD) study [3,18–20], with their 1-year drug-dispensing data captured by the Regenstrief electronic medical record system [17,21,22].

We hypothesized that after adjusting for potential confounders and in comparison with primary care patients who were not exposed to ACs, those who were exposed to at least one severe AC or to three mild ACs for at least 2 months would have a higher risk of cognitive impairment, as defined by positive screening results for dementia, having a diagnosis of MCI, or suffering from dementia.

2. Methods

2.1. Data source and sample

Subjects were selected from the IDSD study, which has been described in detail in previous reports [3,18–20]. Briefly, the IDSD study targeted 4197 participants aged ≥ 65 years who were receiving primary care within the Wishard Health Services (WHS) in Indianapolis from January 2002 until October 2003. A two-stage procedure was used to screen eligible participants for dementia, based on both the six-item

screener [23] and an abbreviated version of the Community Screening Instrument for Dementia (CSI-D) [18,24].

Subjects with cognitive impairment were invited to participate in formal diagnostic assessments, which included a standardized neuropsychological testing, neurological examinations, medical record review, and a structured interview with an informal caregiver such as spouse, child, or other relative. Approximately half of these patients refused participation in the diagnostic assessment. Those who agreed to participate were younger (73.8 vs 75.4, $P = .01$) and had poorer CSI-D performance (18.3 vs 19.2, $P = .07$) compared with those who declined. There were no group differences in race, gender, comorbid conditions, psychotropic use, or chart documentation of dementia or depression [19].

Using the diagnostic assessment results, a team consisting of a psychologist, a neuropsychologist, a geriatrician, and a geriatric psychiatrist made the final diagnosis of dementia or MCI [18–20,25–27]. For this study, we merged the IDSD screening and diagnostic data with the Regenstrief Medical Record System (RMRS), an electronic system that has captured Indianapolis medical data since 1972, including drug-dispensing data at pharmacies affiliated with the Wishard Memorial Hospital and the 39 health care clinics within the WHS [17,21,22]. RMRS captures $>85\%$ of the drug-dispensing data of all participants receiving care within the WHS system [17,21,22]. Patients with no RMRS-based drug-dispensing information have private insurance and are more affluent than those with drug-dispensing data captured by the RMRS [17,21,22]. We had access to 1 year of drug-dispensing data before the patients' screening and final diagnosis. Five hundred seven of the 4197 participants did not have any drug-dispensing record during this study period and were excluded. These excluded patients were slightly more likely to be female and nonwhite and to have no cognitive impairment. Our analyses focused on the remaining 3690 participants.

2.2. Cognitive outcomes

Based on the aforementioned screening and diagnosis process, 562 participants (of the 3690 eligible participants) were considered to have cognitive impairment, that is, with positive results on the six-item screener and the CSI-D. The six-item screening instrument is a brief tool measuring temporal orientation and new learning ability [23]. The CSI-D evaluates multiple cognitive domains (language, memory, attention, and calculation, among others) and includes a standardized interview regarding physical and social function with a caregiver informant or relative if available [24]. Patients who made at least one mistake on the six-item screener and subsequently scored ≤ 24 on the CSI-D were considered to have cognitive impairment requiring further diagnostic evaluation.

The second outcome of interest was the final diagnoses of participants, that is, diagnosis of dementia ($n = 129$) or MCI ($n = 93$). Patients with negative results on the six-item

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