

Featured Article

Bladder antimuscarinics and cognitive decline in elderly patients

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Abstract

Introduction: The evidence on the impact of bladder antimuscarinics initiation on cognitive function in older adults is inconsistent.

Methods: A retrospective analysis of data from the National Alzheimer's Coordinating Center (NACC) on enrollees 65 years and older evaluated the association between antimuscarinic initiation and cognitive decline. We defined decline from baseline (yes/no) for cognitive assessments included in the NACC Uniform Data Set 2.0 battery. New users were matched on year of enrollment and time in the cohort to randomly selected nonusers. Analyses were conducted using inverse probability of treatment weights based on baseline propensity scores.

Results: Our analyses included 698 new users and 7037 nonusers. The odds ratio (OR) and 95% confidence interval for cognitive decline in users as compared to nonusers was 1.4 (1.19–1.65) for Mini-Mental State Examination (MMSE), and 1.21 (1.03–1.42) for Clinical Dementia Rating; in addition, the odds of decline were 20% higher in users compared to nonusers for semantic memory/language and executive function. The effect estimate for MMSE was 1.94 (1.3–2.91) for those with mild cognitive impairment, 1.26 (0.99–1.62) in those with normal cognition, and 1.44 (1.04–1.99) in those with dementia at baseline.

Discussion: Our results show that antimuscarinic initiation is associated with cognitive decline and raise questions about their use, especially in those with impaired cognition.

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Keywords:

Bladder antimuscarinics; Cognitive function; National Alzheimer's Coordinating Center; Cholinergic; Alzheimer

1. Introduction

The cholinergic system in the brain plays an important role in working memory, attention, awareness, psychomotor speed, and selection of relevant stimuli from the environment [1]. By blocking cholinergic receptors in the central nervous system (CNS), drugs with anticholinergic activity could potentially cause undesirable effects on these important cognitive functions, depending on the drug bioavailability and metabolism, as well as its ability to cross the blood–brain barrier [2,3]. Changes in the acetylcholine-

mediated neurotransmission and the increased permeability of the blood–brain barrier caused by aging inflate the risk of CNS adverse effects of anticholinergic drugs. Similar effects are the result of different comorbidities (e.g., diabetes mellitus, Alzheimer's disease [AD], vascular dementia), which are also more prevalent in the elderly population [4–6]. Previous studies showed that drugs with anticholinergic properties could result in cognitive decline and even precipitate dementia in older adults [7,8]. Moreover, a recent prospective cohort study investigating the effect of cumulative anticholinergic exposure demonstrated an increased risk of dementia with higher use of anticholinergics in adults aged 65 years and older [9].

Bladder antimuscarinics (referred to as antimuscarinics hereafter), the main pharmacological option for treating

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urge and mixed urinary incontinence, are among the most commonly used drugs with anticholinergic properties in the elderly [9]. Of the available antimuscarinics, the most frequently used by patients is oxybutynin, a nonselective agent that can bind to receptors throughout the body, including CNS [9]. Previous studies investigating the potential role of antimuscarinics in causing cognitive decline in older adults included a small number of patients, measured cognitive performance with scales less sensitive to longitudinal change, or followed participants for a short period and led to inconclusive results. Some of the studies suggested that in patients with AD, antimuscarinics produce cognitive, behavioral, and physiological changes [10,11], but other studies failed to support these findings [12]. The primary objective of our study was to further evaluate the association of antimuscarinic initiation with cognitive decline in older adults by using the rich data collected as part of the ongoing National Alzheimer's Coordinating Center (NACC) cohort and to address some of the limitations of previous studies.

2. Methods

2.1. Setting

We conducted a retrospective evaluation using data collected as part of the prospective NACC cohort. Data available from the Uniform Data Set (UDS) between September 1, 2005 and December 31, 2013 were used to identify new antimuscarinic users [13] and nonusers as controls and conduct all of the analyses described in the following.

2.2. Participants

A description of the NACC cohort, its eligibility criteria, and data collection are available elsewhere [14–17]. In summary, NACC was established in 1999 with the purpose of facilitating research related to AD. This cohort includes not only patients with AD and related disorders but also cognitively normal subjects and those with mild cognitive impairment (MCI). Beginning in 2005, UDS data were collected through standardized evaluations of enrollees from National Institute on Aging-funded Alzheimer's Disease Centers (ADC). Each ADC has its own recruitment protocol, and participants are recruited through clinician or self-referral (patients or family members), or through active community recruitment strategies. Of the 32,532 participants enrolled in NACC between 2005 and beginning of 2016, about 89% were 60 years or older, 80% were white, 70% had 12 or more years of education, 37% had normal cognition at enrollment, about 21% had MCI, and about 37% had dementia. In addition to the ADC-specific inclusion/exclusion criteria, the eligibility criteria for our investigation included (1) participants enrolled on or after September 1, 2005 with a minimum of one follow-up visit; (2) age 65 years and older at the visit when antimuscarinic use was first reported (or the equivalent visit for nonusers—see the following for

additional information regarding nonusers selection); (3) with medication data available at all visits, and (4) with no antimuscarinics reported at enrollment. We excluded participants with non-MCI or non-AD-related cognitive impairment, specifically (1) cognitive status categorized as “impaired not mild cognitive impairment”; (2) frontotemporal dementia; (3) primary progressive aphasia; (4) progressive supranuclear palsy; (5) corticobasal degeneration; (6) Huntington's disease; (7) prion disease; (8) Down's syndrome; (9) CNS neoplasm; (10) traumatic brain injury; (11) hydrocephalus; (12) alcohol-related dementia; (13) dementia of undetermined etiology. A flow diagram to describe the participants' selection process and the groups included in the analyses is depicted in Fig. 1.

Exposure to antimuscarinics was identified from the self-reported data collected at enrollment and yearly thereafter using the “brown bag” medication review approach (i.e., the participant or a family member were asked to bring all current medications to the research assessment) on prescription and over-the-counter medications for the two-week window preceding the index date [15]. Antimuscarinic exposure was measured as antimuscarinics yes/no by identifying at least one mention of the following medications: oxybutynin, tolterodine, flavoxate, hyoscyamine, darifenacin, trospium, solifenacin, fesoterodine, propantheline. Antimuscarinic exposure was further categorized based on muscarinic receptor selectivity: nonselective antimuscarinics (oxybutynin, tolterodine, flavoxate, hyoscyamine, trospium, fesoterodine, propantheline) and M₃ selective antimuscarinics (darifenacin or solifenacin). When exposure to more than one antimuscarinic was reported, exposure category was assigned as nonselective in the presence of at least one nonselective drug. Antimuscarinic users were considered prevalent users if antimuscarinic exposure was reported at enrollment and incident (new) users if exposure was first

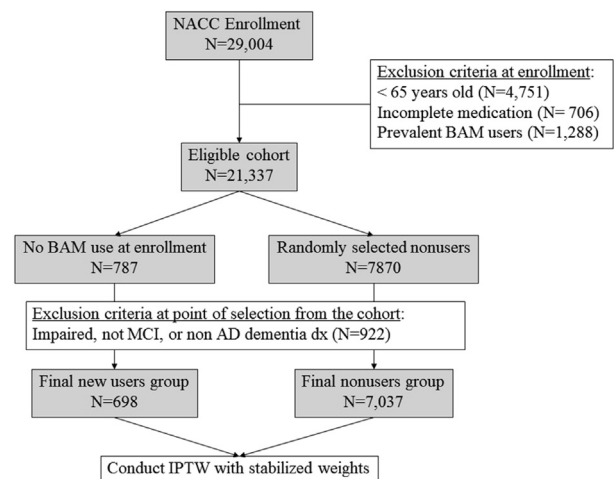


Fig. 1. Inclusion/exclusion cascade and study groups. Abbreviations: BAM, bladder antimuscarinics; IPTW, inverse probability of treatment weights; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Center.

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