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Association of the Prescribing of Anticholinergic Medications with Incident Delirium: A Cohort Study

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Abstract

Objectives—Describe the association of anticholinergic medications with incident delirium among hospitalized older adults with cognitive impairment (CI). We tested the hypothesis that anticholinergics would increase the risk of incident delirium.

Design—Observational cohort study.

Setting—The study was performed at an urban public hospital in Indianapolis, IN.

Participants—The study included 147 participants aged 65 years or older with CI who screened negative for delirium at the time of admission to a general medical ward.

Measurements—Cognitive function at the time of admission was assessed using the Short Portable Mental Status Questionnaire (SPMSQ). We evaluated anticholinergic medication orders between the time of admission and the final delirium assessment. Anticholinergic medication orders were identified using the Anticholinergic Cognitive Burden (ACB) scale. Delirium was assessed using the Confusion Assessment Method (CAM).

Results—Fifty-seven percent of our cohort received at least one order for possible anticholinergics and 28% received at least one order for definite anticholinergics. The incident rate for delirium was 22% among the entire cohort. After adjusting for age, gender, race, baseline SPMSQ score, and Charlson comorbidity index, the odds ratio (OR) for developing delirium among those having orders for possible anticholinergics was 0.33 (95% confidence interval (CI) 0.10–1.03). The OR for developing delirium among those with orders for definite anticholinergics was 0.43 (95% CI 0.11–1.63).

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Conflict of Interest:
All authors report no conflict of interest

Author Contributions:
All authors were responsible for the study concept, design, acquisition of data, analysis and interpretation of data and preparation of the manuscript.

Conclusion—Our results did not support the hypothesis that prescription of anticholinergic medications increases the risk of incident delirium among hospitalized older adults with cognitive impairment. This relationship needs to be established using prospective study designs with medication dispensing data to improve the performance of predictive models of delirium.

Keywords

anticholinergic; delirium; hospitalized elderly

INTRODUCTION

Older adults with cognitive impairment (CI) are known to be at high risk of poorer outcomes during hospital admissions, including episodes of delirium and use of Foley catheters and tethers.[1–9] Those older adults experiencing delirium during their hospital stay endure longer lengths of stays, are more likely to be discharged to an institution, and have a higher 30-day mortality rate.[10,11] Anticholinergic medication use in this vulnerable population might contribute to both acute and long-term cognitive dysfunction.[12,13] Despite the well-recognized potential for cognitive decline with anticholinergic agents, their use continues even within the cognitively vulnerable populations.[14,15] We recently reported the generation of a list of anticholinergic medications, derived through both a systematic review of the medical evidence and expert opinion, focused specifically on the impact on cognitive function.[16] This list has been previously used to evaluate medication use and cognitive function amongst older adult populations in both the United Kingdom and the United States.[13,17]

Despite a multitude of case reports describing the relationship of anticholinergic medications with delirium,[18–21] no prospective studies have systematically evaluated the impact of medications on the incidence of delirium utilizing validated cognitive assessments along with a comprehensive review of medication use. Similarly, few if any studies have evaluated the cognitive impact of anticholinergic medications in a hospitalized older adult population with a significant number of African-Americans. The goal of this study was to explore the relationship between anticholinergic medications and the development of delirium in the acute care environment. Based on the existing literature, we employed the hypothesis that anticholinergic medications will increase the risk of developing delirium in a vulnerable hospitalized population.

METHODS

Study Design, Setting, and Population

This study was an observational cohort study taking place in an urban, public, safety-net hospital in Indianapolis, IN. Patients eligible for the study were (1) aged 65 or older, (2) screened positive for cognitive impairment, (3) admitted to a general medical ward of the hospital, (4) able to speak English, and (5) delirium-free at the time of admission. Patients were not approached if they had been previously enrolled in the study, were aphasic or unresponsive at the time of admission, or were enrolled in other studies at the time of admission. The study was approved by the Indiana University Purdue University of Indianapolis Institutional Review Board and complies with the ethical rules for human experimentation as stated in the Declaration of Helsinki.

Cognitive Assessment

Baseline cognitive function was assessed using the Short Portable Mental Status Questionnaire (SPMSQ)[22,23] chosen for its accuracy and utility as a verbally administered

tool. The SPMSQ is a brief 10-item screening test with a sensitivity of 86% and specificity of 99% for dementia among medical inpatients. Patients having two or more errors, indicating a score of 8 or less on the SPMSQ after adjusting for race and education, were considered to have cognitive impairment.

At the time of admission and throughout the inpatient stay, delirium was detected using the Confusion Assessment Method (CAM). The CAM assessment was performed by a trained research assistant who collected information from the medical record, nurse interview, and participant's cognitive interview. The CAM is a standardized delirium assessment tool recommended by national guidelines[24,25] with acceptable psychometric properties. The CAM score is determined by examining the patient for (a) acute and fluctuating changes in mental status, (b) inattention, (c) disorganized or incoherent thinking, and (d) altered level of consciousness. A CAM score is considered to be positive if the patient displays both a and b, and either c or d. The CAM diagnosis of delirium has been previously validated against the DSM-III-R delirium criteria determined by a psychiatrist and found to have a sensitivity of 97% and a specificity of 92%.[24]

Data Source

Regenstrief Medical Record System—The computerized Regenstrief Medical Record System (RMRS) is the primary instrument for processing data and monitoring patient and physician activity for WMH.[28] This system collects all order entry activity for each inpatient and outpatient visit for each interaction within the WMH medical system. The RMRS is a modular system, composed of Registration and Scheduling, Laboratory, Pharmacy, and Database modules; and maintains a number of other databases including vital signs, results of laboratory and diagnostic tests, discharge summaries, and inpatient and outpatient charges. The Pharmacy module contains information on medication orders captured by computerized physician order entry (CPOE). The Database module stores the above data by date in a fully-coded form.

Anticholinergic Cognitive Burden List

We identified anticholinergic medications by using the Anticholinergic Cognitive Burden (ACB) list.[12,16] The ACB has been previously used to identify an increased risk of cognitive impairment amongst an ambulatory population of African-Americans using definite anticholinergics.[13] The ACB identifies medications with varying degrees of anticholinergic activity. Based on our previous experience using the ACB[13] we stratified anticholinergic medications into two groups, those with possible and definite anticholinergic effects. Medications with "possible" anticholinergic effects are defined as those with serum anticholinergic activity or in vitro activity to muscarinic receptors, but with no published reports of cognitive dysfunction. Medications considered "definite" anticholinergics were defined as those with published and clinically relevant effects on cognitive function. Using the ACB list, a pharmacist (NLC) reviewed medication orders for appropriate categorization into possible, definite, or no anticholinergic activity.

This study defined the exposure variable as any order for anticholinergic medications between the time of admission and either the day before delirium (for those in the incident delirium group) or the day before the final delirium assessment (for those not experiencing delirium). We chose this time limitation to improve our accuracy in evaluating only anticholinergic medications ordered during the exposure period and not medications that may have been ordered in response to delirium. The endpoint of interest was the first day a participant screened positive on the CAM indicating delirium.

Statistical Analysis

We used Fisher's exact test and analysis of variance (ANOVA) to compare demographic data, cognition, and chronic comorbidity across levels of anticholinergic exposure. Fisher's exact test and t-tests were used to compare demographic data, cognition, anticholinergic exposure, and chronic comorbidity with incidence of delirium. Logistic regression analysis was used to model the association of delirium with anticholinergic exposure to control for demographic, cognition, and comorbidity. Analyses were performed using SAS software, version 6.0 (SAS Institute, Inc., Cary, NC).

RESULTS

Demographics of the study population are stratified by exposure to ACB medication orders as shown in Table 1. The overall population had a mean age of 77 years, included a population of 63% females and nearly 60% African-Americans. The mean SPMSQ at study entry was not significantly different between those receiving orders for ACB medications and those not receiving orders for ACB medications. No differences existed in gender, race, and comorbidity scores between exposure groups.

Medications with possible anticholinergic activity were ordered for 57% of the study population, whereas medications with definite anticholinergic properties were ordered for 28% of the study population. The most common possible anticholinergics ordered were: metoprolol, furosemide, and morphine. The most frequently ordered definite anticholinergic medications included: promethazine, diphenhydramine, and amitriptyline.

The incident rate for delirium among the entire cohort was 22%. In those developing delirium during the inpatient stay, differences in gender, race, and baseline cognitive function achieved statistically significant differences as shown in Table 2. Those developing delirium during the hospital stay were less likely to be female (no delirium, 69.7% female vs. delirium, 42.4% female; $p = 0.005$), and were more likely to be African-American (54.4% vs. 75.8%; $p = 0.032$). Additionally, those developing delirium had lower cognitive function scores at baseline (mean SPMSQ 6.1 vs. 4.7; $p = 0.007$).

As shown in table 2 and in the bivariate analyses, the rate of incident delirium was the highest among those who did not receive an order for any anticholinergics (36.4%). In comparison, those receiving an order for possible anticholinergics experienced delirium at a rate of 20.2%, and among those receiving an order for definite anticholinergics, 19.5% experienced delirium ($p=0.014$). Attributing scores of 1 for mild or possible anticholinergics, 2 for probable or moderate anticholinergics, and 3 for definite for strong anticholinergics as in the original ACB list[12] did not result in a cumulative or additive effect on the outcome of delirium (odds ratio (OR) 0.95, 95% confidence interval (CI) 0.80 – 1.13, $p = 0.591$).

Multivariate logistic regression results are shown in Table 3 and investigate the association between the incidence of delirium and the exposure to anticholinergic orders after adjusting for potential confounders. The odds ratio for incident delirium in those receiving orders for possible ACB medications compared to those not receiving orders for ACB medications was 0.33 (95% CI 0.10 – 1.03). The odds ratio for incident delirium between those receiving orders and those not receiving orders for definite anticholinergic medications was 0.43 (95% CI 0.11 – 1.63). Incidentally, we found that increasing scores on the SPMSQ and being female were associated with a decreased incidence of delirium. Similarly, race was found to be associated with delirium, with African-Americans having an odds ratio of 2.63 (95% CI 0.99 – 6.97) for incident delirium.

DISCUSSION

Our results present an unexpected finding in an analysis of the prescribing of medications with anticholinergic effects and the incidence of delirium in hospitalized older adults with cognitive impairment. Without knowing whether patients actually received the anticholinergic medications (as some could have been ordered/prescribed on an as needed basis and patients may never have received the medication), one can only conclude that incident delirium is not associated with the prescribing of anticholinergic medications. This result contradicts previous studies suggesting anticholinergic-induced delirium that exists in the medical literature.[12,29] The difference between our findings and previous literature results may be due to our focus on delirium incidence, the characteristics of our population (60% African-American in an urban setting), and the use of physician orders of anticholinergics instead of drug dispensing data.

Previous studies measured the prevalence of delirium during hospitalization instead of incidence.[12] Agostini and colleagues describe an increased risk of delirium in users of definite anticholinergics, though studied a population mix of 85% Caucasians, whereas we report a population that included 60% African-Americans.[29] At least one case-control study involving inpatients with new-onset stroke has been published and suggests anticholinergic medications used prior to and during the hospitalization increase the risk of incident delirium.[30] This study evaluated 74 participants that used the Delirium Rating Scale to identify delirium severity. Significant differences in study design, population, medications evaluated, and diagnostic strategies likely explain the differences with our results.

Other than age, no statistically significant differences in demographics were identified amongst those receiving orders for anticholinergic medications, suggesting little prescribing bias in our cohort. Possible anticholinergic medications included in the ACB list are commonly used to treat cardiovascular disorders, such as CHF exacerbations, hypertension, and acute or chronic coronary artery disease. Our results may reflect the importance of the therapeutic impact of anticholinergic medications in controlling or treating an acute diagnosis rather than the potential adverse cognitive effects.

Interpretation of our results is restricted by several limitations that should be identified when considering our results. First, the data set did not contain complete routine cognitive assessments following the admission data collection period. This may have resulted in an under-reporting of delirium episodes and underestimated the association of anticholinergic medications with incident delirium. Second, as noted above, we evaluated the parameter of medication exposure using medication orders from RMRS and not medication dispensing to measure the types and number of medications participants received. Third, we did not include a measure of acute severity of illness as a covariate in the final regression model. Utilizing the Charlson comorbidity index restricted to inpatient diagnoses did not reveal a significant difference in the study outcome. Fourth, although we adjusted our results for known risk factors for delirium, we could not account for unknown or unmeasured risk factors. Confounding by indication may have been introduced in this observational study and had an impact on our findings. Lastly, we were not able to systematically evaluate medications used prior to admission, therefore are unable to identify whether anticholinergic medications used by participants were new orders or persistent medications. These limitations should be addressed in future work evaluating the impact of medications on delirium incidence.

Interestingly, incident delirium was less likely to develop in two groups that were not expected: females and non-African-Americans. An explanation for the difference of gender in the development of delirium is unclear. There was no difference in gender in the

prescribing practice of ACB medications, although males were more likely to develop delirium. A difference in rates of dementia has been previously described between sexes; however, to our knowledge, this is the first report of an uneven distribution of incident delirium between genders.

In conclusion, our results do not support the hypothesis that prescription of anticholinergic medications increases the risk of incident delirium in hospitalized older adults. Since we did not detect such a relationship using medication orders rather than dispensing data for this analysis, the relationship must be studied with a design and data sources that overcome the limitations recognized in this work. We must also continue to understand the relationship that race and gender may have as risk factors for the incidence of delirium.

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Sponsor's Role:

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Table 1

Characteristics of participants with and without orders for anticholinergic medications during the observation period

	No ACB use (n=22)	**Possible ACB use only (n=84)**	**Any Definite ACB use (n=41)**	***p* value**
Mean Age	78.9 (8.8)	77.1 (8.3)	73.9 (6.2)	0.013
% Female	72.7	58.3	68.3	0.375
% African-American	68.2	57.1	58.5	0.641
Mean SPMSQ at Screen	5.5 (2.4)	5.6 (2.7)	6.3 (2.2)	0.284
Mean Charlson Comorbidity	2.5 (2.8)	2.9 (2.3)	3.2 (1.9)	0.567

ACB = Anticholinergic cognitive burden; SPMSQ = Short portable mental status questionnaire

Table 2

Characteristics of participants who did and did not develop delirium during the study period.

	Delirium − (N=114)	**Delirium + (N=33)**	***p* value**
Mean Age	76.6 (8.0)	76.7 (8.2)	0.956
% Female	69.3	42.4	0.005
% African-American	54.4	75.8	0.028
Mean SPMSQ at Screen	6.1 (2.3)	4.7 (2.7)	0.007
Mean Charlson Comorbidity	3.1 (2.3)	2.4 (1.9)	0.133
ACB orders			0.236
% No ACB order	63.6	36.4	
% Possible ACB order	79.8	20.2	
% Definite ACB order	80.5	19.5	

ACB = Anticholinergic cognitive burden; SPMSQ = Short portable mental status questionnaire

Table 3

The association between ACB use and incident delirium.

	OR Delirium	95% CI	*p* value*
ACB use			0.161
None (Reference)	1.00		
Any possible ACB use	0.33	(0.10, 1.03)	
Any definite ACB use	0.43	(0.11, 1.63)	
Age	0.97	(0.92, 1.03)	0.383
Female vs. male	0.24	(0.10, 0.62)	0.003
African-American vs. others	2.63	(0.99, 6.97)	0.052
SPMSQ at Screen	0.78	(0.66, 0.93)	0.004
Charlson Comorbidity	0.86	(0.68, 1.08)	0.191

* *p*-value adjusted using logistic regression model that included age, gender, race, SPMSQ, and Charlson comorbidity score as covariates. ACB = Anticholinergic cognitive burden; SPMSQ = short portable mental status questionnaire.