Brief Report

Delirium Following Anticholinergic Use in Hospitalized Patients With Dementia

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Abstract

We sought to explore rates of delirium amongst hospitalized patients with dementia following orders for anticholinergic medications. We hypothesized that patients receiving anticholinergic medications would have higher rates of delirium than similar, unexposed patients. We performed a retrospective chart review of 23 031 hospitalized individuals with Alzheimer's disease, vascular dementia, or unspecified dementia from 2011-2018. Rates of delirium diagnosis and haloperidol orders following anticholinergic administration were compared to patients with dementia without anticholinergic orders. Significant differences in rates of delirium and orders for haloperidol were observed between exposed and unexposed groups, with delirium having a relative risk of 2.3 and orders for haloperidol having a relative risk of 10.4. The number needed to harm for anticholinergic exposure was 5.45 for delirium and 7.09 for haloperidol. The identified difference suggests that inpatient use of anticholinergic medications may increase the risk of delirium in hospitalized patients with dementia. Despite this risk, our review suggests that anticholinergic administration is common during hospital stays among patients with dementia. Anticholinergic use may be a modifiable risk factor for delirium prevention, which could improve inpatient management of patients with dementia.

Keywords

dementia, anticholinergics, delirium

Introduction

Dementia constitutes a group of brain disorders characterized by progressive cognitive decline and worsening functional impairment. Nearly 50 million people in the United States are living with dementia,[1] often experiencing acute changes in health status, due to falls, infections, and acute declines in mental status.[2] Approximately 75% of hospitalized persons with dementia (PwD) experience behavioral and psychological symptoms, including acute confusional states, often called delirium.[3] Delirium, defined as acute change in consciousness from baseline leading to inattention, disorganized thinking and acute behavioral disturbances, is associated with higher rates of antipsychotic use, physical restraints, and increased mortality.[4]

Anticholinergic medications are frequently prescribed in the inpatient setting for many reasons, including allergic reactions, nausea, or anxiety. Known side effects include cognitive changes such as confusion, memory loss, and delirium, especially within older individuals.[5,6] Research suggests an association between anticholinergics and risk of cognitive impairment in older adults,[5] with important implications for inpatient management.

We sought to explore rates of delirium amongst hospitalized PwD following orders for anticholinergic medications. We hypothesized that patients receiving anticholinergic medications would have higher rates of delirium than similar, unexposed patients.

Methods

We performed a retrospective chart review of PwD hospitalized within the University of Colorado Health system between January 1st, 2011 and December 31st, 2018. We identified 23 031 hospitalized individuals with Alzheimer's disease, vascular dementia, or unspecified dementia through diagnosis codes (ICD-10: G30.1, F02.81, F01.50, & F03.90). We queried inpatient orders for medications from an anticholinergic medication list (Supplement 1).[7] We examined outcomes of delirium using diagnosis codes (F05, *F*293.0, &

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Table 1. Patient Outcomes With and Without Anticholinergic Exposure.

Outcomes	Anticholinergic Orders (N = 2333)	No Anticholinergic Orders (N = 20 698)	Relative Risk (95% CI)	Number Needed to Harm (NNH)	*P*-value
Delirium diagnosis	772 (33.1%)	3033 (14.7%)	2.3 (2.1-2.4)	5.45	<.0001
Haloperidol Order	364 (15.6%)	312 (1.5%)	10.4 (9.0-12.0)	7.09	<.0001

R41.0) and orders for haloperidol. Rates of delirium diagnosis and haloperidol orders following anticholinergic administration were compared to PwD without anticholinergic orders through two-tailed Fisher's exact tests. The measures of delirium above were used to calculate relative risk. Number Needed to Harm (NNH) was calculated from absolute risk difference. Significance for this study was set at $P < .05$.

We utilized the University of Colorado (CU) Health Data Compass (Compass) platform as our data source. Compass is a multi-institutional data warehouse administratively housed in the Colorado Center for Personalized Medicine. It provides limited, de-identified data sets for research purposes, including inpatient and outpatient electronic medical record (EMR) data extracted from state-level all-payers claims data, 2 EMRs, and the state of Colorado death registry. Compass is certified as Health Insurance Portability and Accountability Act (HIPAA) compliant. This study was exempt from Institutional Review Board (IRB) approval given the de-identified nature of the dataset.

Results

We identified 23 031 hospitalized PwD from 2011-2018, of which 2333 patients (10.1%) had at least 1 order for an anticholinergic medication. Of these patients, 33.1% had a subsequent diagnosis of delirium and 15.6% had orders for haloperidol, compared to 14.7% and 1.5% of PwD without anticholinergic orders, respectively (Table 1). The NNH for anticholinergic exposure was 5.45. Significant differences in rates of delirium and orders for haloperidol were observed between exposed and unexposed groups, with delirium having a relative risk of 2.3 (95% CI: 2.1-2.4, $P < .0001$) and orders for haloperidol having a relative risk of 10.4 (95% CI: 9-12.0, $P < .0001$). The 3 most common anticholinergics prior to delirium were diphenhydramine (15.7%), cyclobenzaprine (5.9%), and meclizine (5.0%).

Discussion

Our retrospective chart review confirmed our hypothesis that PwD receiving anticholinergic medications would have higher rates of delirium and haloperidol use. The difference suggests that inpatient use of anticholinergic medications may increase the risk of delirium in hospitalized PwD. Specifically, when anticholinergics are used, more than 1 in 6 PwD will experience an episode of delirium, and 1 in 7 will be managed with haloperidol. Despite this risk, our review suggests that anticholinergic administration is common during hospital stays among PwD. As delirium often necessitates an increased length of stay, with higher healthcare utilization,[4] providers should consider prudently using anticholinergics in PwD, especially when conducting medication reconciliation of prescriptions used prior to admission.

While anticholinergic medications are known to contribute to delirium, our findings suggest there is a need to further reduce their use. Despite the existence of tools like the Beers List which identify anticholinergics as "potentially inappropriate medications" for use in older adults, over 10% of PwD at this large medical center were administered anticholinergic use.[8] It is possible that the deliriogenic effect of anticholinergic medications is not widely known or is too abstract to prevent use in common medical practice. Given the wide variety of uses for anticholinergic medications, our findings of NNH <6 and RR >2 offer a concrete facet for the provider considering anticholinergic use.

Our study has limitations due to its retrospective nature. Furthermore, restricting our study to 1 geographic region limits generalizability. While we utilized inpatient orders, the dataset does not easily allow for verification of administration, or to control for medications that may have been routinely used prior to admission and continued inpatient. Due to the deidentified use of PwD as the unit of analysis, we could not examine restraint orders, medical orders for a personal sitter, nor incidence of delirium across multiple hospitalizations. Another limitation for our study is the use of ICD codes to identify patients with dementia, which may not be accurate in all cases, although ICD codes have been shown to be generally accurate in patients with dementia.[9] Finally, the chart review nature of our study may underestimate the effect of anticholinergic medications, as delirium is recognized as being underdiagnosed and under-reported in ICD codes.[10] Therefore, our NNH and RR may offer a conservative limit, while the real effect may be much stronger.

Our findings of 10% of PwD receiving anticholinergic medication indicates a need for further education and awareness of anticholinergic use in this patient population. Minimizing delirium in patients with cognitive impairment is an important goal for inpatient providers, and this study may aid the clinician by providing actionable data for use in

medication considerations. Through careful consideration of the potential for harm, we may reduce the frequency of use of these medications and improve inpatient management of patients with dementia.

Author's Note

EWH and ZAM served as co–first authors, each with equal contribution to the manuscript, including drafting and revision. PSP served as senior author, including contributions to study conception and critical revision.

Declaration of Conflicting Interests

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