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ORIGINAL RESEARCH

Incidence of Cholinesterase Inhibitor Therapy Initiation Among Hospitalized Patients

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BACKGROUND: Initiation of cholinesterase inhibitor (ChEI) therapy for delirium during hospitalization is ineffective and may be associated with increased morbidity and mortality.

OBJECTIVE: To describe the incidence of initiating ChEI therapy during hospitalization.

DESIGN: A retrospective cross-sectional study.

SETTING: A tertiary-care academic medical center.

PATIENTS: Inpatient admissions from September 2010 through March 2011 with ChEI administration.

INTERVENTION: None.

MEASUREMENTS: Incidence of ChEI exposure, initiation of ChEI therapy, initiation of antipsychotics and benzodiazepines, infection, in-hospital mortality, and hospital length of stay.

RESULTS: The incidence of adult admissions with ChEI exposure and ChEI initiation was 23.2 (95% confidence interval: 21.2–25.4) and 2 (95% confidence interval 1.5-2.8) per 1000 admissions, respectively. Of 476 admissions receiving ChEI, 9% (n = 42) initiated therapy during the hospital stay and 91% (n = 434) continued on previously started therapy. Patients initiated on ChEI therapy frequently had infection (20 of 42) and were commonly initiated on antipsychotics (14 of 42) and benzodiazepines (13 of 42). Patients were hospitalized for a median of 2 days (interquartile range, 1–4) before initiation of ChEI and were exposed to therapy for a median of 3 days (interquartile range, 2–6). Of the 41 patients discharged from the hospital, 90% (n = 37) had orders to continue the ChEI postdischarge.

CONCLUSIONS: Despite a lack of evidence to support the practice, 9% of patients who received ChEI therapy were initiated during the inpatient setting. These patients were not routinely screened for delirium and frequently received treatments associated with delirium. *Journal of Hospital Medicine* 2013;8:304–308. © 2013 Society of Hospital Medicine.

Altered mental status is a frequent finding among hospitalized geriatric patients and may be a sign of dementia, delirium, or delirium superimposed upon dementia.[1,2] Delirium occurs in 20% of acute care patients and is 15 times more likely to occur in patients with prior dementia.[3] A hospitalized patient's baseline cognitive status can be difficult to ascertain in clinical practice, which makes it difficult to discriminate dementia from delirium or recognize dementia with superimposed delirium.

The cholinergic pathway has been implicated in the etiology of both dementia and delirium.[4,5] Medications that decrease cholinergic activity are associated with cognitive decline in the elderly population,[6] are proposed risk factors for developing delirium,[7] and are listed as harmful drugs for the elderly by the American Geriatrics Society's 2012 Beers Criteria.[8] Cholinesterase inhibitors (ChEIs) increase the availability of acetylcholine in the neuronal synapse and are indicated in treatment of mild to moderate dementia.[9] However, ChEI therapy is not currently recommended for the treatment of delirium.

Three randomized, double-blind, placebo-controlled studies of ChEI therapy given before and after elective inpatient surgery found that neither rivastigmine[10] nor donepezil[11,12] were able to reduce the incidence of delirium in hospitalized patients. Most strikingly, a multicenter, randomized, double-blind, placebo-controlled trial of rivastigmine for the treatment of delirium in critically ill patients was prematurely terminated because rivastigmine was associated with a sharp trend toward increased mortality (22% vs 8%, $P = 0.07$), longer duration of delirium (median days, 5 vs 3, $P = 0.06$), and increased hospital length of stay (LOS) (median days, 29 vs 25, $P = 0.06$) compared with placebo.[13] These studies suggest that the clinician should use ChEI therapy with caution in patients who have delirium, as these medications are unlikely to

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improve the delirium and may have unfavorable safety outcomes.

The safety and efficacy of ChEI initiation for dementia in hospitalized patients, when delirium may coexist, is unknown. This study evaluated the incidence of ChEI initiation for inpatients when the presence or absence of delirium was unknown. This study will provide descriptive data on patients who initiated ChEI therapy during the inpatient setting.

PATIENTS AND METHODS

Design

This was a retrospective cross-sectional study at a single tertiary-care academic medical center describing the incidence of ChEI initiation. Patient data were obtained from electronic medical records at The Methodist Hospital (TMH) and from the University HealthSystem Consortium Clinical Data Base/Resource Manager (UHC CDB/RM; http://www.uhc.edu). The institutional review board at TMH Research Institute (Houston, TX) approved this study with a waiver of informed consent.

Inclusion Criteria

All patients admitted to TMH from September 6, 2010, through March 31, 2011, and who were dispensed a ChEI (defined as donepezil, galantamine, and rivastigmine) were included. The study start date (September 6, 2010) coincided with adoption of a new feature in the electronic medical record that allowed for improved tracking of patient home medications before admission.

Exclusion Criteria

Patients were excluded if they were age <18 years or if information for the index admission was not available in the UHC CDB/RM.

Data Variables

The first hospitalization during the study period where a ChEI was dispensed was considered the index admission, and all data are based on this index admission. Investigators used a database of home medications, history and physical notes, and daily progress notes contained in the electronic medication record to categorize patients into 1 of 2 groups: (1) initiation of ChEI therapy and (2) continuation of ChEI therapy. Investigators reviewed all daily progress notes and consult notes that were documented for the index admission and all admissions in the 60 days prior to the index admission to elicit information regarding previous ChEI exposure. A clinical pharmacist performed a medication-history interview of all patients admitted through the emergency department. This reconciliation process was supported with 4 months of prescription-medication claim history from insurance companies and pharmacies that participate in the Health Care Systems Medication Reconciliation report (Health Care Systems, Inc., Montgomery, AL). Patients directly admitted to the hospital received medication reconciliation from a clinical pharmacist, physician, or nurse.

If documentation was found indicating ChEI exposure within 60 days prior to the index admission, the patient was categorized as continuation of ChEI therapy. If there was no prior documentation of ChEI therapy, or if there was clear documentation of ChEI initiation for a new diagnosis, the patient was categorized as initiation of ChEI therapy. To improve accuracy, 2 investigators (K.C.W. and N.T.-M.) categorized patients independently, and a third investigator (J.T.S.) settled all discrepancies.

The UHC CDB/RM provided patient admission severity of illness (mild, moderate, major, and extreme) generated from 3M All Patient Refined Diagnosis Related Groups software (APR-DRG; 3M Health Information Systems, Salt Lake City, UT), which accounts for 29 comorbidities that are correlated with resource utilization and severity of illness.[14]

Data Analysis

Mean with standard deviation was used for continuous data with a normal distribution. Median with interquartile range (IQR) was used for ordinal data or continuous data that did not have a normal distribution. Data were tested for normality using the Anderson-Darling Normality Test, with a P value of <0.05 signifying nonparametric data. In-hospital mortality was compared using 2×2 contingency tables and the Fisher exact test or χ^2 test. Hospital LOS and ICU LOS were compared using a Mann-Whitney U test. To estimate the crude association between each factor and LOS, univariate linear regression analysis was conducted for each predictor variable. The following variables were considered as possible predictors: categorization as ChEI initiation or ChEI continuation, age, admission severity of illness, and admission risk of mortality. Variables that had a P value <0.20 in the univariate linear regression analysis were entered into a multivariate model. Statistics were performed using GraphPad Prism, version 5 (GraphPad Software, Inc., La Jolla, CA), and Minitab, version 16 (Minitab, Inc., State College, PA). An α value of 0.05 was set for statistical significance.

RESULTS

Demographic Data

During the 7-month study period, there were 20,516 adult admissions to TMH. Four hundred seventy-six patients were admitted to TMH, dispensed a ChEI, and met our inclusion criteria. Of these 476 patients, 434 (91%) were continued on ChEI therapy that was started prior to hospital admission and 42 (9%) were initiated on ChEI therapy in the inpatient setting. Four patients who otherwise met inclusion criteria were excluded because their information was not

TABLE 1. Demographics and Baseline Characteristics

Variable*	Initiation of ChEI Therapy (N = 42)	Continuation of ChEI Therapy (N = 434)
Age, y, median (IQR)	81 (74–88)	83 (76–87)
Sex, F	22 (52)	262 (60)
Race		
Caucasian	24 (57)	281 (65)
African American	8 (19)	68 (16)
Other	10 (24)	85 (20)
Admission severity of illness		
Mild	4 (10)	32 (7)
Moderate	17 (40)	159 (37)
Major	18 (43)	189 (44)
Extreme	3 (7)	54 (12)
ChEI inpatient exposure		
Donepezil†	35 (83)	335 (77)
Rivastigmine†	8 (19)	75 (17)
Galantamine	0 (0)	25 (6)

NOTE: Abbreviations: ChEI, cholinesterase inhibitor; F, female; ICU, intensive care unit; IQR, interquartile range; y, year.

*Data are represented as n (%) unless otherwise indicated.

†Two patients were dispensed both rivastigmine and donepezil during the same hospitalization. One patient was in the initiation group (2%, 1 of 42), and 1 patient was in the continuation group (0%, 1 of 434).

TABLE 2. Characteristics of Patients Who Initiated ChEI Therapy

Variable*	Patients (N = 42)
Presumed indication of ChEI therapy	
Unclassified dementia	26 (62)
Alzheimer disease	5 (12)
Mixed dementia	5 (12)
Vascular dementia	3 (7)
Dementia with Lewy bodies	1 (2)
Frontotemporal dementia	1 (2)
Unknown indication†	1 (2)
Physician service line that ordered ChEI	
Neurology	24 (57)
Internal medicine	5 (12)
Geriatrics	4 (10)
Psychiatry	3 (7)
Hospitalist	3 (7)
Other	3 (7)
Location at initiation of ChEI	
Acute care ward	40 (95)
ICU	2 (5)
Hospital LOS, median (IQR), d	6.5 (4–9.3)
Hospital days prior to ChEI initiation, median (IQR)	2 (1–4)
Days of ChEI exposure, median (IQR)	3 (2–6)
Discharged on ChEI‡	37 (90)
Exposure to antipsychotics	18 (43)
Initiation of antipsychotics	14 (33)
Continuation of antipsychotics§	4 (10)
Exposure to benzodiazepines	15 (36)
Initiation of benzodiazepines	13 (31)
Continuation of benzodiazepines§	2 (5)
Initiation of both antipsychotics and benzodiazepines	7 (17)
Presumed infection treated with antibiotics	20 (48)
UTI	15 (36)
Pneumonia	5 (12)

NOTE: Abbreviations: d, day; ChEI, cholinesterase inhibitor; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; UTI, urinary tract infection.

*Data are represented as n (%) unless otherwise indicated.

†After reviewing all electronic medical record physician documents, the investigators were unable to determine the indication of ChEI therapy.

‡One patient died in the hospital, so only 41 patients were discharged from the hospital. §Continuation is defined as continuation of a home medication that was being used prior to hospital admission.

available in the UHC CDB/RM. The prevalence of ChEI exposure and incidence of new ChEI initiation was 23.2 (95% confidence interval [CI]: 21.2–25.4) and 2 (95% CI: 1.5-2.8) per 1000 adult admissions, respectively. Patients exposed to ChEI therapy were geriatric (median age, 82 years; IQR, 76–87), predominantly white (64%), and predominately female (60%). Baseline characteristics were similar between patients who initiated ChEI therapy and patients who continued ChEI therapy in regard to age, sex, race, and admission severity of illness (Table 1). Based on Major Diagnostic Categories (MDC) for admission APR-DRG, 52% (22 of 42) of the ChEI initiation group were admitted for a disease that was not mental health related or neurological in nature.

Cholinesterase Inhibitor Selection

Donepezil (78%) was the most frequently prescribed ChEI in both study groups, followed by rivastigmine (17%) and galantamine (5%). No patients in the ChEI initiation group received galantamine. All patients in the continuation group were continued on the same ChEI agent as an inpatient, except for 1 patient admitted on donepezil who was switched to rivastigmine and 1 patient admitted on rivastigmine who had donepezil added.

Cholinesterase Inhibitor Initiation and Course of Therapy

Detailed characteristics of the 42 patients who were initiated on ChEI as inpatients are listed in Table 2. The most common presumed indication for initiation of ChEI was unclassified dementia (62%), followed by Alzheimer disease (12%) and mixed dementia (12%). The most common physician service lines that ordered the ChEI were neurology (57%), internal medicine (12%), and geriatrics (10%). Patients were hospitalized for a median of 2 days before initiation of ChEI and were exposed to therapy for a median of 3 days. Of patients discharged from the hospital, 90% (37 of 41) had orders to continue the ChEI postdischarge. Cholinesterase Inhibitor therapy was initiated within 48 hours of discharge and continued through discharge in 10 (24%) of patients.

Antipsychotic and benzodiazepine therapy was initiated (no documented use before admission) in 33% (14 of 42) and 31% (13 of 42) of admissions, respectively. Both antipsychotic therapy and benzodiazepine therapy were initiated in 17% (7 of 42). The incidence of infection that was treated with antibiotic therapy was 48% (20 of 42).

Only 2 patients (5%) were initiated on ChEI while admitted to an ICU. Both of these patients were screened with the Confusion Assessment Method for

the ICU (CAM-ICU) and tested positive for delirium.[15] One of these 2 patients accounted for the only mortality that occurred in the group of 42 patients who were initiated on ChEI. This patient was started on donepezil in the medical ICU on hospital day 4 and continued on therapy for 14 days until death. During this hospital stay, the patient was also initiated on both haloperidol and lorazepam and received antibiotics for pneumonia. A detailed description of the other patient is listed under patient 3 in Appendix 1 (see Supporting Information, Appendix 1, in the online version of this article).

Sensitivity Analysis

To minimize the impact of incomplete documentation of a previous ChEI exposure, a sensitivity analysis was conducted that excluded all patients who received an order for ChEI within 24 hours of admission from the ChEI initiation group (9 of 42). In this analysis, the incidence of ChEI initiation was 7% (33 of 476) and the proportion of adult admissions with ChEI initiation was 1.6 (95% CI: 1.1-2.3) per 1000 admissions. The incidences of infection (52%), initiation of antipsychotics (33%), and initiation of benzodiazepines (31%) were similar to the original ChEI initiation group. The median LOS before ChEI initiation was 3 days (IQR, 2–4.5). The median hospital LOS was 7 days (IQR, 4.5–9.5). Ninety percent of patients were discharged home on ChEI therapy. Eighteen percent were readmitted within 30 days.

Outcome Data

In-hospital mortality was low (2.5%,12 of 476) in this patient cohort, with no observed difference between patients initiated on ChEI therapy (2%, 1 of 42) and patients continued on ChEI therapy (3%, 11 of 434). The rate of 30-day readmission was 15% (6 of 41) for patients initiating ChEI therapy and 13% (56 of 423) for patients continuing ChEI therapy. Hospital LOS was 1.5 days longer in patients initiated on ChEI (median, 6.5 days for initiation vs 5 days for continuation, $P = 0.0147$). Patients who initiated ChEI therapy experienced a 32% increase in hospital LOS compared with patients who continued ChEI therapy in a multivariate linear regression analysis that accounted for admission severity of illness and admission risk of mortality ($P = 0.007$). Rates of ICU admission were low (24%, 115 of 476) and there was no observed difference between groups (14% [6 of 42] for initiation vs 25% [109 of 434] for continuation, $P = 0.117$).

Eleven of the 12 deaths were in patients who were treated with donepezil; however, there was no observed difference in the incidence of mortality for patients treated with donepezil vs patients treated with either rivastigmine or galantamine (3% vs 1%, $P = 0.479$).

DISCUSSION

This study shows that despite lack of evidence, adult patients are initiated on ChEI therapy during 2 admissions per 1000 hospital admissions. The patients who were initiated on ChEI therapy were geriatric and had multiple risk factors for delirium, such as infection and exposure to benzodiazepines. One-third of patients were initiated on antipsychotic therapy during their hospitalization, and this may be a surrogate marker for delirium. It is hypothesized that many of these patients had delirium around the time of ChEI initiation.

Data from the 2000 US Census estimate that there were 209 million citizens who were age $\geq$18 years.[16] In the year 2000, approximately 1,132 per 10,000 were admitted to a short-stay hospital each year.[17] If ChEI therapy was started in 0.2% of these 23 million admissions per year, we estimate that >45,000 patients will be initiated on ChEI annually during the inpatient setting.

Limitations

The major limitation to this study is that the true incidence of delirium in this population is unknown. Unfortunately, acute care patients admitted to our hospital during this study period were not consistently screened for delirium using a validated screening tool. A previous study found that clinicians are unable to diagnose 70% of cases of delirium when a validated delirium screening tool is not used.[18] Therefore, we did not attempt to quantify the incidence of delirium using progress notes or diagnosis codes, as this incidence would be falsely low and unreliable. Our hospital is currently improving the culture of awareness of delirium, and efforts are being made to establish and improve routine screening for delirium in both the acute care and critical care setting.

There were limitations to the outcomes of mortality, readmission, and hospital LOS that were reported. Reported in-hospital mortality did not account for patients who were transferred for hospice care or patients who were transferred to another facility and subsequently died. Only hospitalizations to TMH were counted for 30-day readmission rates; admissions to another hospital were unknown. The sample size was too small to estimate the effects of ChEI initiation on 30-day readmission rates and in-hospital mortality. Physicians may have been more likely to prescribe ChEI therapy in patients who had prolonged hospital LOS, and the prolonged LOS observed in the ChEI-initiation group may be confounded by selection bias.

CONCLUSION

At a tertiary-care, academic medical center, approximately 9% of patients who received ChEI therapy during their hospitalization were initiated on therapy during their admission. Due to the presence of delirium risk factors (infection and use of psychoactive medications), it is likely that these patients had delirium superimposed on their dementia when the ChEI therapy was initiated. These results suggest that

ChEI therapy initiation may be better suited to an outpatient setting where the risk of delirium is lower and physicians are better able to evaluate the baseline cognitive function of their patients.

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K.C.W. generated the initial hypothesis. All authors (J.T.S., K.C.W., N.T.-M., and G.E.T.) participated in study design. K.C.W. and N.T.-M. conducted chart review of paper and electronic medical records at The Methodist Hospital. J.T.S. collected electronic data from the University HealthCare Consortium Clinical Database/Resource Manager, managed the study database, and performed statistical analysis of the data. Both J.T.S. and K.C.W. drafted the original manuscript and contributed equally to the study. All authors revised and approved the final version of the manuscript.

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