METHODOLOGIC FRAMEWORK TO IDENTIFY POSSIBLE ADVERSE DRUG REACTIONS USING POPULATION-BASED ADMINISTRATIVE DATA

by

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FINAL READING APPROVAL

To the Graduate Council of the University of Utah:

I have read the thesis of Brian C. Sauer in its final form and have found that (1) its format, citations, and bibliographic style are consistent and acceptable; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the supervisory committee and is ready for submission to The Graduate School.

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ABSTRACT

We present a framework for detecting possible adverse drug reactions (ADRs) using Utah Medicaid administrative data. We examined four classes of ADRs associated with treatment of dementia by acetylcholinesterase inhibitors (AChEIs): known reactions (gastrointestinal, psychological disturbances), potential reactions (respiratory disturbance), novel reactions (hepatic, hematological disturbances), and death.

Our cohort design linked drug utilization data to medical claims from Utah Medicaid recipients. We restricted the analysis to beneficiaries 50 years and older who had a dementia-related diagnosis. We compared patients treated with AChEIs to patients untreated with antidementia medication therapy. We attempted to remove confounding by establishing propensity-score-matched cohorts for each outcome investigated; we then evaluated effects of drug treatment by conditional multivariable Cox-proportional-hazard regression. Acute and transient effects were evaluated by a crossover design using conditional logistic regression.

Propensity-matched analysis of expected reactions found that AChEI treatment was associated with gastrointestinal episodes (hazards ratio [HR]: 2.02; 95% confidence interval [CI]: 1.28-3.2) but not psychological episodes, respiratory disturbance, or death. Among the tested unexpected reactions, the risk was higher with hematological episodes (HR: 2.32; 95% CI: 1.47-3.6) but not hepatic episodes.

We also noted a trend towards an increase in the odds of experiencing acute hematological events in the treated group (odds ratio [OR]: 3.0; 95% CI: 0.97-9.3).

We observed an expected association between AChEIs and gastrointestinal disturbances and detected a signal of hematological adverse drug events (ADEs) after treatment with AChEIs in this pilot study. Using our analytic framework may raise awareness of potential ADEs and generate hypotheses for future investigations.

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

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Finally, I would like to acknowledge the key contributors to the conceptualization and design of this research. Dr. Nebeker conceptualized the framework that included evaluating both expected and unexpected adverse drug reactions (ADRs). Dr. Samore provided key design and analysis guidance, most of which occurred from a cell phone while driving out west with his family during vacation. Dr. Kathleen Lohr and Dr. Suzanne West provided outstanding feedback and editing of the final manuscript.

CHAPTER 1

BACKGROUND

I have not failed, I've just found 10,000 ways that won't work.
(Thomas Alva Edison, 1847-1931)

Pharmaceuticals, like all healthcare interventions, offer benefits to patients but also pose risks of harm in the form of negative side effects and adverse events. The U.S. Food and Drug Administration (FDA), in regulating drugs for the U.S. marketplace, relies in part on safety data generated by randomized controlled trials, but the limitations of such data are widely recognized because of the characteristics of such trials (e.g., highly selected settings and patient populations, short duration of studies, and less reporting of such information than of positive outcomes). Other sources of information, including various types of observational studies, voluntary schemes for reporting adverse events, and more organized postmarketing surveillance studies, contribute to the knowledge base about drug safety and tolerability.

Recent reports underscore the need for such methods, particularly to detect serious but rare adverse events that were not discovered during premarketing trials. For example, cyclooxygenase 2 inhibitor nonsteroidal anti-inflammatory drugs (commonly known as COX-2 inhibitors, used for pain management) are documented to increase cardiac morbidity (1,2); antipsychotic medications (especially atypical antipsychotics) are associated with an increased risk of mortality in the elderly (3). These types of findings also prompt questions about morbidity and mortality in elderly or frail individuals who are exposed to other classes of drugs.

The enactment of the Medicare Prescription Drug, Improvement and Modernization Act of 2003, which introduced the Part D benefit for outpatient medications for Medicare beneficiaries, affords an opportunity to examine adverse

events in large administrative claims databases through linking prescription drug claims with medical claims. Because Medicare beneficiaries often have a complex array of health issues managed by multiple medications, this population is at risk for complications resulting from drug safety issues. The presumed availability of information from the Center for Medicare and Medicaid Services, including databases that would combine Part A, Part B, and Part D information, is expected to provide a unique opportunity to study how prescription drugs are used in this population, the positive and negative effects of prescription use, and the outcomes of such use.

The Agency for Healthcare Research and Quality requested the Research Triangle Institute's Developing Evidence to Inform Decisions About Effectiveness Center to take on a specific project to develop methods for identifying adverse drug events (ADEs) and adverse drug reactions (ADRs) in databases that could mimic those eventually presumed to be available to Medicare beneficiaries. In principle, Medicare pharmacy and claims databases will be ideal for large postmarketing surveillance studies of ADRs. In practical terms, databases that include outpatient pharmacy data are not yet available from the Center for Medicare and Medicaid Services because the Part D benefit is so new. For that reason, the Agency for Healthcare Research and Quality assigned us the task of exploring how best to use similar databases and to develop and test methods and measures for studying medication safety in the elderly.

To apply methods and test measures appropriately, research must examine the application of measures before implementing them nationally. In proceeding this way,

the Agency for Healthcare Research and Quality aims to offer new resources and tools for numerous stakeholders, including those in pharmacoepidemiology and pharmacoeconomics, for studying and understanding the use, benefits, and risks of pharmaceuticals, and for doing so in advance of the appearance of Parts A, B, and D Medicare data. Our work contributes to this methodological toolbox and develops a data analytical framework for pharmacoepidemiological research on ADRs using population-based claims and administrative data sources.

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CHAPTER 2

METHODOLOGIC FRAMEWORK TO IDENTIFY POSSIBLE ADVERSE DRUG REACTIONS USING POPULATION-BASED ADMINISTRATIVE DATA

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Abstract

Purpose

We present a framework for detecting possible adverse drug reactions (ADRs) using Utah Medicaid administrative data. We examined four classes of ADRs associated with treatment of dementia by acetylcholinesterase inhibitors (AChEIs): known reactions (gastrointestinal, psychological disturbances), potential reactions (respiratory disturbance), novel reactions (hepatic, hematological disturbances), and death.

Methods

Our cohort design linked drug utilization data to medical claims from Utah Medicaid recipients. We restricted the analysis to beneficiaries 50 years and older who had a dementia-related diagnosis. We compared patients treated with AChEIs to patients untreated with antidementia medication therapy. We attempted to remove confounding by establishing propensity-score-matched cohorts for each outcome investigated; we then evaluated effects of drug treatment by conditional multivariable Cox-proportional-hazard regression. Acute and transient effects were evaluated by a crossover design using conditional logistic regression.

Propensity-matched analysis of expected reactions found that AChEI treatment was associated with gastrointestinal episodes (hazards ratio [HR]: 2.02; 95% confidence interval (CI): 1.28-3.2) but not psychological episodes, respiratory disturbance, or death. Among the tested unexpected reactions, the risk was higher with hematological episodes (HR: 2.32; 95% CI: 1.47-3.6) but not hepatic episodes.

We also noted a trend towards an increase in the odds of experiencing acute hematological events in the treated group (odds ratio: 3.0; 95% CI: 0.97-9.3).

Conclusions

We observed an expected association between AChEIs and gastrointestinal disturbances and detected a signal of hematological adverse drug events (ADEs) after treatment with AChEIs in this pilot study. Using our analytic framework may raise awareness of potential ADEs and generate hypotheses for future investigations.

Introduction

Despite its limitations, the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) has successfully identified rare and unexpected adverse events (1-3). In many studies, administrative data sources have been used to estimate the extent of the problem or to confirm safety signals identified from AERS (4,5). However, fewer studies have demonstrated the potential of administrative data for first-line adverse drug reaction (ADR) surveillance (6). In this pilot study, we present a framework for directed discovery of possible ADRs using population-based administrative data sources, an approach intended to complement the FDA's adverse reporting system.

We examined associations between drug use and possible ADRs resulting from treatment of dementia with acetylcholinesterase inhibitors (AChEIs), namely, donepezil hydrochloride, rivastigmine tartrate, and galantamine hydrobromide. We measured associations for four classes of ADEs—established reactions (gastrointestinal

and psychological disturbances), potential reactions based on drug pharmacology (respiratory disturbance), novel unexpected reactions (hepatic and hematological disturbances), and death. Hepatic and hematologic syndromes were evaluated because they are two examples of potentially fatal reactions that have been found in postmarketing surveillance of drug-induced disease (7).

Methods

The directed discovery framework consists of clinical framing, data preparation, event detection, and hypothesis generating and testing. The first three components are described in the Methods; hypothesis generating and testing are explored in the Discussion.

Clinical Framing and Data Preparation

Clinical framing consisted of reviewing the medical literature and consulting clinical experts to define the treatment groups, inclusion criteria, drug courses, outcomes, and covariates.

Sources. Data consisted of pharmacy and medical claims and enrollment status from Utah Medicaid recipients in the fee-for-service program between 1/01/2003 and 12/31/2005. We linked Utah death certificate data to Medicaid recipients by a deterministic method using social security number. To protect patients' privacy, all potentially traceable personal identifiers were removed. The University of Utah Institutional Review Board approved this study.

Subjects. We studied Utah Medicaid recipients' ages 50 and older with a dementia-type diagnosis (**Appendix A**). As Medicaid enrollment occurs on a monthly basis, we tracked membership enrollment and deenrollment and censored patients when enrollment was terminated and not reestablished within the study period. Because of the relatively high rate of sustained enrollment, approximately 99% of the cohort were enrolled for at least 80% of the months from their first until their last month of eligibility or until the study period ended. We did not limit inclusion to continuously enrolled recipients.

Treatment groups. We inferred patient AChEI use by reconstructing courses of AChEI therapy from pharmacy claims data. To achieve greater homogeneity among users' disease stage and risk for adverse reactions (8), we restricted the AChEI cohort to the first incident course of AChEI therapy, which was defined as their first course with at least a 180-day drug-free period. To ensure that patients were receiving medical care during the 180-day drug-free period and not receiving the drug elsewhere, recipients had to be enrolled and to have at least one medical claim during the 180-day drug-free (baseline) period. We defined a course of AChEI therapy as beginning on the week the drug was first dispensed and ending on day 60 after a continuous gap in their drug supply of $\geq$ 60 days (**Figure 2.1**).

The untreated comparison group consisted of Medicaid recipients 50 years and older with a dementia-like diagnosis who did not receive AChEI therapy. We established a 180-day baseline period during which recipients were enrolled and had at least one medical claim. The index date for individuals in the untreated group

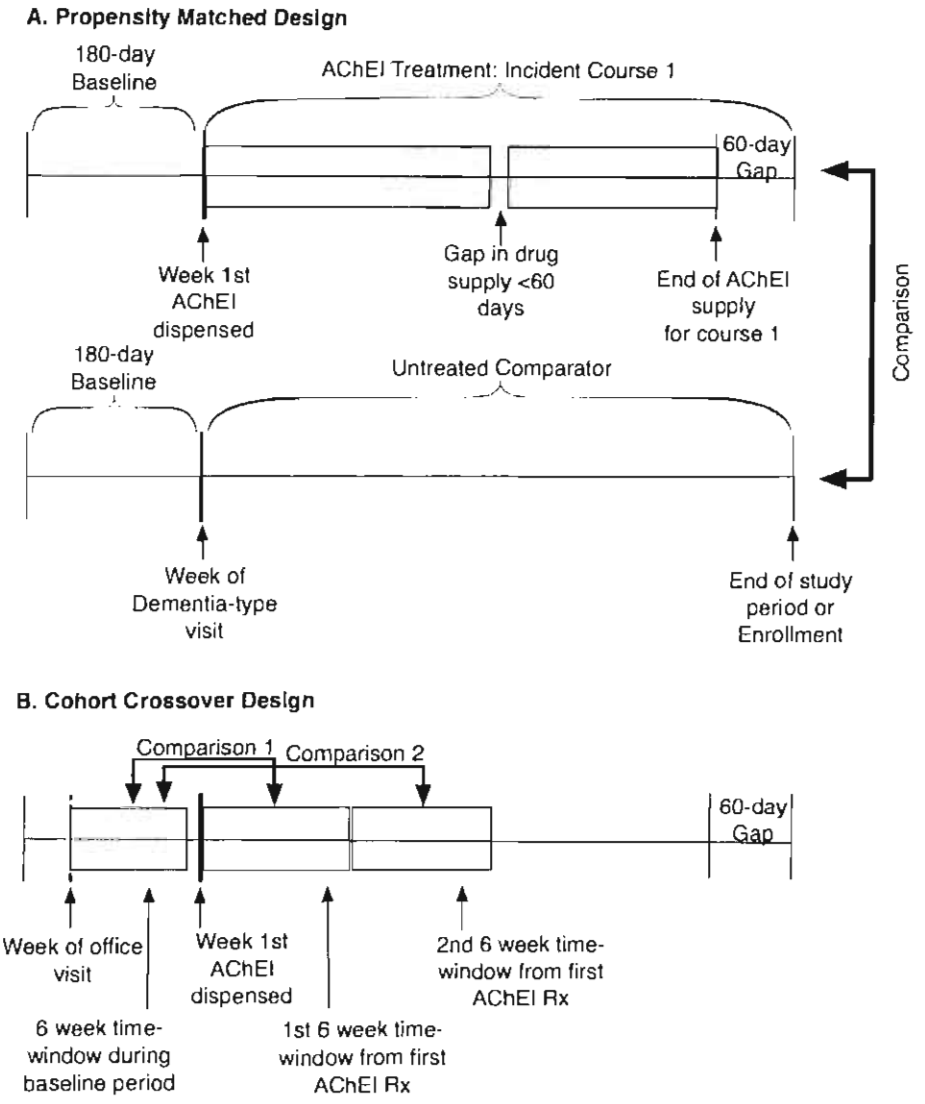

Figure 2.1. **Treatment time windows for cohort and cohort crossover study.**

AChEI = acetylcholinesterase inhibitors
Rx = dispensed prescription

began at the first dementia-related outpatient visit that allowed for a 180-day baseline period. Starting time zero with a dementia-related outpatient visit established an indicated population that was engaging the healthcare system.

Outcomes. As noted earlier, our primary clinical outcomes were gastrointestinal, psychological, respiratory, hematological, and hepatic conditions, and death. We identified healthcare visits related to each clinical outcome in professional and facility claims using Healthcare Cost and Utilization Project (HCUP) Clinical Classification Software (CCS) codes, which are documented in **Appendix A**. As primary diagnosis typically indicates the reason for seeking medical care or the most important problem at the visit, we limited outcome detection to primary diagnosis codes. We tailored outcome classifications for each study design, which are described under Event Detection. Our analysis also measured the association of AChEI use with death.

Potential confounding. We assessed demographic variables, comorbidities, drug therapy, and indicators of healthcare utilization as potential confounders. Comorbidity indices included HCUP comorbidity software version 3.2 and the modified RxRisk-V (RxRisk-Vm) score, which infers comorbidity using pharmacy claims (9). We measured healthcare utilization by the number of outpatient visits, hospitalizations, and emergency department visits, and we also accounted for the use of hospice services and nursing home care.

We considered specific classes of medications as potential confounders, specifically, antianxiolytics, anticonvulsants, Parkinson's treatment, antidepressants,

antipsychotics, steroids, narcotics, respiratory agents, anticoagulants, corticosteroids, and sedatives. We treated use of statin drugs as an indicator of health status because they are preferentially prescribed to healthier, less frail patients who are not at the end of life (10).

Person time units. We constructed the final analytic table using 1-week discrete time intervals; that is, changes in covariate status, medication use, and outcomes are captured weekly. This interval maximizes efficiency without omitting clinically important changes in patient outcome and covariate status. All database manipulation was conducted in SAS 9.2.

Event Detection

Cohort Design

We used an open cohort design with a matching propensity score to explore associations between data on drug utilization and possible ADRs. We used propensity scores to address covariate imbalance using logistic regression models to predict AChEI treatment. We included confounders and risk factors in the propensity score models (11). Because we included risk factors along with confounders, we built separate propensity score models and matched cohorts for each study outcome. Two physicians who routinely treat patients with dementia independently selected variables to construct propensity score models. They discussed disagreements to arrive at consensus. Variables for each model are listed in **Appendix B**.

Our analyses included propensity score matching followed by additional matching on key prognostic covariates (12). For example, we performed propensity

matching with covariate matching for whether an individual had a gastrointestinal visit during the baseline period when evaluating the gastrointestinal outcome. Analysis of death consisted of propensity score matching and covariate matching for baseline age and hospice care.

Clinical endpoints were intended to measure increased healthcare utilization associated with specific diagnoses. We defined episodes of care to differentiate clusters of events and to reduce the impact of immediate clinical exuberance associated with a new episode of care. A 4-week gap in claims for each clinical outcome was required to initiate a new episode. For each study endpoint, we calculated incidence densities per 100 patient years.

We established matched untreated cohorts using Mahalanobis metric matching (13). Baseline characteristics of patients in the AChEI treated and matched untreated cohorts were compared using Student's *t* tests and chi-square tests. We used conditional, multivariable, Cox-proportional hazard models that allowed for recurrent events to assess the effect of AChEI on specific clinical endpoints (14). All statistical analyses were performed with Stata MP 9.2 for Windows.

Cohort-Crossover Design

We established three 6-week time windows (i.e., pretreatment, first treatment, and second treatment) to assess acute and transient effects of AChEI treatment (**Figure 2.1**). The index week for the pretreatment window was the week following the most recent clinic visit for any condition during the baseline period.

To capture *acute* effects of AChEI treatment, we used the week the AChEI was first dispensed as the index week for the first treatment window. We compared the odds of experiencing an event during that window with the odds of experiencing an event during the pretreatment window to identify acute treatment effects. To evaluate the *transience* or *stability* of possible ADRs, we compared the odds of experiencing an event during the second treatment window with the odds of experiencing an event during the pretreatment window. Patients were noted as having an event if they had a medical claim with the primary clinical diagnosis code of interest; we used only one event per time window. Odds ratios between the referent and treatment windows were computed using conditional logistic regression.

Results

Description of Study Population

Of the 29,046 eligible patients in the study populations, 4,109 had a medical claim with a dementia diagnosis between 1/01/2003 and 12/31/2005. The AChEI-treated cohort consisted of 976 total users and 332 users with incident courses; of the latter, 224 were started on donepizil, 59 on rivastigmine, and 49 on galantamine. Because numbers of incident users of specific AChEIs were small, we did not assess potential ADRs for individual drugs. In the AChEI treated group, the median duration of incident courses was 33.4 weeks with an interquartile range from 15 to 68.5 weeks. The median proportion of weeks for which the AChEI treated group was estimated to have access to the medication at least 1 day during the week was 100%, with an interquartile range of 95%-100%. The untreated cohort consisted of 2,968

patients who were diagnosed with dementia but did not receive medication to treat the disorder during the study period (**Figure 2.2**).

Basic characteristics of the study population during the 6-month baseline period are presented in **Table 2.1**. Compared with the untreated population, incident AChEI users were slightly younger, had fewer HCUP comorbidities, fewer clinic visits, and a lower frequency of hospice care. Incident AChEI users also had a higher frequency of statin use and nursing home care. RxRisk-Vm scores and the average numbers of hospitalizations and emergency department visits were similar for AChEI users and nonusers (untreated patients).

After propensity score matching for each clinical endpoint, the two groups were similar on all variables for each outcome-based cohort, except for the average number of emergency department visits, which were slightly higher in the untreated matched groups for the evaluation of respiratory and hepatic episodes (**Appendix B**). In general, the lack of statistically significant differences between the AChEI treated and untreated groups on propensity-adjusted variables suggests balance in measured covariates between treatment groups.

Table 2.2 presents incidence densities per 100-person years and 95% confidence intervals for the complete untreated population and propensity-matched comparisons. **Table 2.3** presents hazards ratios for all unadjusted and matched comparisons.

Crude analyses. In bivariate analysis (**Table 2.3**), we did not observe a higher rate of gastrointestinal episodes in the group treated with AChEIs than in the

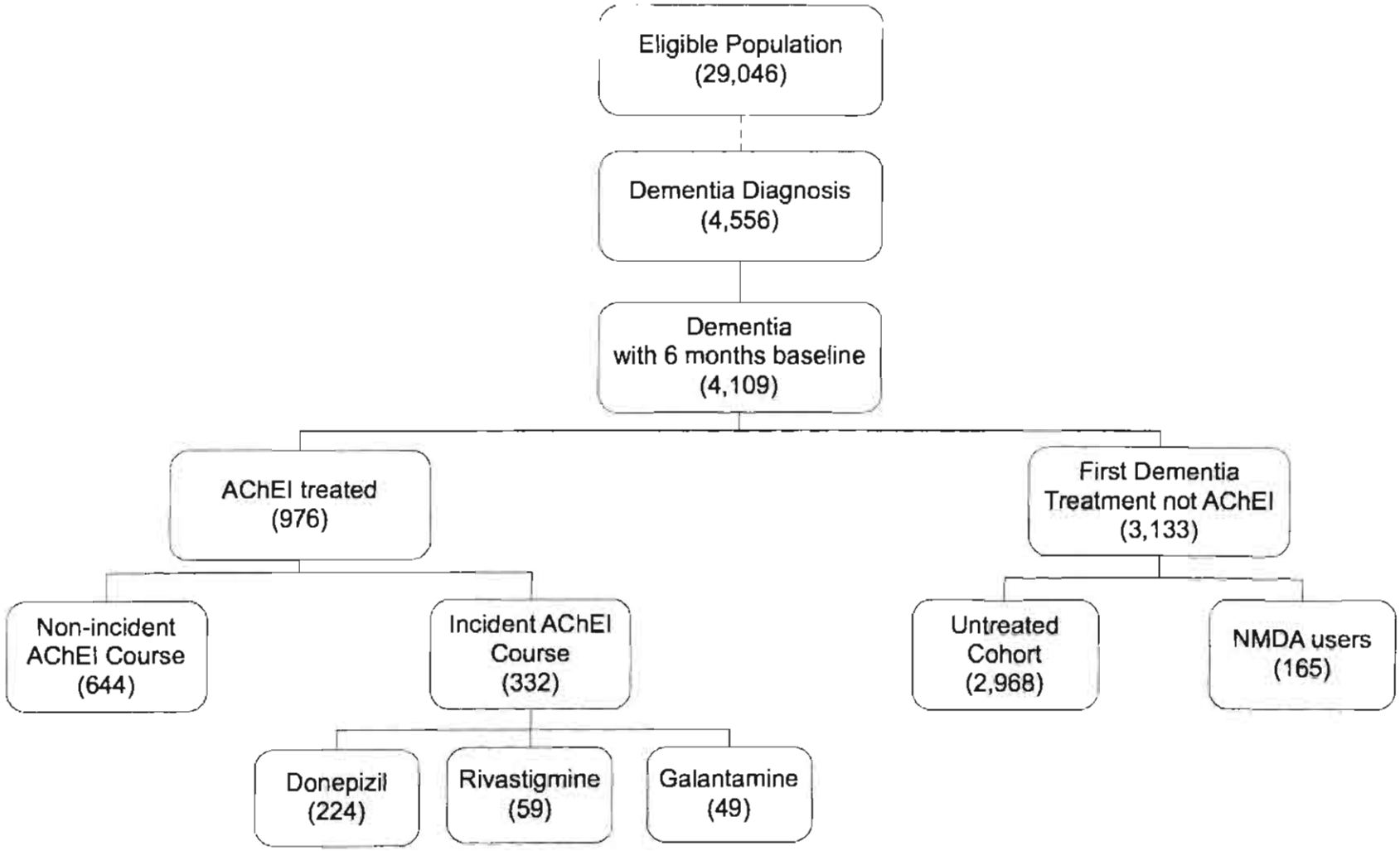

Figure 2.2. **Dementia diagnosis and AChEI drug treatment in the eligible study population.**

Table 2.1. **Basic Characteristics of the Study Population, 2003-2005**

Patient Characteristics	AChEI Cohort (n = 332)	Untreated Cohort (n = 2,968)	P Value
Average age, years (*SD*)	76.4(11.4)	77.9(12.4)	0.02
Frequency female (Yes = 1)	71%	72.6%	0.53%
Average number of HCUP comorbidities (*SD*)	1.1(1.5)	1.3(1.6)	< 0.00
Average RxRisk-Vm (*SD*)	4.4(3.1)	4.5(3.3)	0.58
Average number of hospitalizations (*SD*)	0.19(0.45)	0.17(0.5)	0.44
Average number of ED visits (*SD*)	0.11(0.51)	0.11(0.58)	0.17
Average number of clinic visits (*SD*)	15.9(14.3)	16.7(16)	< 0.00
Receiving hospice care (Yes = 1)	0.6%	3.2%	< 0.00
Frequency of statin dispensed (Yes = 1)	25.6%	16.4%	< 0.00
Frequency of nursing home stay (Yes = 1)	25.9%	14.4%	< 0.00

AChEI = acetylcholinesterase inhibitors
HCUP= Healthcare Cost and Utilization Project
SD = standard deviation
% = percent
ED = emergency department
RxRisk-Vm = modified RxRisk-V

Table 2.2. **Crude Incidence Densities (Per 100-Person Years) of Target Events in AChEI Treated and Untreated Groups**

	AChEI Treated Cohort			Untreated Cohort			Matched Untreated Cohort		
	N	Incidence Density	95% CI	*N*	Incidence Density	95% CI	*N*	Incidence Density	95% CI
Expected reactions									
Gastrointestinal episodes	78	27.6	24.5, 30.7	878	25.7	24.8, 26.5	63	17.3	15.1, 19.5
Psychological episodes	141	50.0	45.8, 54.2	1399	40.9	39.8, 42.0	159	56.4	52.5, 60.3
Suspected reactions									
Respiratory episodes	91	32.2	28.9, 35.6	1004	29.4	28.4, 30.3	84	23.8	21.1, 26.4
Unexpected reactions									
Hematological episodes	70	24.8	21.8, 27.8	651	19.0	18.3, 19.8	55	14.9	12.9, 16.9
Hepatic episodes	13	4.6	3.3, 5.9	121	3.5	3.2, 3.9	12	3.2	2.3, 4.1
Death	83	21.1	18.8, 23.4	1100	32.2	31.2, 33.1	92	23.6	21.1, 26.1

CI = confidence interval

Table 2.3. **Unadjusted and Matched Analysis Comparing Target Outcomes for Groups Treated and Untreated With AChEI Therapy**

	Crude			Propensity Matched		
Outcome	HR	*P* Value	95% CI	HR	*P* Value	95% CI
Expected reactions						
Gastrointestinal episodes	1.01	0.95	0.8, 1.27	2.02	<0.00	1.28, 3.2
Psychological episodes	1.12	0.2	0.94, 1.33	1.13	0.35	0.87, 1.47
Suspected reactions						
Respiratory episodes	1.03	0.76	0.83, 1.28	1.21	0.35	0.81, 1.79
Unexpected reactions						
Hematological episodes	1.26	0.07	0.98, 1.62	2.32	0.00	1.47, 3.67
Hepatic episodes	1.18	0.56	0.67, 2.1	1.77	0.24	0.68, 4.6
Death	0.66	<0.01	0.52, 0.82	1.07	0.5	0.74, 1.54

HR = hazards ratio
CI = confidence interval

untreated group. The rates of psychological episodes, respiratory episodes, hematological episodes, and hepatic episodes were slightly higher, but not statistically significant, in the group treated with AChEIs than in the untreated group. The rate of death was significantly lower in the group treated with AChEIs than in the untreated group.

Propensity-matched analyses. We observed significantly higher rates of gastrointestinal episodes (HR: 2.02; 95% CI: 1.28-3.2) and hematologic episodes (HR: 2.32; 95% CI: 1.47-3.67). in the AChEI-treated group than in the propensity-matched untreated group (**Table 2.3**). For psychological episodes, respiratory episodes, and hepatic episodes, we observed higher, but not statistically significant, rates in the AChEI-treated group than in the propensity-matched untreated group. We observed a weak and nonsignificant association between AChEI treatment and mortality.

Cohort-crossover analysis. In cohort-crossover analysis, we did not observe an increased odds of experiencing gastrointestinal events during either the first or second treatment windows. We observed an acute, but nonsignificant, effect of AChEI treatment on the odds of experiencing a psychological event during the first-treatment window; it was not sustained during the second-treatment window. We observed acute, but nonsignificant, effects of AChEI treatment on the odds of experiencing a respiratory event and hematological events during the first-treatment window; both rates appeared to decrease during the second-treatment window. The acute effect of AChEI treatment on the odds of experiencing a hepatic event during the first-

treatment window was imprecise and appeared to decrease during the second-treatment window (**Table 2.4**).

Discussion

We developed a cohort-based framework for using population-based administrative data to identify known ADRs and to discover ADRs that may have gone unnoticed during clinical trials. We evaluated AChEI therapy in persons with dementia, considering a composite of possible ADRs (i.e., expected, suspected, unexpected reactions, and death) to demonstrate that our analytic techniques produced expected results. We used propensity score matching and a within-subject design in an attempt to handle confounding. Our pilot study examined data from patients diagnosed with dementia for both cumulative effects of AChEI treatment and acute effects following initiation of AChEI therapy. We demonstrated our approach with Medicaid data from the state of Utah; nonetheless, the framework presented here can be transferred for use with other health insurer databases, including the Medicare Parts A, B, and D data now available.

A pervasive issue in pharmacoepidemiologic studies is confounding by indication (15). This problem arises because factors that influence treatment choices made by clinicians also influence outcomes. Confounding by indication can bias the crude association between drug treatment and outcomes in either direction and with unknown magnitude. Propensity score models are one method used in pharmacoepidemiologic studies to balance measured confounders with the goal of making the treatment groups exchangeable.

Table 2.4. **Cohort Crossover Design: Evaluation of Acute and Transient Effects of AChEI Treatment**

Type of Reactions	Measures	Pretreatment (n = 271)	First Treatment Window (n = 312)	Second Treatment Window (n = 303)
Expected reactions				
Gastrointestinal events	Events	11	10	11
	OR (95% CI)	†	0.7 (0.27, 1.84)	0.86 (0.29, 2.6)
	P value		0.47	0.78
Psychological events	Events	28	39	30
	OR (95% CI)	†	1.5 (0.72, 3.3)	0.86 (0.40, 1.9)
	P value		0.26	0.7
Suspected reactions				
Respiratory events	Events	12	14	15
	OR (95% CI)	†	1.4 (0.44, 4.4)	1.2 (0.37, 3.9)
	P value		0.57	0.76
Unexpected reactions				
Hematological events	Events	5	13	9
	OR (95% CI)	†	3 (0.97, 9.3)	1.75 (0.51, 6.0)
	P value		0.06	0.37
Hepatic events	Events	2	6	1
	OR (95% CI)	†	5 (0.58, 42.8)	0.5 (0.05, 5.5)
	P value		0.14	0.57

OR = odds ratio
CI = confidence interval

In this study, we addressed confounding by indication by developing propensity score models for each study outcome. Theoretical confounders available in the data were included in each model to reduce bias. Before matching, the untreated group appeared to be more frail than the treated group; they had a higher proportion of hospice care, more comorbidity, and a lower proportion of statin users, which suggested less aggressive care because of poorer health. As one would expect, the unadjusted analysis made AChEI treatment appear protective against mortality when compared with the untreated group (HR: 0.66; 95% CI: 0.52-0.82), which is not supported by clinical trials or other observation studies (16,17). After propensity and covariate matching, we found no difference between the AChEI treated and untreated groups (HR: 1.07; 95% CI: 0.74-1.54). This illustrates the importance of addressing confounding by indication when designing ADE surveillance systems.

An alternative approach to addressing confounding is to use inverse probability weighting methods to model time-varying treatments and confounders. In simulation studies, these methods were less biased than conventional methods when time-varying confounding was present (18). When allowing treatment to be time-varying, we observed gastrointestinal disturbance and discovered hematological disturbance; we noted the same findings as if follow-up began at initiation of drug treatment (data not shown). Future work should explore the presence of time-varying confounding and the benefits of using inverse probability weighting methods to discover novel ADEs associated with drug treatments.

To evaluate possible acute and transient effects of AChEI treatment, we employed cohort-crossover analyses. Typically, in cohort-crossover analyses, events are compared between treated and untreated time windows for each individual. A major benefit of this within-subject design is that each person acts as his or her own control (19,20). It also accounts for confounding by indication and other time-invariant and difficult-to-measure confounders. The drawback of such designs involves changes in treatment utilization that are influenced by health status or the study endpoints in question (21). For example, when day-level drug utilization data are inferred from dispensing history, determining whether adverse effects are truly transient or the result of a decrease or discontinuation of drug treatment is difficult. Ultimately, we deemed cohort-crossover analysis the best option to discover acute and transient effects because of its simplicity and ability to remove time-invariant confounding by indication.

Hypothesis Generating and Testing

The method described here is a promising approach for discovering possible ADRs such as the association we found between AChEI use and hematological disturbance. In support of the analytical effectiveness of these procedures, our approach observed an association with an expected reaction, gastrointestinal disturbances. The findings from the two study designs, however, were not consistent. Our inability to find an acute increase of gastrointestinal events in the first-treatment time window may be attributable to insensitivity of claims-based coding to identify symptoms of gastrointestinal disturbance.

Despite the fact that our approach detected a significant association with one expected reaction, gastrointestinal disturbance, it failed to identify a strong positive association with the second expected reaction, psychological disturbance. We found a higher rate of psychological episodes in the propensity-matched analysis; nevertheless, the association was not statistically significant. We did, however, observe higher odds of experiencing psychological events in the first-treatment time window than in the pretreatment time window. Even though the higher odds ratio was expected, it did not reach significance. This result can likely be attributed to a combination of factors. First is the low power in the crossover design, and second may be insensitivity of claims-based coding to identify symptoms of psychological disturbance.

We discovered no clear associations between AChEIs and respiratory disturbance or death. In a recent sequence symmetry analysis, initiators of AChEI had no detectable increased rate of complications of chronic airway disorders (22). We found no clear evidence of an increase or decrease in mortality associated with AChEI treatment in published studies or meta-analysis with which to compare our results (16).

Our analysis of unexpected reactions discovered a statistically significant positive association between AChEI treatment and hematological episodes. Hematological events also appeared to be positively associated with early AChEI treatment. A detailed review of results with hematological event subcategories (not reported here) found that the rate of anemia was much higher in the AChEI treated group than in the untreated group during the first 6 weeks of drug treatment. Further

analysis is required to determine if this higher rate is causally associated with initiating antidementia drug treatment. At present, no known pharmacologic or obvious empirical reasons can explain the reasons that recently marketed AChEI drugs cause hematological toxicity.

The incidence of hepatic disturbance appeared to be higher in the treated group, although nonsignificant, in both the crossover and propensity matched design. Hepatotoxicity was a major safety concern with tacrine, which is one reason it is not commonly used; hepatotoxicity has not been reported for other AChEIs (23). Larger observational studies are needed to determine whether an association exists between AChEIs and hepatotoxicity.

Limitations

The results from this study are considered hypothesis generating rather than identifying causal treatment effects. Causal studies require validation of treatments, outcomes, and covariate classifications. Furthermore, causal studies require a stronger theoretical understanding and explication of the underlying causal relationships between the treatment and outcomes.

We compared AChEI treated patients, with an incident AChEI course of therapy, with an untreated cohort of patients with a dementia diagnosis. Other options were to compare directly the safety of AChEI products with one another or to compare the safety of AChEI therapy with the safety of other classes of medications used to treat such patients' dementia. We did not have power to compare individual drug products. Treatment with AChEIs is not directly comparable to treatment with

memantine, a glutamaterginc N-methyl D-aspartate (NMDA) receptor antagonist because memantine is typically not first-line treatment for dementia; rather, it is used in addition to an AChEI therapy, complicating any comparison.

In pharmacoepidemiologic studies, an untreated referent group can also be defined as patients with an incident course of a medication that is not associated with the indication or evaluated outcomes. This type of "active control group" is likely to be more similar to the treated group with regard to activation of the healthcare system than the indicated but untreated group (17). Drug dispensing signifies that the patient has activated the health system. In addition, prescription of a new medication is likely to result in closer monitoring and evaluation of an individual's health status. The primary concern when comparing treated with untreated groups is underrecording of health conditions, making the members of the comparison group seem healthier than they really are, which can lead to overestimation of the effect of drug treatment.

Because of the multiple outcomes in this study, we were unable to identify a single medication that could yield comparable cohorts for all events. Instead, we used a dementia-related visit, not drug dispensing, as the index date for the untreated group. For both cohorts, the median amount of time to a clinic visit following the index date was 3 weeks, and the longitudinal visit process was also similar. These patterns suggest that healthcare access and followup may have been similar for the two groups.

Another limitation of this study is the small number of subjects in the AChEI treatment group. This markedly limited our ability to confirm expected adverse effects

of AChEI treatment and discover adverse events that may have gone undetected in clinical trials.

Future Research

Discovery of an association between a drug treatment and a theoretical reaction, an idiosyncratic reaction, or death is considered hypothesis generating. Confirmation requires additional observational and possibly experimental studies. Ideally, discovered associations would first be confirmed in large, disparate data sources to reproduce evidence of the association across different populations. In May 2008, the FDA published The Sentinel Initiative report to present the national strategy for monitoring medical product safety (24). Their approach primarily establishes a nationwide health information network for confirmation of safety signals across multiple large databases. Additional observational studies using richer clinical information such as electronic health records or prospectively designed studies, however, may be needed to characterize the causal relationship between a drug treatment and adverse outcome.

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CHAPTER 3

SIGNIFICANCE

Previous adverse drug reaction (ADR) studies have often relied on data from federal reporting agencies such as MedWatch at the U.S. Food and Drug Administration and on information from randomized controlled trials. Our study presents a methodological framework for researchers to use in working with observational data, specifically from pharmacy and medical claims databases. The methods outlined in this report and the stepwise approach (i.e., clinical framing, data preparation, event detection, and hypothesis generation) can be adapted for other comparative safety and effectiveness research questions and for other types of clinical and administrative data.

Data available from Medicaid claims, employer claims, and (eventually) Medicare claims can be used to examine specific drug classes and agents within those drug classes for ADRs. The framework of initially examining known events from the clinical trials and then potentially severe but unobserved events (as, in our study, hepatological and hematological events) will further our understanding of drug safety. The advantage of the framework and method outlined in this work is that they allow claims databases to be used for identification of novel signals for previously unrecognized ADRs as well as to examine the number of previously identified ADRs.

Lessons Learned

The use of Medicaid data to support detection of ADRs presents a number of significant challenges. One requirement is to perform data quality checks meticulously in order to identify obvious errors that might compromise study validity. We followed a standard template to evaluate data integrity (1). This useful and timesaving step

identified a discrepancy, which was subsequently corrected, in the way data were extracted across different years.

One important condition in developing a research database is to fully understand the original data source. Utah Medicaid data and death certificate data are stored in a complicated warehouse. Relationships among different data tables, definitions, and labels of data field are not always clearly documented (or documented at all). For example, we had four different client identifications. With careful consultation from Medicaid data experts, we used each of the identifiers to link client records according to the source of records and purpose of linkage.

The Utah Medicaid program updates its data warehouse structure periodically, posing special challenges for standardizing longitudinal data over the years. We learned that the method of downloading the 2003 pharmacy claims differed from the method used for later years. The Utah Department of Health spent considerable resources to prepare and reprepare the raw data files and intermediate tables for researchers to produce analysis tables for this study. Other state Medicaid data warehouses and Medicare data may face similar challenges. We recommend that researchers who are new users of a state's Medicaid data obtain adequate technical support from the relevant Medicaid program(s) and share their data integrity analysis with their data suppliers.

Future Work

The framework presented here is just the tip of the iceberg in the development of methodological approaches for comparative safety and effectiveness research using

medical claims and clinical data. Additional work is needed to standardize data quality evaluation, assess drug exposure, validate covariate and outcome assessment, design and statistically evaluate unique with comparative effectiveness research, and report these steps.

This research has led to further refinement of the SAS modules used to classify drug exposure (i.e., course generator) and modules used to organize data by discrete time units. The goal is to develop a library of publically available, production quality SAS modules with specific functions (e.g., polypharmacy detector; course generator; time-structure generator; and programs to organize data for nested case-control, cross-over, and longitudinal designs) to share with other pharmacoepidemologists in order to improve transparency and reproducibility of comparative safety and effectiveness research. These modules will also support rapid evaluation to newly suspected or possible ADRs.

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APPENDIX A

DEMENTIA CODES AND TARGETED OUTCOMES CODES FROM THE HEALTHCARE COST AND UTILIZATION PROJECT

Table A.1. **Dementia Codes and Targeted Outcomes Codes From the Healthcare Cost and Utilization Project**

HCUP CCS Codes	Description
Dementia Diagnoses	
5.3.1	Senile dementia; uncomplicated
5.3.2	Arteriosclerotic dementia
5.3.5	Presenile dementia; uncomplicated
5.3.6	Senile dementia with delirium
5.3.7	Other senility and organic mental disorders
Gastrointestinal Outcomes	
9.4.3	Gastritis and duodenitis
9.4.4	Other disorders of stomach and duodenum
9.11	Noninfectious gastroenteritis
9.12.3	Other and unspecified gastrointestinal disorders
17.1.6	Nausea and vomiting
17.1.7	Abdominal pain
Hematological Outcomes	
4.1	Anemia
4.2	Coagulation and hemorrhagic disorders
4.3	Diseases of white blood cells
4.4	Other hematological conditions
Hepatic Outcomes	
9.8	Liver disease
Psychological Outcomes	
5.4	Affective disorders
5.6	Other psychoses
5.7	Anxiety, somatoform, dissociative, and personality disorders
5.9	Other mental conditions
Respiratory Outcomes	
8.2	Chronic obstructive pulmonary disease and bronchiectasis

HCUP = Healthcare Cost and Utilization Project
CCS = Clinical Classification Software

APPENDIX B

BASELINE COMPARISONS FOR ALL VARIABLES INCLUDED IN EACH MATCHED COHORT ANALYSIS

Table B.1. **Baseline Comparisons for All Variables Included in Each Matched Cohort Analysis**

	AChEI	Gastrointestinal		Psychological		Respiratory		Hepatic		Hematologic		Death	
Baseline	Tx	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value
Age (years)	76.4	78.2	0.39	76.5	0.89	76	0.66	74.7	0.06	74.9	0.1	76.5	0.29
No. HCUP comorbidities	1.11	1.09	0.43	1.06	0.96	1.04	0.57	0.93	0.06	1.02	0.63	1	0.39
RxRisk score	4.38	4.5	0.95	4.57	0.30	4.63	0.44	4.7	0.2	4.2	0.39	4.33	0.70
Sex (male)	89	74	0.17	82	0.52	75	0.20	85	0.72	96	0.53	74	0.17
Statin medications	85	94	0.38	89	0.66	81	0.72	85	0.2	82	0.76	85	1
Hospice care	2	2	1	1	1	2	1	3	1	5	0.25	2	1
No. ED visits	0.11	0.18	0.80	1.12	0.7	0.17	0.04*	0.17	0.04*	0.17	0.2	0.12	0.39
No. hospitalizations	0.19	0.16	0.11	0.23	0.33	0.15	2.0	0.13	0.06	0.21	0.15	0.18	0.59
Clinic visits (>5)	284	295	0.16	285	1	280	0.61	284	1	277	0.37	282	0.80
No. with gastrointestinal episode	65	65	1										
No. with hematologic episode	27									27	1		
No with hepatic episode	15							15	1				

Table B.1. **(Continued)**

	AChEI	Gastrointestinal		Psychological		Respiratory		Hepatic		Hematologic		Death	
Baseline	Tx	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value
No. with psychologic episode	84			84	1								
No. with respiratory episode						45	1						
Respiratory medications	6					11	0.27						
Steroids	34	43	0.23	45	0.18	39	0.53			47	0.11		
NSAIDs	124	137	0.29							113	0.35		
Gastroprotective medications	117	117	1										
Anxiolytics	103	103	1	98	0.67	111	0.49	88	0.19			109	0.60
Anticonvulsants	85			81	0.71	90	0.66	98	0.25	97	0.29	77	0.43
Parkinson's medications	37			26	0.19							40	0.81
Antipsychotics	135	135	1	128	0.55	111	0.05	140	0.67			149	0.27
Antidepressants	209	222	0.27	196	0.26	2.11	0.86	200	0.46			203	0.63
Narcotics	157	165	0.53	157	1	159	0.87	161	0.76			165	0.53
Sedatives	54	55	0.91	65	0.26	57	0.75	45	0.32			47	0.43

Table B.1. **(Continued)**

	AChEI	Gastrointestinal		Psychological		Respiratory		Hepatic		Hematologic		Death	
Baseline	Tx	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value
Liver toxic medications	80							78	0.77				
Diagnosed alcohol abuse	9	11	0.82	6	0.61	11	0.65	6	0.58	13	0.52	9	1
Diagnosed deficiency anemia	39	34	0.63					44	0.65	40	0.87	28	0.22
Diagnosed blood loss anemia	4	3	1					4	1	2	0.69	1	0.38
Diagnosed pulmonary disease	57					62	0.38			67	0.30	47	0.35
Diagnosed depression	65	69	0.70	71	0.49							58	0.50
Diagnosed diabetes	71	70	0.92	77	0.05					68	0.76	66	0.63
Diagnosed hypertension, complicated	150											139	0.36
Diagnosed hypothyroidism	62	69	0.49	67	0.60	66	0.67			56	0.53	58	0.67
Diagnosed liver disease	9	6	0.61			9	1	8	1	7	0.80	6	0.61

Table B.1. **(Continued)**

	AChEI	Gastrointestinal		Psychological		Respiratory		Hepatic		Hematologic		Death	
Baseline	Tx	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value
Diagnosed fluid and electrolyte disorder	47	40	0.36			48	0.91	33	0.1	56	0.33	43	0.63
Diagnosed paralysis	7											8	1
Diagnosed peripheral vascular disorder	72	77	0.65			70	0.85	60	0.24			64	0.42
Diagnosed metastatic cancer	1	2	1	1	1					5	0.22	0	1
Diagnosed psychoses	84	79	0.63	75	0.30							88	0.70
Diagnosed pulmonary circulation disorder	5					4	1	3	0.73	6	1	4	1
Diagnosed obesity	7	11	0.34			7	1	11	0.46			9	0.80
Diagnosed renal failure	3									2	1	2	1
Diagnosed chronic peptic ulcer disease	2	2	1	1	1					1	1	3	1

Table B.1. **(Continued)**

	AChEI	Gastrointestinal		Psychological		Respiratory		Hepatic		Hematologic		Death	
Baseline	Tx	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value	UnTx	*P* Value
Diagnosed coagulation deficiency	12	11	1					6	0.18	13	1	13	1
Diagnosed valvular disease	18					19	1			16	0.86	19	1
Diagnosed weight loss	38	33	0.50	40	0.80	39	0.90			40	0.80	35	0.80

AChEI = acetylcholinesterase inhibitors
Tx = treated
UnTx = untreated
HCUP= Healthcare Cost and Utilization Project
No. = number
ED = emergency department
NSAIDs = nonsteroidal anti-inflammatory drug
P Value = < 0.05