FINAL PROGRESS REPORT

ANTICHOLINERGICS AND COGNITIVE DECLINE IN THE ELDERLY WITH DEPRESSION

TITLE: Anticholinergics and Cognitive Decline in the Elderly with Depression

PRINICIPAL INVESTIGATOR: Aparasu, Rajender R.[1]

TEAM MEMBERS: Chen, Hua[1]; Johnson, Michael L.[1]; Carnahan, Ryan M.[2]; Chatterjee, Satabdi[1]; Bali, Vishal[1]

ORGANIZATION: [1]University of Houston, [2]University of Iowa

INCLUSIVE DATES OF THE PROJECT: October 30, 2012 - July 31, 2018

FEDERAL PROJECT OFFICER: Deborah Perfetto

GRANT MANAGEMENT SPECIALIST: Brian L. Campbell

ACKNOWLEDGEMENT OF AGENCY SUPPORT: Agency for Healthcare Research and Quality

GRANT NUMBER: 1R01HS021264-01A1

ABSTRACT

PURPOSE: Using the previously validated Anticholinergic Drug Scale (ADS), the study evaluated the central adverse effects profile of medications with significant anticholinergic activity in elderly residents with depression. The central adverse effects included dementia, cognitive impairment, hip/femur fracture, and all-cause mortality associated with anticholinergic use.

SCOPE: Despite significant use of anticholinergic medications in elderly nursing home residents, little is known about the adverse impact of these agents in the elderly with depression, a highly vulnerable patient population.

METHODS: A population-based, nested, case-control study was conducted using 2007-2010 Minimum Data Set (MDS)-linked Medicare data to examine the risks of dementia, mild-to-moderate cognitive impairment, fractures, and mortality with anticholinergic use. The base cohort included Medicare beneficiaries aged ≥65 years with depression as of 2007 and with any MDS assessment in 2007. For each aim, cases (with the outcome) were matched to controls (without the outcome) on age and sex using incidence density sampling. Prescription of clinically significant anticholinergic medications (ADS level 2/3) preceding the event date formed the primary exposure. Conditional logistic regression models stratified on matched case-control sets were used to assess each outcome after controlling for potential risk factors.

RESULTS: After adjusting for other risk factors, clinically significant anticholinergic use was associated with increased risks of dementia (odds ratio [OR], 1.26; 95% confidence interval [95% CI], 1.22-1.29), fractures (OR, 1.14; 95% CI, 1.11-1.17), and mortality (OR, 1.31; 95% CI, 1.28-1.34). An increased risk of mild-to-moderate cognitive impairment was also observed with a cumulative ADS score of 3 or more at 60 days (OR 1.16; 95% CI, 1.04-1.30) before the event date.

KEYWORDS: Anticholinergic; Elderly; Nursing home; Depression; Cognitive impairment; Dementia; Fractures; Mortality

PURPOSE

Using the previously validated Anticholinergic Drug Scale (ADS), the proposed study evaluated the central adverse effects profile of medications with significant anticholinergic activity in elderly residents with depression. Specific aims were to:

1. Examine the risk of dementia associated with clinically significant anticholinergics,
2. Assess the impact of clinically significant anticholinergics on cognitive performance, and
3. Evaluate other significant central adverse effects of clinically significant anticholinergics.

A population-based, nested, case-control study was conducted using 2007-2010 Minimum Data Set (MDS)-linked Medicare data to test the following research hypotheses:

(i) For specific aim 1, the risk of developing dementia will be greater in users of clinically significant anticholinergics versus non-users;
(ii) For specific aim 2, there will be a greater risk of mild-to-moderate cognitive impairment in users of clinically significant anticholinergics versus non-users; and
(iii) For specific aim 3, the risk of hip/femur fracture will be greater in residents using clinically significant anticholinergics versus non-users (3a), and the risk of all-cause mortality will be greater in residents using clinically significant anticholinergics versus non-users (3b).

SCOPE

Medications with anticholinergic properties belong to a wide range of therapeutic categories.[1-3] Several anticholinergic medications for diseases like irritable bowel syndrome, Parkinson's disease, urinary incontinence, and motion sickness provide their intended therapeutic effect by blocking the muscarinic receptors. Other medication classes, such as antidepressants, antipsychotics, and antihistamines, have considerable unwanted anticholinergic effects that are not related to their therapeutic effects.[4] Anticholinergic drugs are

often nonselective; consequently, their prolonged use may lead to severe central adverse events, such as cognitive impairment or dementia.[5,6] Several studies have examined the risk of cognitive decline with anticholinergic medication use in elderly patients and found that anticholinergic use was consistently associated with poor cognitive performance in various settings.[7-12] However, little is known regarding the central adverse effects of anticholinergic medications on nursing home residents with depression, a major risk factor for dementia. [13]

Although centrally mediated anticholinergic activity can lead to sedation, confusion, and, consequently, falls or fractures, few studies have evaluated this association using population-based data sources. Falls and related fractures constitute a significant public health concern among the elderly.[14] The rate of falls in nursing homes is twice as high as that in the community.[15] Approximately 1.4 million, or 5%, of the US population aged 65 years and above reside in nursing homes.[16] However, nursing home residents account for 20% of deaths occurring from falls. Around 10-20% of nursing home falls cause serious injuries; 2-6% of the falls result in fractures.[17] Medications are considered as a potentially modifiable risk factor for falls and fractures. A meta-analysis found that use of benzodiazepines, antipsychotics, and antidepressants was consistently associated with risk of falls and fractures.[18] Some commonly used antidepressants and antipsychotics possess a high degree of anticholinergic activity.[19] However, limited evidence exists regarding the risk of fractures associated with anticholinergics.[20-26]

At the time of the study, few studies had evaluated the association between anticholinergic exposure and mortality.[27-31] Except for the study by Panula et al. (2009), which found increased risk,[27] other studies by Wilson et al. (2011),[28] Kumpula et al. (2011),[29] Agar et al. (2010),[30] and Uusvaara et al. (2011)[31] did not report a statistically significant association between anticholinergic use and mortality among the elderly. Recently, a study by Juola et al. (2016) found that medications with anticholinergic properties were not associated with mortality in the elderly living in Finnish assisted living facilities and nursing homes.[32] However, studies in other vulnerable populations have found a significant association between anticholinergic use and mortality.[33-34] Overall, studies evaluating mortality risk with anticholinergic use have been conducted in various settings in diverse samples of patients, and several of them were small-scale studies that collected data from independent academic centers or geriatric units.[30,34-36] Overall, the findings of mortality risk with anticholinergic use have not been consistent, and none were conducted in an institutionalized population in the United States (US).

In light of the increasing concerns regarding the cognitive and clinical safety profiles of anticholinergic medications in the elderly, the current study used a population-based, nested, case-control design to evaluate the cognitive impact of anticholinergics in the above population and further examined the risks of fractures and all-cause mortality in these patients. The research focused on elderly nursing home residents with depression, because underlying diseases like depression can make the elderly more susceptible to centrally mediated effects of anticholinergics as a result of significant cognitive deficits associated with the disease. Also, depression is among the most common mental disorders in nursing homes, with estimates ranging from 11% to as high as 78%.[37] Previous studies reported that over 50% of nursing home residents use anticholinergic medications.[38-41] Therefore, the current study was conducted to provide a strong evidence base regarding the central adverse events of potent anticholinergic medications in elderly nursing home residents with depression.

METHODS

Data Sources

The rich longitudinal data from the Medicare and Minimum Data Set (MDS) for 4 years (2007-2010) and from all states were used to achieve the study objectives. Elderly persons aged 65 years or older are usually covered by Medicare. Medicare Part A provides hospital coverage, and supplementary medical insurance is offered through Part B.[42,43] Part A coverage for Medicare beneficiaries is automatic for eligible elderly persons, but the Part B premium requires payment. Part A covers inpatient care, including hospital care, initial care in skilled nursing facilities, hospice care, and some home healthcare. Part B covers services such as laboratory, ambulance, outpatient mental health, and some preventive and wellness care services including physical exams, wellness care, and other medical services that are not included in Part A. Part D, launched in 2006, provides prescription benefits for Medicare beneficiaries, but its structure differs from Part A and B benefits. For Part D, Medicare enrollees sign up for prescription drug plans administered by a private third party payer, such as a pharmaceutical benefit management company or health insurer.

In 2010, Medicare provided coverage for 39 million elderly persons aged 65 years or older.[44,45] About 95% of these beneficiaries have Part B coverage, and 27.6 million beneficiaries were enrolled in a Part D plan in 2010. Medicare data files are available as Research Identifiable Files and a Limited Data Set from the CMS upon request. The Research Data Assistance Center (ResDAC) is a CMS contractor that provides free assistance to researchers in using Medicare data.[46] Medicare Standard Analytical Files (SAFs) are available on a per-state and per-year basis from the CMS. These data files are restricted to claims submitted by fee-for-service (FFS) enrollees, and they do not include patients from Medicare managed care plans. SAFs include specific files on inpatients, outpatients, skilled nursing homes, home health, hospice, carriers, and durable medical equipment as well as the MedPAR File, Denominator File, Vital Status File, and Part D Files. The Part D files include enrollment, prescription event data, and a Part D characteristics file.[47] The current study research involved Medicare Parts A, B, and D from the Chronic Condition Data Warehouse (CCW). The CCW files consist of Medicare Provider Analysis and Review (MEDPAR) files (Part A), outpatient and carrier files (Part B), prescription claims filed (Part D), and a Master Beneficiary Summary File (MBSF) that includes a Chronic Condition (CC) segment file. The MBSF includes information on each enrollee's demographic characteristics, such as age, sex, race, and monthly and yearly enrollment in Medicare parts A, B, and D for each member during each year of the study period.[42] The CC segment of the MBSF consists of 27 disease-specific variables that indicate treatment of the condition of interest. The conditions are identified using a claims-based algorithm that includes yearly, mid-yearly, and ever flags for each condition. Additional details regarding the above datasets can be found elsewhere.[42,43]

The multiyear Minimum Data Set (MDS) linked with Medicare claims data was used to achieve the study objectives. The MDS is a national, standardized assessment tool that forms the foundation of a comprehensive assessment of all residents in federally (Medicaid and Medicare) certified nursing home facilities.[48,49] The MDS captures extensive information on individual residents that includes not only demographic characteristics, medical diagnoses, treatments, and source of payment but also data on physical and psychosocial functioning, behavioral symptoms, use of psychosocial intervention programs, physical restraints, and more. All Centers for Medicaid & Medicare Services (CMS)-certified nursing homes are required to complete comprehensive MDS assessments on each resident admission annually and when the resident shows "significant change in status." A subset of the full MDS assessment is conducted quarterly. The admission assessment in MDS is completed within 14 calendar days of admission to the facility, and the annual assessment is completed within 366 days of the admission assessment but not more than 92 days from a quarterly assessment.

The MDS contains over 350 variables designed to provide extensive clinical and assessment data for individual residents, including physical and psychosocial functioning, clinical diagnosis, treatments, and mental health services along with demographics and payer sources.[48,49] Most of these data elements reflect a resident's condition during the 7 days prior to the assessments. They are documented by the nursing staff, who are trained in MDS standardized assessments, and then submitted electronically. The MDS also captures information on selected medication exposure; however, data on exposure to other medication classes, individual medications, and doses are not captured in MDS. Thus, claims data from Medicare are essential for providing complete diagnostic and utilization histories. Previous studies reported strong inter-rater reliability and internal consistency of scales used in MDS assessments.[50,52] The MDS data received by the researcher contain two file types, the individual assessment data and the MDS facility file. The MDS assessment data contain individual-level assessment data, and the facility file contains basic-level institutional information about every facility represented in the assessment data.

Combining multiyear Medicare claims data with MDS provides unique opportunities to examine comparative safety and effectiveness of not only drugs classes but also individual medications. This study used data files involving 100% of the national cohort of elderly nursing home residents with depression. Therefore, MDS linked to Medicare files using a unique patient identifier provided detailed longitudinal information on residents, including comorbidities, co-medications, duration of therapy, and severity of illness as well as other clinical data, to achieve the study objectives. This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

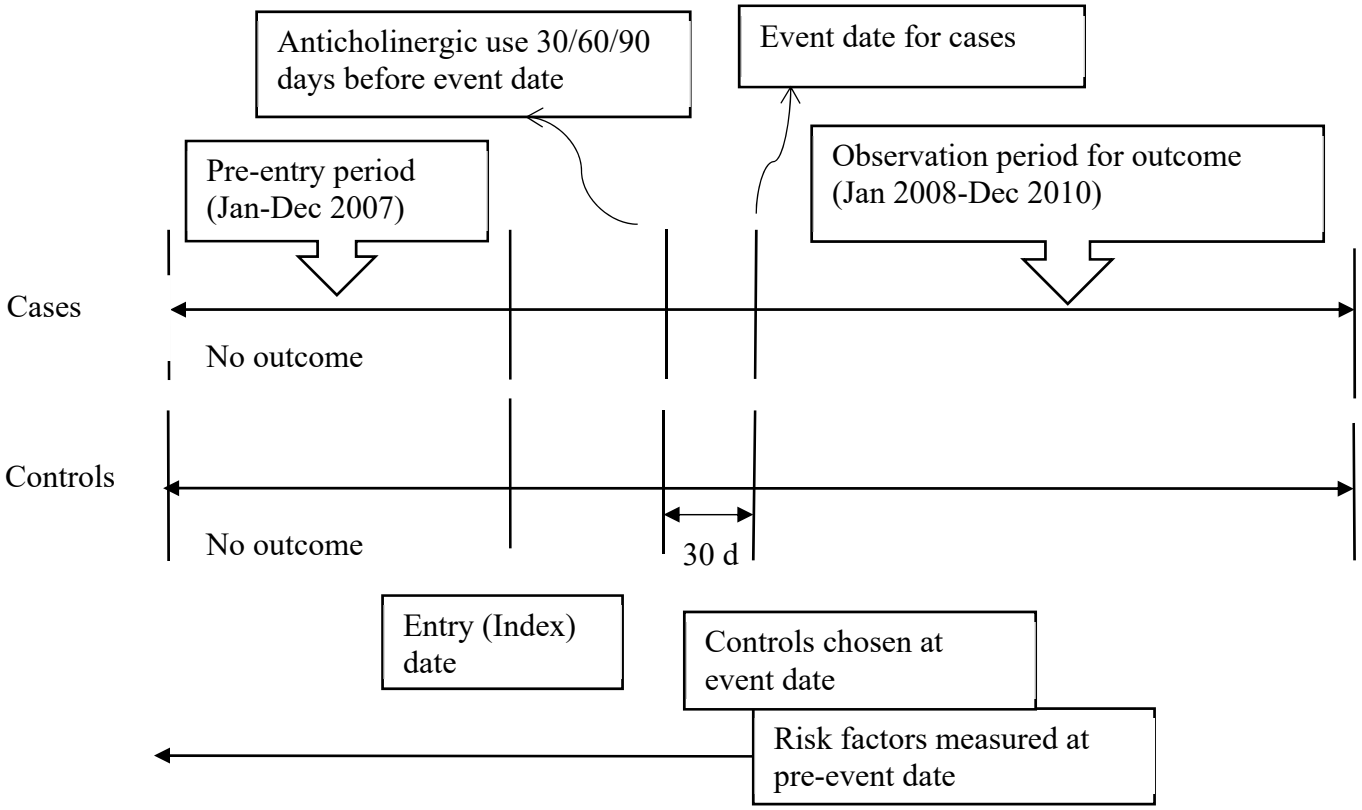
Study Design and Sample

The study used a population-based, nested, case-control design within a cohort of elderly patients with depression to achieve the study objectives. The nested design was the study design of choice, as the study focused on a defined source population of elderly patients with depression, and the anticholinergic exposure consisted of drugs from a wide range of therapeutic categories.[1] The nested, case-control design is a well-established study design for studying multiple drug exposures in epidemiological research.[53-55] The base population, from which cases and controls were sampled, had at least one MDS assessment, had depression based on the CCW definition, and were 65 years or older at the time of the depression diagnosis (base period). Thus, the sample included individuals who had resided in a nursing home but were not necessarily current nursing home residents. The index date for the study was defined as the study entry date of the patients into the base cohort. Figure 1 shows a schematic representation of the study design.

Identification of Cases and Controls

For specific aim 1, cases were identified as depression patients who had an incident diagnosis of dementia and related disorders based on CCW files following entry into the base cohort. The event date for the cases was defined as the date of the first ever diagnosis of dementia. The cases were ascertained any time between the start of follow-up (January 1, 2008) and study end date (December 31, 2010). Controls were identified from the study base cohort of depression patients using incidence density sampling. In the incidence density sampling methodology, the cohort is sampled throughout the study period.[56] Controls are sampled from the base cohort at any given time at a rate that is proportional to the disease incidence rate at that time. The use of incidence density sampling in this study entailed that potential controls for the study were those who remained in the risk set on the date of dementia diagnosis for the corresponding case.[57] Cases and controls were matched on age (±1 year) and sex. In this study, four controls were selected per case at random, with a potential for replacement.[56-57] That is, a subject could serve as a control for more than one case and could later become a case if he/she was diagnosed with dementia.

Figure 1: Schematic representation of the nested, case-control study



For specific aim 2, the base population, from which cases and controls were sampled, was 65 years or older, had at least one MDS assessment between 2007-2010, had a depression diagnosis based on the CCW file between 2007 and 2010, had intact cognition (MDS cognition score of 0 or 1), was not comatose, and did not have dementia based on MDS in 2007 (base period). Cases for the study were identified as patients who had

mild-to-moderate cognitive impairment, defined by score of 2-4 on the MDS cognition scale.[51,58] The event date for the cases was defined as the date of the first occurrence of mild-to-moderate cognitive impairment. The cases were ascertained anytime between the start of follow-up (January 1, 2008) and study end date (December 31, 2010). Residents with moderate-to-severe impairment (MDS cognition score 5-8) and severe-to-very severe impairment (MDS cognition score 9-10) were excluded from the case definition, because these patients usually suffer from irreversible worsening of memory functioning and activities of daily living, pronounced disability, and feeding problems; therefore, they present with a poor prognosis,[59] which is likely to lower life expectancy and influence oral administration of medications. Controls included those with intact cognition from the study base cohort using incidence density sampling. Cases and controls were matched on age (±1 year) and sex. In this study, one control was selected per case at random, with a potential for replacement.

For specific aim 3(a), the base population had at least one MDS assessment between 2007 and 2010, had depression based on the CCW definition as of 2007, was aged 65 years and older at the time of the depression diagnosis, and did not have inpatient/outpatient claim for falls/fractures in 2007. Cases were identified as patients who had an incident diagnosis of hip or femur fractures[60] after entry into the base cohort. The event date for the cases was defined as the date of the first inpatient/outpatient visit for fractures based on Medicare claims data. The cases were ascertained anytime between the start of follow-up (January 1, 2008) and study end date (December 31, 2010). Four age (±1 year) and sex-matched controls were selected per case at random, with a potential for replacement. For specific aim 3(b), cases were identified as patients who died in the nursing home anytime between the start of follow-up (January 1, 2008) and study end date (December 31, 2010).The event date for the cases was defined as the date of death. For each case, four (±1 year) and sex-matched controls were identified from the study base cohort using incidence density sampling, with replacement.

For all aims, the event date for the controls was defined as the date of entry into the study cohort plus the number of days of event-free follow-up contributed by the corresponding case.

Anticholinergic Exposure

Anticholinergic exposure was defined based on the Anticholinergic Drug Scale (ADS).[61] The ADS classifies drugs into four categories on the basis of their level of anticholinergic activity and groups them using an ordinal scale of 0 to 3. Level 0 contains drugs with no known anticholinergic activity; level 1 includes drugs with potential anticholinergic activity, as evidenced by receptor binding studies; level 2 includes drugs for which anticholinergic adverse events are sometimes noted, usually at higher doses; and level 3 indicates drugs with marked anticholinergic activity. The ADS scores have shown to be significantly associated with serum anticholinergic activity.[62] The primary exposure definition for each aim is detailed below:

For specific aims 1 (risk of dementia) and 3a (risk of fractures), the primary exposure was defined as a prescription of higher-level anticholinergic medication (level 2/3) 30 days preceding the event date. Patients who were not exposed to these medications 30 days before the case event were non-users and formed the reference group.

For specific aim 2 (risk of cognitive impairment), the anticholinergic burden was calculated by summing the ADS scores of all the individual anticholinergic drugs taken by each patient at 30 days preceding the event date. Higher cumulative anticholinergic burden was defined as a score of 3 or more; consequently, patients whose cumulative scores were <3 formed the reference group.

For specific aim 3b (mortality), the primary exposure was defined as a prescription of higher-level anticholinergic medication (level 2/3) 60 days preceding the event date. Consequently, patients who were not exposed to these medications 60 days before the event date were defined as non-users and formed the reference group.

Central Adverse Outcomes

The primary outcomes in the study were dementia, mild-to-moderate cognitive impairment, hip/femur fractures, and all-cause mortality.

Dementia cases were defined based on incident dementia diagnosis, using the CCW files, anytime between January 1, 2008, and December 31, 2010.

Mild-to-moderate cognitive impairment was defined by a score of 2-4 on the MDS cognition scale between January 1, 2008, and December 31, 2010. The MDS cognition scale measures cognition on an 11-point scale ranging from 0 (intact cognition) to 10 (very severe impairment).[51,58] This scale assesses various domains of cognition, such as memory, orientation, etc., and is a valid tool for measuring cognition in nursing homes.[51,52]

Fracture was defined by ICD-9-CM codes 820 and 821[60] and was ascertained between January 1, 2008, and December 31, 2010.

All-cause mortality was measured as the occurrence of death in nursing home between the start of follow-up (January 1, 2008) and the study end date (December 31, 2010).

Other covariates

In addition to matching on age and sex, other variables were risk factors of each outcome and were controlled for in the analyses. Variables were limited to their availability in the Medicare and MDS databases.

For specific aim 1 (risk of dementia), based on an evidence-based report recently released by Agency for Healthcare Research and Quality (AHRQ),[63] other conditions included hypertension; hyperlipidemia; diabetes; and use of medications, including antihypertensive medications, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. Additionally, duration of depression was used as a covariate and was categorized as 0-2 years, >2-5 years, and >5 years based on the earliest date of depression diagnosis for the beneficiary as recorded in the CCW files. All medical diagnoses were captured using the CCW files 1 year before the event date, and co-medications were captured 30 days before the event date using Medicare Part D data.

For specific aim 2 (risk of mild-to-moderate cognitive impairment), the medical comorbidities captured were hyperlipidemia, diabetes, hypertension, chronic heart failure, stroke, acute myocardial infarction, ischemia, cerebrovascular events, mood disorders, schizophrenia, anxiety, Parkinson's disease, insomnia, and movement disorders. Use of medications, such as antihypertensive medications (like ACE inhibitors or ARBs), statins, and psychotropic medications that were not scored on the ADS scale and were likely to affect cognition, were included. All medical diagnoses were captured using the CCW files and MEDPAR inpatient and outpatient files 1 year before the event date, and co-medications were captured 30 days before the event date using Medicare Part D data.

For specific aim 3a (risk of fractures), additional covariates consisted of medications and medical conditions based on their association with fractures. The medications included use of cardiovascular agents and psychotropic agents (30 days before the event date) based on previous literature.[18] The medical conditions included mood disorder, dementia, other mental health disorders (anxiety, schizophrenia), insomnia, Parkinson's disease, movement disorders, rheumatoid arthritis, osteoarthritis, and osteoporosis. Additionally, duration of depression was used as a covariate and was categorized as 0-2 years, >2-5 years, and >5 years based on the earliest date of depression diagnosis for the beneficiary as recorded in the CCW files. All medical diagnoses were captured 1 year before the event date, and co-medications were captured 30 days before the event date using Medicare Part D data.

For specific aim 3b (risk of all-cause mortality), covariates included medical conditions identified by the Charlson Comorbidity Index. The Charlson Comorbidity Index is a validated risk adjustment tool that classifies or weighs patients' comorbid conditions to predict short- and long-term mortalities using medical records.[64-65] Additionally, duration of depression was used as a covariate and was categorized as 0-2 years, >2-5 years, and >5 years based on the earliest date of depression diagnosis for the beneficiary as recorded in the CCW files. All medical diagnoses were captured using the CCW files 1 year before the event date, and co-medications were captured 60 days before the event date using Medicare Part D data.

Statistical Analyses

The differences in covariate distributions between the cases and controls were assessed using chi-square tests for categorical variables and t-tests for continuous variables. For each outcome, a conditional logistic regression model stratified on the matched case-control sets was utilized, with exposure to ADS levels 2 or 3 as the main independent variable and other risk factors of the outcome as additional explanatory variables. Because this was a nested, case-control study in which cases were ascertained as per the objective, there were different study samples for each specific aim, as opposed to a retrospective study design with a defined cohort based on drug exposure. For each objective, separate models were used to evaluate anticholinergic exposure based on levels 2 or 3 of the ADS (excluding level-3 drug users from the level 2-specific analysis and vice versa) and ADS score of 3 or more as the main independent variables. The odds ratios (ORs) that estimate the risk associated with anticholinergic use, along with the 95% confidence intervals (95% CIs), are analogous to time-to-event analyses in cohort studies, because incidence density sampling was used. [66]

Sensitivity Analyses

For specific aim 1 (risk of dementia), the first sensitivity analysis included use of any of the anti-dementia drugs, namely acetylcholinesterase inhibitors (donepezil, tacrine, rivastigmine, and galantamine) and the n-methyl-d-aspartate antagonist memantine, as additional markers for dementia. The event date among the cases was defined as the date of dementia diagnosis or the date of medication initiation, whichever occurred earlier. In the second sensitivity analysis, the base cohort was defined as elderly patients with depression (based on MDS or CCW files) who did not have dementia in 2007 and who had an MDS assessment in 2007. Cases for this analysis were ascertained based on dementia diagnosis in the MDS or CCW files. For those who had both CCW and MDS assessments, the earlier date of dementia diagnosis was chosen as the event date. A third sensitivity analysis was performed and included patients who had depression diagnosis confirmed by both MDS and CCW files. As before, the earlier date of occurrence was considered the event date. Also, patients were excluded if they had a dementia diagnosis based on either of the files in 2007. In the fourth sensitivity analysis, cases were selected if they had dementia based on the MDS only. For the purpose of this analysis, patients were excluded from the base cohort if they had a dementia diagnosis based on MDS and CCW in 2007. Additionally, this definition ensured that the patient was a nursing home resident at the time of case ascertainment, and controls were selected from the nursing home base cohort.

For specific aim 2 (risk of mild-to-moderate cognitive impairment), in order to rule out that the study findings were influenced by choice of the anticholinergic scale, the analysis was repeated using the Anticholinergic Cognitive Burden (ACB) score.[67] The ACB scale places each of the medications into a possible or definite anticholinergic category based on the severity of cognitive effects, namely into one of three groups (1, mild; 2, moderate; 3, severe). The added total score reflects the accumulated cognitive burden contributed by the combination of all medications with anticholinergic activities; a score of 3 or greater is considered clinically relevant. The current study also examined the association of cumulative anticholinergic burden and cognitive decline. The total anticholinergic burden score for each patient was calculated by summing the ACB scores of all the individual drugs taken by the patient. Similar to ADS burden, the analyses focused on those with three or more cumulative scores and were conducted for 30 days, 60 days, and 90 days preceding the event date.

For specific aim 3a (risk of fractures), the operational definition of anticholinergic exposure was extended to 60 days and 90 days before the event date to assess the robustness of the study findings. In addition, patients who experienced falls or fractures in the year 2007 were also excluded in the main analysis, because prior falls history can mediate future fracture risk in the main 30-day analysis. To evaluate whether excluding those with a fall history would change the risk estimate, an additional sensitivity analysis was conducted excluding only those patients who experienced fractures during the baseline period (2007). Because prior studies on fractures that validated case definitions mainly considered inpatient hospitalizations, the analysis was also repeated using only cases with inpatient claims for fracture. Also, patients who resided in long-term care, skilled nursing facilities, and home health settings 3 months before the event date were excluded from the analysis to ensure the continuum of care. Finally, the analysis was repeated by using cumulative burden, defined based on the ADS as well as the ACB scale to assess the robustness of the study findings.

For specific aim 3b (risk of all-cause mortality), the operational definition of anticholinergic exposure was extended to 90 days before the event date to assess the robustness of the study findings. However, sensitivity analyses were conducted whereby anticholinergic exposures 60 days and 90 days before the event date were assessed after excluding prescription records 30 days before the event date. This evaluated the potential impact of end-of-life treatments on the findings, as anticholinergics are used to manage end-of-life symptoms, such as terminal respiratory secretions.[68]

Subgroup Analyses

In order to test whether the effects of anticholinergics hold true for drug classes, a retrospective, propensity score-matched cohort study was conducted to examine the risks of dementia, cognitive impairment, fractures, and all-cause mortality with the use of paroxetine (anticholinergic level-2 drug) versus other nonanticholinergic selective serotonin reuptake inhibitors (SSRIs). The analyses focused on antidepressants, because the cohort consisted of patients with depression. The study population included elderly depressed nursing home patients who were new users of SSRIs based on 2007-2010 MDS-linked Medicare data. Index SSRI exposure was measured using prescription Medicare Part D claims data. SSRIs were classified into paroxetine and other SSRIs. Other SSRIs included sertraline, citalopram, fluoxetine, fluvoxamine, and escitalopram. Patients were followed for a maximum of 2 years after index SSRI use. The risks of dementia, fractures, and all-cause mortality were modeled using separate robust Cox proportional hazards models to account for the clustering within matched paroxetine and other-SSRI users. For the cognitive impairment objective, the primary outcome was cognition score based on the MDS cognition scale, and the repeated-measure mixed model was used to examine the effect of paroxetine on cognition after controlling for other factors.

RESULTS AND DISCUSSION

Risk of Dementia[69]

The study population of depression patients consisted of 28,388 cases who developed dementia between January 1, 2008, and December 31, 2010, and 113,552 controls (incidence density ratio, 1:4) during the same time period. As expected by incidence-density matching, the distribution of age and gender was similar across cases and controls. Overall, the use of medications with clinically significant anticholinergic properties (ADS level 2/3) was significantly higher among cases than controls (19.19% vs 16.45%; p<.0001). Level-2 anticholinergic drugs were more often prescribed in cases than in controls (7.79% vs 5.75%; p<.0001). Among the cases, the commonly prescribed drugs were paroxetine (695, 2.46%), quetiapine (966, 3.42%), solifenacin (257, 0.91%), and darifenacin (168, 0.59%). Use of level-3 medications was also higher in cases than in controls (10.89% vs 10.18%; p<.0001). The most commonly prescribed level-3 medications among the cases were oxybutynin (557, 1.97%), tolterodine (553, 1.96%), promethazine (357, 1.12%), olanzapine (390, 1.38%), meclizine (276, 0.98%), amitriptyline (248, 0.88%), and hydroxyzine (219, 0.78%).

After controlling for other factors, the main analysis revealed that exposure to higher-level anticholinergic medications was associated with a moderately higher risk of dementia (OR, 1.26; 95% CI, 1.22-1.29) compared with no exposure (Table 1). Level-specific analysis indicated that use of level-2 medications was associated with a 37% higher risk of dementia compared with no use (OR, 1.37; 95% CI, 1.31-1.44), whereas level-3 use was associated with a 15% higher risk (OR, 1.15; 95% CI, 1.10-1.19). The risk estimates for dementia remained consistent for both the study groups across different study periods and levels of anticholinergic potency.

The main study findings did not change when dementia was defined based on the CCW dementia flag or the use of anti-dementia medications (level 2/3 use vs no use: OR, 1.27; 95% CI, 1.24-1.30). The study estimates were small but significant when either the MDS or the CCW definition was used to define base cohort and dementia cases (level 2/3 use vs no use: OR, 1.08; 95% CI, 1.05-1.11). The strength of the findings increased when both MDS and CCW files were used to define the base cohort and capture dementia cases (level 2/3 use vs no use: OR, 1.47; 95% CI, 1.38-1.56). Additionally, when only MDS files were used to capture dementia, the study found a higher estimate for overall anticholinergic use as well as level-specific analyses (level 2/3 use vs no use: OR, 1.49; 95% CI, 1.42-1.58).

Table 1: Risk of Dementia Associated With Use of Higher-Level Anticholinergic (ADS Levels 2/3) Medications Versus No Use Across Various Exposure Time Periods

Variable ǂ	Adjusted Odds Ratio, OR	95% Confidence Interval, 95% CI	P value
Model for anticholinergic use 30 days before event date			
Level 2/3 use vs no use (28,838 cases and 113,552 controls)	1.26	1.22-1.29	<.0001*
Level 2 use vs no use (23,274 cases and 95,322 controls)	1.37	1.31-1.44	<.0001*
Level 3 use vs no use (24,509 cases and 101,813 controls)	1.15	1.10-1.19	<.0001*
Model for anticholinergic use 60 days before event date			
Level 2/3 use vs no use (28,838 cases and 113,552 controls)	1.35	1.31-1.39	<.0001*
Level 2 use vs no use (21,464 cases and 90,002 controls)	1.45	1.38-1.51	<.0001*
Level 3 use vs no use (24,796 cases and 103,792 controls)	1.23	1.18-1.27	<.0001*
Model for anticholinergic use 90 days before event date			
Level 2/3 use vs no use (28,838 cases and 113,552 controls)	1.36	1.32-1.39	<.0001*
Level 2 vs no use (20,427 cases and 86,703 controls)	1.42	1.36-1.49	<.0001*
Level 3 vs no use (22,830 cases and 97,201 controls)	1.24	1.20-1.28	<.0001*

* indicates statistically significant values at alpha level of 0.05

ǂ The models were adjusted for demographic characteristics like race; comorbidities like diabetes, hyperlipidemia, and hypertension; co-medications like statins, ACE/ARBs; and duration of depression.

Risk of Cognitive Impairment[70]

The study population consisted of 3,707 cases with mild-to-moderate cognitive impairment between January 1, 2008, and December 31, 2010, and 3,707 controls without impairment during the same time period. As expected by incidence-density matching, the distribution of age and sex was similar across cases and controls. Overall, the cumulative anticholinergic burden was significantly higher among cases than among controls (27.41% vs 24.76%; p=0.009). Among cases, the commonly prescribed ADS level-2 drugs were paroxetine (45, 1.21%), quetiapine (69, 1.86%), solifenacin (20, 0.54%), and cyclobenzaprine (18, 0.49%). The most commonly prescribed ADS level-3 medications among cases were oxybutynin (44, 1.19%), tolterodine (51, 1.38%), promethazine (44, 1.19%), olanzapine (37, 1.00%), meclizine (27, 0.73%), amitriptyline (20, 0.54%), and hydroxyzine (21, 0.57%).

The multivariate analysis showed that cumulative exposure to anticholinergics was not associated with mild-to-moderate cognitive impairment (OR, 1.07; 95% CI, 0.95-1.21) when anticholinergic exposure was captured 30 days before the event date. When the duration of exposure was expanded, a cumulative ADS score of 3 or more was associated with significantly increased risks of cognitive impairment at 60 days and 90 days before the event date (OR for 60-day exposure, 1.16; 95% CI, 1.04-1.30; model for 90-day exposure, 1.28; 95% CI, 1.14-1.44) (Table 2).

Table 2: Risk of Mild-to-Moderate Cognitive Impairment Associated with Cumulative Anticholinergic Score of 3 or More Versus <3 Across Various Exposure Time Periods based on the Anticholinergic Drug Scale (ADS)

Variable ǂ	Adjusted Odds Ratio, OR	95% Confidence Interval, 95% CI	P value
Cumulative anticholinergic use 30 days before event date			
ADS score of 3 or more vs <3	1.07	0.95-1.21	0.25
Cumulative anticholinergic use 60 days before event date			
ADS score of 3 or more vs <3	1.16	1.04-1.30	0.008*
Cumulative anticholinergic use 90 days before event date			
ADS score of 3 or more vs <3	1.28	1.14-1.44	<.0001*

* indicates statistically significant values at alpha level of 0.05

ǂ The models were adjusted for demographic characteristics like race; comorbidities like diabetes, hyperlipidemia, hypertension, chronic heart failure, acute myocardial infarction, atrial fibrillation, ischemia, stroke, cerebrovascular events, mood disorders, schizophrenia, anxiety, Parkinson's disease, insomnia, and movement disorders; and co-medications like statins, ACE/ARBs, and psychotropics.

The main findings remained consistent when anticholinergic exposure was defined using the ACB scale (OR, 1.08; 95% CI, 0.95-1.23). When the duration of anticholinergic exposure was expanded, a cumulative ACB score of 3 or more was associated with 14% (OR, 1.14; 95% CI, 1.02-1.28) and 19% (OR, 1.19; 95% CI, 1.06-1.33) increased risks of cognitive impairment at 60 days and 90 days preceding the event date, respectively.

Risk of Fractures[71]

The study population consisted of 40,452 cases that experienced fractures between January 1, 2008, and December 31, 2010, and 161,808 controls during the study period. With matching, the distribution of age and sex was similar across cases and controls. Cases significantly differed from controls with respect to nearly all the risk factors, which were adjusted for in subsequent multivariable analyses. Nearly 65.81% of the cases filled prescription for at least one anticholinergic medication 30 days before the index date, compared with 62.21% in the controls (p<.0001). Use of level-2 anticholinergic drugs was significantly higher among cases than controls (12.71% vs 11.07%; p<.0001). Overall, the use of medications with clinically significant anticholinergic properties (ADS level 2/3) was higher in cases (26.14%) than controls (23.56%, p<.0001).

After controlling for other risk factors, the results of conditional logistic regression revealed that exposure to higher-level anticholinergic medications was associated with an increased risk of fractures (OR, 1.14; 95% CI, 1.11-1.17) compared with no exposure. Level-specific analysis indicated high fracture risk with level-2 as well as level-3 medication use (level-2 anticholinergic use vs no use: OR, 1.15; 95% CI, 1.11-1.19; level-3 anticholinergic use vs no use: OR, 1.10; 95% CI, 1.07-1.5). The risk estimates for fractures increased for both the study groups across different study periods and levels of anticholinergic potency (Table 3).

Among patients with no history of fractures, exposure to high-level anticholinergics was significantly associated with fractures across all the different study periods (model for 30 days: OR, 1.15; 95% CI, 1.13-1.18; model for 60 days: OR, 1.21; 95% CI, 1.18-1.23; model for 90 days: OR, 1.22; 95% CI, 1.19-1.25). The main study findings remained consistent when cases of fractures were defined based on inpatient claims and after excluding those with prior long-term care or skilled nursing facility/home health stays. When cumulative anticholinergic burden was used to define anticholinergic exposure as a total score of 3 or more, the study findings remained unchanged (ADS scale: OR, 1.12; 95% CI, 1.09-1.14; ACB scale: OR, 1.11; 95% CI, 1.08-1.14).

Table 3: Risk of Fractures Associated with Use of Anticholinergic Medications Across Anticholinergic Levels and Time Periods

Variable ǂ	Adjusted Odds Ratio, OR	95% Confidence Interval, 95% CI	P value
Model for anticholinergic use 30 days before event date			
Level 2/3 use vs no use (40,452 cases and 161,808 controls)	1.14	1.11-1.17	<.0001*
Level 2 use vs no use (33,991 cases and 138,129 controls)	1.15	1.11-1.19	<.0001*
Level 3 vs no use (35,310 cases and 148,902 controls)	1.10	1.07-1.15	<.0001*
Model for anticholinergic use 60 days before event date			
Level 2/3 use vs no use (40,452 cases and 161,808 controls)	1.20	1.17-1.23	<.0001*
Level 2 use vs no use (32,170 cases and 132,646 controls)	1.22	1.17-1.26	<.0001*
Level 3 use vs no use (34,187 cases and 140,864 controls)	1.16	1.12-1.19	<.0001*
Model for anticholinergic use 90 days before event date			
Level 2/3 use vs no use (40,452 cases and 161,808 controls)	1.21	1.18-1.24	<.0001*
Level 2 use vs no use (31,136 cases and 129,230 controls)	1.23	1.18-1.27	<.0001*
Level 3 use vs no use (33,656 cases and 139,157 controls)	1.18	1.14-1.21	<.0001*

* indicates statistically significant values at alpha level of 0.05

ǂ The models were adjusted for demographic characteristics like race; comorbidities like dementia, mood disorders, anxiety, schizophrenia, Parkinson's disease, insomnia, cerebrovascular events, osteoarthritis, osteoporosis, and rheumatoid arthritis; co-medications like cardiovascular drugs, antidepressants, anticonvulsants, antipsychotics, benzodiazepines; and duration of depression.

Risk of All-Cause Mortality[72]

The study population consisted of 44,948 cases who died between January 1, 2008, and December 31, 2010, and 179,792 matched controls during the study period. As expected, matching resulted in similar distribution of age and sex across cases and controls. However, cases significantly differed from controls with respect to nearly all the risk factors, and all these factors were adjusted for in subsequent multivariable analyses. Nearly 73.75% (33,150) of cases filled prescriptions for at least one anticholinergic medication 60 days before the event date, compared with 66.69% (119,898) of controls (p<.0001). Use of level-2 anticholinergic drugs was significantly higher among cases than controls (12.71% vs 11.07%; p<.0001). Overall, the use of medications with clinically significant anticholinergic properties (ADS level 2/3) was higher in cases than controls (31.43% vs 26.39%; p<.0001). The most frequently used anticholinergics among cases and controls, respectively, were atropine (676, 1.50% vs 128, 0.07%), benztropine (281, 0.63% vs 1,236, 0.69%), cyclobenzaprine (251, 0.56% vs 940, 0.52%), cyproheptadine (208, 0.46% vs 483, 0.27%), darifenacin (110, 0.24% vs 713, 0.40%), dicyclomine (112, 0.25% vs 526, 0.29%), hydroxyzine (536, 1.19% vs 2,117, 1.18%), olanzapine (1,430, 3.18% vs 4,480, 3.05%), oxybutynin (744, 1.66% vs 4,266, 2.34%), and paroxetine (1,065, 2.37% vs 4,400, 2.45%).

After controlling for other risk factors, the results of conditional logistic regression revealed that exposure to clinically significant anticholinergic medications was associated with a modest increase in risk of death (OR, 1.31; 95% CI, 1.28-1.34) compared with no exposure. Level-specific analysis indicated significantly higher mortality risk with only level-3 medication use (ADS level-2 anticholinergic use vs no use: OR, 1.02, 95% CI, 0.98-1.06; ADS level-3 anticholinergic use vs no use: OR, 1.46, 95% CI, 1.42-1.51). The risk estimates remained consistent for all the study groups when anticholinergic exposure was assessed 90 days before the event date (Table 4).

Table 4. Risk of All-Cause Mortality Across Anticholinergic Drug Scale (ADS) Levels and Time Periods

Variable [a]	Adjusted Odds Ratio, OR	95% Confidence Interval, 95% CI	P value
Model for anticholinergic use 60 days before event date			
ADS level 2/3 use vs no use (44,948 cases and 179,792 controls)	1.31	1.28-1.34	<.0001*
ADS level 2 use vs no use (35,123 cases and 150,655 controls)	1.02	0.98-1.06	0.28
ADS level 3 use vs no use (38,907 cases and 156,431 controls)	1.46	1.42-1.51	<.0001*
Model for anticholinergic use 90 days before event date			
ADS level 2/3 use vs no use (44,948 cases and 179,792 controls)	1.37	1.34-1.40	<.0001*
ADS level 2 vs no use (33,926 cases and 147,580 controls)	1.10	1.06-1.14	<.0001*
ADS level 3 vs no use (38,158 cases and 155,090 controls)	1.50	1.46-1.55	<.0001*

* indicates statistically significant values at alpha level of 0.05
[a] The models were adjusted for demographic characteristics such as race; comorbidities such as myocardial infarction, heart failure, vascular diseases, dementia, cerebrovascular events, rheumatological diseases, mild liver disease, pulmonary disorders, renal diseases, ulcer, hemiplegia, diabetes, cancer, metastasis, and moderate/chronic liver disease; and duration of depression.

The study findings did not vary when anticholinergic exposure was defined using ACB (ACB level-2/3 use vs no use: OR, 1.17; 95% CI, 1.15-1.22; ACB level-2 anticholinergic use vs no use: OR, 1.28; 95% CI, 1.17-1.40; ACB level-3 use vs no use: OR, 1.16; 95% CI, 1.13-1.19). Additionally, when cumulative anticholinergic burden was used to define anticholinergic exposure as a total score of 3 or more, the study findings remained unchanged (ADS scale: OR, 1.28; 95% CI, 1.25-1.31; ACB scale: OR, 1.14; 95% CI, 1.10-1.16). The risk estimates remained significant when prescription records 30 days before the event date were excluded. Finally, the main study findings were similar when the analysis was repeated excluding those residing in SNFs, long-term care, or home health settings 90 days before the event date.

Cognitive and Clinical Safety with Use of Paroxetine Versus Other SSRIs[73-76]

A propensity score-matched retrospective cohort study was conducted using 2007-2010 Minimum Data Set-linked Medicare data to test whether the effects of anticholinergics hold true for drug classes. Specifically, risks of dementia, cognitive impairment, fractures, and all-cause mortality with the use of paroxetine (anticholinergic level-2 drug) versus other nonanticholinergic selective serotonin reuptake inhibitors (SSRIs) were evaluated. The study population included elderly, depressed nursing home patients who were new users of SSRIs. Patients were followed for maximum of 2 years after index SSRI use. The risks of dementia, fractures, and all-cause mortality were modeled using the robust Cox proportional hazards model to account for the clustering within matched paroxetine and other-SSRI users. The repeated-measure mixed model was used to examine the effect of paroxetine on cognition after controlling for other factors.

The unmatched elderly cohort with depression included 19,952 new users of SSRIs; 1,898 used paroxetine and 18,054 used other SSRIs. In the propensity-matched cohort of 3,796 elderly patients, the unadjusted incidence of dementia was 7.5% for paroxetine and 8.6% for other SSRI users. Results from the robust Cox proportional-hazard model showed that there was no difference in the risk of dementia for paroxetine users (hazard ratio [HR], .99; 95% CI, .79-1.23) compared with the other SSRI users. These study findings were robust in multiple sensitivity analyses involving measures of MDS and anti-dementia medications. Overall, use of paroxetine was not associated with higher risk of dementia compared with the other SSRIs in the elderly nursing home patients with depression.[73]

There were 1,518 nursing home residents who met the inclusion and exclusion criteria and had at least one quarterly assessment during the follow-up. Of these, 1,081 were new users of SSRIs. Among the SSRI users, 63 (5.83%) received paroxetine and 1,018 received other SSRIs (94.17%). The baseline MDS cognition scale measures for paroxetine (n=63) and other SSRI users (n=1,018) were 2.02 (+1.85) and 2.50 (+2.39), respectively. The repeated-measure mixed model did not find statistically significant difference in cognition with the use of paroxetine (β=0.02 [95% CI, -0.16, 0.21]) compared with other SSRIs. There was no differential effect of paroxetine on cognition compared with other SSRIs.[74]

Analysis of 2007-2010 MDS-linked Medicare data yielded 57,571 new users of SSRIs between January 2008 and December 2009 after applying inclusion and exclusion criteria. Of these, 4,620 (8.02%) received paroxetine and 52,951 received other SSRIs (91.98%). Results from the propensity score matching revealed

4,620 patients in each of the two treatment groups. In total, 430 cases of hip fractures were observed in the matched cohort during the follow-up period. Of these, 213 (4.6%) cases were in the paroxetine group and 217 (4.7%) were in the other-SSRIs group. The robust Cox proportional hazard model did not find any significant difference in risk of hip fractures between paroxetine users (HR, 1.09; 95% CI, .91-1.32) and other-SSRI users. Results from the sensitivity analysis supported the main findings. Overall, there was no differential risk of hip fractures between paroxetine and other SSRIs.[75]

Analysis of 2007-2010 MDS-linked Medicare data yielded 57,571 new users of SSRIs between January 2008 and December 2009 after applying inclusion and exclusion criteria. Of these, 4,620 (8.02%) received paroxetine and 52,951 received other SSRIs (91.98%). Results from the propensity score matching revealed 4,620 patients in each of the two treatment groups. The unadjusted incidence of mortality was 269 (2.9%) for paroxetine and 288 (3.1%) for other-SSRI users in the matched cohort. Robust Cox proportional-hazard model did not find any significant difference in the risk mortality between the two groups (hazard ratio, 1.01; 95% CI, 0.86-1.19). Overall, the study did not find any significant difference in the risk of mortality between users of paroxetine and other SSRIs among elderly nursing home patients with depression. There is need for further evaluation of other adverse effects of paroxetine due to its anticholinergic effects in geriatric population.[76]

In conclusion, the new-user retrospective cohort study found that there were no statistically significant differences between paroxetine and other SSRIs with respect to dementia (hazard ratio, HR, 0.99; 95% CI, 0.79-1.23), cognition (β=0.02 [95% CI, -0.16 to 0.21]), fractures (HR, 1.09; 95% CI, 0.91-1.32), and all-cause mortality (HR, 1.01; 95% CI, 0.86-1.19).[73-76] Future studies are needed to evaluate anticholinergic effects of paroxetine.

SUMMARY FINDINGS

In summary, our research study found that anticholinergic exposure, categorized by levels as well as by cumulative score, was associated with 14%-31% higher risks of dementia, fractures, and all-cause mortality; with respect to cognition, the study found that cumulative ADS score of 3 or more was associated with modestly high risk of mild-to-moderate cognitive impairment only when anticholinergic exposure was evaluated 60 days and 90 days before the event date. The main findings were robust to multiple sensitivity analyses involving the exposure, outcome, and duration of anticholinergics. This research is among the first population-based studies that looked at relevant clinical and cognitive outcome measures that could be linked to higher-level anticholinergic exposure in elderly nursing home residents with depression. The past studies, although revealing similar findings, consisted of small study samples and were conducted at independent academic centers or evaluated outcomes in community-dwelling elderly. [8,29,30,32]

The fact that the study findings did not reveal significant differences in risk when paroxetine (ADS level-2 anticholinergic) versus other SSRIs was considered suggests that these antidepressants exhibit similar clinical and cognitive safety profiles. Nevertheless, given that anticholinergic agents have the propensity to cause adverse outcomes in the vulnerable elderly, there is a strong need to be careful before prescribing these agents. In this regard, categorical anticholinergic exposure to high-level drugs (level 2/3) as well as cumulative anticholinergic burden are modifiable risk factors; therefore, providers should evaluate the existing anticholinergic burden before initiating anticholinergic treatment in elderly nursing home residents, especially those with depression. Providers should consider effective nonanticholinergic alternatives or nonpharmacological treatments for patients with high anticholinergic burden. Reducing anticholinergic burden is critical to minimize the risk of dementia and prevent other adverse outcomes among these at-risk patients.

LIMITATIONS

Several study limitations should be acknowledged. Because dispensing data were captured using pharmacy claims, whether the patients used the dispensed medications could not be ascertained. The diagnoses data were limited to those available from the Medicare claims and MDS data. The covariates included in the conditional logistic regression model were limited to those available in the data source; thus, the presence of unmeasured confounders might have affected the study findings. However, the use of incidence density sampling and matching helped obtain closely matched controls who were at risk of each outcome at the time the cases were selected, thereby obtaining a fair sample of the base cohort. Prescription drugs used during stays at skilled nursing facilities (SNF), hospice enrollment, and hospitalizations are not generally covered by Medicare Part D. Medicare Part D also did not cover benzodiazepines (an established risk factor for fractures) during the study period, so exposure to these medications can be assumed to be under-ascertained. Although lack of this information can likely be regarded as nondifferential misclassification, this information would have been helpful in quantifying the risk of fractures associated with anticholinergic use as well as benzodiazepine use. Because some anticholinergic agents, like diphenhydramine and meclizine, are available over the counter, the use of prescription data did not accurately reflect usage of these medications. For the cognition objective, cases were defined based on the MDS cognition scale. Although it has yet to be validated to study medication-induced cognitive outcomes in the elderly population, the MDS cognition scale is quite strongly correlated with the Mini-Mental State Exam (MMSE)[52] and has been found to detect a reasonably high proportion of cognitively impaired residents in nursing homes (MDS 65% vs MMSE 70%).[58] Additionally, the study did not use a new-user design and thus may be susceptible to selection bias resulting from inclusion of prevalent anticholinergic users who tolerated these drugs. This would be expected to bias findings toward the null. Finally, the study population included elderly nursing home residents with depression; as a result, the findings may not be generalized to other populations or settings.

CONCLUSIONS

The current population-based, nested, case-control study evaluated the risk of dementia, mild-to-moderate cognitive impairment, fractures, and all-cause mortality among a cohort of elderly residents with depression and found that exposure to high-level anticholinergic medications as well cumulative exposure for prolonged duration was associated with a significantly higher risk of adverse outcomes after controlling for several risk factors. The findings remained consistent across several sensitivity analyses. The study additionally found that a cumulative anticholinergic score of 3 or more evaluated based on the ADS as well as the ACB scale was associated with increased risks. Given the safety concerns, there is a strong need to minimize anticholinergic use in this vulnerable population. Concerted efforts are need to optimize anticholinergic use in the elderly to improve quality of pharmaceutical care. Therefore, effective nonanticholinergic alternatives or nonpharmacological treatments should be used for patients with high anticholinergic burden.

REFERENCES

1. Doraiswamy PM, Husain MM. Anticholinergic drugs and elderly people: a no brainer? Lancet Neurol. 2006 May; 5(5):379-80. PMID: 16632303.
2. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med. 2000 Sep; 93(9):457-62.PMID: 11089480.
3. Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs Aging. 1993 Jul-Aug; 3(4):335-48.PMID: 8369593.
4. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry. 2001; 62 Suppl 21:11-4. PMID: 11584981.
5. Peters N. Antimuscarinic side-effects of anticholinergic medications in the elderly. Arch Intern Med. 1989; 149: 2414-20. PMID: 2684071.
6. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging. 2009; 4: 225-33. PMID: 19554093.
7. Ancelin ML, Artero S, Portet F, et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ. 2006 Feb 25;332(7539):455-9. PMID: 16452102.

8. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med. 2001 Apr 23; 161(8):1099-105. PMID: 11322844.
9. Carrière I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009 Jul 27;169(14):1317-24. PMID: 19636034.
10. Cancelli I, Beltrame M, Gigli GL, et al. Drugs with anticholinergic properties: cognitive and neuropsychiatric side-effects in elderly patients. Neurol Sci. 2009 Apr; 30(2):87-92. PMID: 19229475.
11. Kalisch Ellett LM, Pratt NL, et al. Multiple anticholinergic medication use and risk of hospital admission for confusion or dementia. J Am Geriatr Soc. 2014 Oct;62(10):1916-22. PMID: 25284144.
12. Gray SL, Anderson ML, Dublin S, et al. Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study. JAMA Intern Med. 2015 Mar; 175(3):401-7. PMID: 25621434.
13. Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. Gerontology. 2000 Jul-Aug; 46(4):219-27. PMID: 10859462.
14. Morley JE. A fall is a major event in the life of an older person. J Gerontol A Biol Sci Med Sci. 2002 Aug; 57(8):M492-5. PMID: 12145361.
15. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. Annals Intern Med. 1994; 121:442–51. PMID:8053619.
16. Harrington C, Carrillo H, Garfield R. Nursing Facilities, Staffing, Residents and Facility Deficiencies 2009 through 2014. Available at: http://kff.org/medicaid/report/nursing-facilities-staffing-residents-and-facility-deficiencies-2009-through-2014/ (Accessed April 2014).
17. Rubenstein LZ, Robbins AS, Schulman BL, et al. Falls and instability in the elderly. J Am Geriatr Soc 1988; 36:266–78. PMID: 3276771.
18. Huang AR, Mallet M, Rochefort CM, et al. Medication-related falls in the elderly: causative factors and preventive strategies. Drugs Aging 2012; 29:5: 359-76. PMID: 22550966.
19. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008 Jul; 56(7):1333-41. PMID: 18510583.
20. Aizenberg D, Sigler M, Weizman A, et al. Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: a 4-year case-control study. Int Psychogeriatr. 2002 Sep; 14(3):307-10. PMID: 12475091.
21. Wilson NM, Hilmer SN, March LM, et al. Associations Between Drug Burden Index and Falls in Older People in Residential Aged Care. J Am Geriatr Soc. 2011 May; 59(5):875-80. PMID: 21539525.
22. Nishtala PS, Narayan SW, Wang T, et al. Associations of drug burden index with falls, general practitioner visits, and mortality in older people. Pharmacoepidemiol Drug Saf. 2014 Jul; 23(7):753-8. PMID: 24723335.
23. Dauphinot V, Faure R, Omrani S, et al. Exposure to anticholinergic and sedative drugs, risk of falls, and mortality: an elderly inpatient, multicenter cohort. J Clin Psychopharmacol. 2014 Oct; 4(5):565-70. PMID: 25933790.
24. Moga DC, Carnahan RM, Lund BC, et al. Risks and benefits of bladder antimuscarinics among elderly residents of Veterans Affairs Community Living Centers. J Am Med Dir Assoc. 2013 Oct; 14(10):749-60. PMID: 23639715.
25. Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls--a prospective study in a large community-dwelling elderly cohort. BMC Geriatr. 2009 Jul 23; 9:30. PMID: 19627577.
26. Rudolph JL, Salow MJ, Angelini MC et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13. PMID:18332297.
27. Panula J, Puustinen J, Jaatinen P, et al. Effects of potent anticholinergics, sedatives and antipsychotics on postoperative mortality in elderly patients with hip fracture: retrospective, population-based study. Drugs Aging. 2009; 26(11):963-71. PMID:19848441.
28. Wilson NM, Hilmer SN, March LM, et al. Associations between drug burden index and mortality in older people in residential aged care facilities. Drugs Aging. 2012; 29: 157-65. PMID: 22276959.
29. Kumpula EK, Bell JS, Soini H, et al. Anticholinergic drug use and mortality among residents of long-term care facilities: a prospective cohort study. J Clin Pharmacol. 2011 Feb; 51(2): 256-63. PMID: 20489026.
30. Agar M, To T, Plummer J, et al. Anti-cholinergic load, health care utilization, and survival in people with advanced cancer: a pilot study. J Palliat Med. 2010 Jun; 13(6):745-52. PMID:20597708.

31. Uusvaara J, Pitkala KH, Kautiainen H, et al. Association of anticholinergic drugs with hospitalization and mortality among older cardiovascular patients: A prospective study. Drugs Aging. 2011 Feb 1;28(2):131-8. PMID: 21275438.
32. Juola AL, Pylkkanen S, Kautiainen H, et al. Burden of potentially harmful medications and the association with quality of life and mortality among institutionalized older people. J Am Med Dir Assoc. 2016 Mar 1;17(3):276.e9-14. PMID: 26805751.
33. Myint PK, Fox C, Kwok CS, et al. Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study. Age Ageing. 2015 Mar; 44(2):219-25. PMID: 24530550.
34. Mangoni AA, van Munster BC, Woodman RJ, et al. Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause postdischarge mortality in older hospitalized patients with hip fractures. Am J Geriatr Psychiatry. 2013 Aug; 21(8):785-93. PMID: 23567395.
35. Luukkanen MJ, Uusvaara J, Laurila JV, et al. Anticholinergic drugs and their effects on delirium and mortality in the elderly. Dement Geriatr Cogn Dis Extra. 2011 Jan;1(1):43-50. PMID: 22163232.
36. Lowry E, Woodman RJ, Soiza RL, et al. Associations between the anticholinergic risk scale score and physical function: potential implications for adverse outcomes in older hospitalized patients. J Am Med Dir Assoc. 2011 Oct; 12(8):565-72. PMID: 21514242.
37. Gaboda D, Lucas J, Siegel M, et al. No longer undertreated? Depression diagnosis and antidepressant therapy in elderly long-stay nursing home residents, 1999 to 2007. J Am Ger Soc. 2011; 59:673–80. PubMed: 21410441.
38. Blazer DG 2nd, Federspiel CF, et al. The risk of anticholinergic toxicity in the elderly: a study of prescribing practices in two populations. J Gerontol. 1983 Jan; 38(1):31-5. PMID: 6129272.
39. Seifert R, Jamieson J, Gardner R Jr. Use of anticholinergics in the nursing home: an empirical study and review. Drug Intell Clin Pharm. 1983 Jun; 17(6):470-3. PMID: 6861639.
40. Kolanowski A, Fick DM, Campbell J, et al. A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. J Am Med Dir Assoc. 2009 May; 10(4):252-7. PMID: 19426941.
41. Chatterjee S, Mehta S, Sherer JT, et al. Prevalence and predictors of anticholinergic medication use in elderly nursing home residents with dementia: analysis of data from the 2004 National Nursing Home Survey. Drugs Aging 2010;27(12):987-97. PMID: 21087068.
42. Centers for Medicare & Medicaid Services. Medicare Standard Analytical Files: Identifiable Data Files. [online] Available at: http://www.cms.hhs.gov/IdentifiableDataFiles/02_StandardAnalyticalFiles.asp (Accessed April 2014).
43. Centers for Medicare & Medicaid Services. CMS Programs & Information. Available at: http://www.cms.hhs.gov/ (Accessed April 2014).
44. The Kaiser Family Foundation: Medicare: A Primer. April 2010. Available at: http://www.kff.org/medicare/upload/7615-3.pdf (Accessed April 2014).
45. A Data Book: Healthcare Spending and the Medicare Program (June 2010) Available at: http://www.medpac.gov/documents/Jun10DataBookEntireReport.pdf (Accessed April 2014).
46. Research Data Assistance Center (ResDAC): Available CMS Data. Available at: http://www.resdac.umn.edu/Available_CMS_Data.asp (Accessed April 2014).
47. Hanlon JT, Donohue J. Medicare Part D data: A valuable tool for pharmacoepidemiology and pharmacoeconomic research. Am J Geriatr Pharmacother. 2010 Dec;8(6):483-4. PMID:21356501.
48. Snowden M, McCormick W, Russo J et al. Validity and responsiveness of the Minimum Data Set. J Am Geriatr Soc 1999;47:1000–4. PMID: 10443863.
49. Mor V. A comprehensive clinical assessment tool to inform policy and practice: applications of the minimum data set. Med Care. 2004 Apr;42(4 Suppl):III50-9. PMID: 15026672.
50. Frederiksen K, Tariot P, De Jonghe E. Minimum Data Set Plus (MDS+) scores compared with scores from five rating scales. J Am Geriatr Soc. 1996 Mar;44(3):305-9. PMID: 8600202.
51. Hartmaier SL, Sloane PD, Guess HA, et al. The MDS Cognition Scale: a valid instrument for identifying and staging nursing home residents with dementia using the minimum data set. J Am Geriatr Soc. 1994 Nov;42(11):1173-9. PMID: 7963204.

52. Cohen-Mansfield J, Taylor L, et al. Estimating the cognitive ability of nursing home residents from the minimum data set. Outcomes Manag Nurs Pract. 1999;3(1):43-6. PMID: 9934198.
53. Wacholder S, McLaughlin JK, Silverman DT et al. Selection of controls in case-control studies. I. Principles. Am J Epidemiol. 1992 May 1;135(9):1019-28. PMID: 1595688.
54. Wacholder S, Silverman DT, McLaughlin JK et al. Selection of controls in case-control studies. III. Design options. Am J Epidemiol. 1992 May1;135(9):1042-50. PMID: 1595689.
55. Wacholder S, Silverman DT, McLaughlin JK et al. Selection of controls in case-control studies. II. Types of controls. Am J Epidemiol. 1992 May 1;135(9):1029-41. PMID: 1595690.
56. Sheehe PR. Dynamic risk analysis in retrospective matched pair studies of disease. Biometrics 1962 18:323-41. doi: 10.2307/2527475
57. Breslow N. Design and analysis of case-control studies. Annu Rev Public Health 1982 3:29-54. PMID: 6756431.
58. Gruber-Baldini AL, Zimmerman SI, Mortimore E, et al. The validity of the minimum data set in measuring the cognitive impairment of persons admitted to nursing homes. J Am Geriatr Soc. 2000; 48(12):1601-6. PMID: 11129749.
59. Vetrano DL, Tosato M, Colloca G, et al. Polypharmacy in nursing home residents with severe cognitive impairment: results from the SHELTER Study. Alzheimers Dement. 2013 Sep; 9(5):587-93. PMID: 24559641.
60. Hudson M, Avina-Zubieta A, Lacaille D, et al. The validity of administrative data to identify hip fractures is high-a systematic review. J Clin Epidemiol. 2013 Mar; 66(3):278-85. PMID: 23347851.
61. Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006; 46: 1481-6. PMID: 17101747.
62. Carnahan RM, Lund BC, Perry PJ, et al. The relationship of an anticholinergic rating scale with serum anticholinergic activity in elderly nursing home residents. Psychopharmacol Bull. 2002 Autumn; 36(4):14-9. PMID: 12858139.
63. Williams JW, Plassman BL, Burke J, et al. Preventing Alzheimer's Disease and Cognitive Decline. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Apr. (Evidence Reports/Technology Assessments, No. 193.) Available at: http://www.ncbi.nlm.nih.gov/books/NBK47456/ (Accessed April 2014).
64. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373-83. PMID: 3558716.
65. Buntinx F, Niclaes L, Suetens C, et al. Evaluation of Charlson's comorbidity index in elderly living in nursing homes. J Clin Epidemiol. 2002 Nov; 55(11):1144-7. PMID: 12507679.
66. Flanders WD, Louv WC. The exposure odds ratio in nested case-control studies with competing risks. Am J Epidemiol 1986;124: 684e92. PMID: 3752062.
67. Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health. 2008; 4(3):311–20. doi: https://doi.org/10.2217/1745509X.4.3.311.
68. Prommer E. Anticholinergics in palliative medicine: an update. Am J Hosp Palliat Care. 2013 Aug ;30(5):490-8. PMID: 22964342.
69. Chatterjee S, Bali V, Carnahan RM, Johnson ML, Chen H, Aparasu RR. Anticholinergic Medication Use and Risk of Dementia Among Elderly Nursing Home Residents with Depression. Am J Geriatr Psychiatry. 2016 Jun;24(6):485-95. PubMed PMID: 26976294.
70. Aparasu RR, Chatterjee S, Johnson ML et al. Cognitive Decline with Anticholinergic Medication Use Among Elderly Nursing Home Residents with Depression. 23rd Annual International Meeting Research Abstracts, Value Health 2018; May 21: S8.
71. Chatterjee S, Bali V, Carnahan RM, et al. Anticholinergic Medication Use and Risk of Fracture in Elderly Adults with Depression. J Am Geriatr Soc. 2016 Jul; 64(7):1492-7. PMID: 27294403.
72. Chatterjee S, Bali V, Carnahan RM, Chen H, Johnson ML, Aparasu RR. Risk of Mortality Associated with Anticholinergic Use in Elderly Nursing Home Residents with Depression. Drugs Aging. 2017 Sep; 34(9):691-700. PMID: 28656508.

73. Bali V, Chatterjee S, Carnahan RM, Chen H, Johnson ML, Aparasu RR. Risk of Dementia Among Elderly Nursing Home Patients Using Paroxetine and Other Selective Serotonin Reuptake Inhibitors. Psychiatr Serv. 2015 Dec 1; 66(12):1333-40. PMID: 26234334.
74. Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, Aparasu RR. Risk of Cognitive Decline Associated With Paroxetine Use in Elderly Nursing Home Patients With Depression. Am J Alzheimers Dis Other Demen. 2016 Dec; 31(8):678-86. PMID: 27765867.
75. Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, Aparasu RR. Comparative risk of hip fractures in elderly nursing home patients with depression using paroxetine and other selective serotonin reuptake inhibitors. J Comp Eff Res. 2016 Aug; 5(5):461-73. PMID: 27426927.
76. Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, Aparasu RR. Risk of Mortality in Elderly Nursing Home Patients with Depression Using Paroxetine. Pharmacotherapy. 2017 Mar; 37(3):287-96. PMID: 28079266.

LIST OF PUBLICATIONS AND PRODUCTS FROM THE FUNDED RESEARCH

PUBLICATIONS

1. Chatterjee S, Bali V, Carnahan RM, Chen H, Johnson ML, **Aparasu RR**. Risk of Mortality Associated with Anticholinergic Use in Elderly Nursing Home Residents with Depression. Drugs Aging. 2017 Sep;34(9):691-700. PMID: 28656508.

2. Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, **Aparasu RR**. Risk of Mortality in Elderly Nursing Home Patients with Depression Using Paroxetine. Pharmacotherapy. 2017 Mar;37(3):287-96. PMID: 28079266.

3. Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, **Aparasu RR**. Risk of Cognitive Decline Associated With Paroxetine Use in Elderly Nursing Home Patients With Depression. Am J Alzheimers Dis Other Demen. 2016 Dec;31(8):678-86. PMID: 27765867.

4. Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, **Aparasu RR**. Comparative risk of hip fractures in elderly nursing home patients with depression using paroxetine and other selective serotonin reuptake inhibitors. J Comp Eff Res. 2016 Aug;5(5):461-73. PMID: 27426927.

5. Chatterjee S, Bali V, Carnahan RM, Chen H, Johnson ML, **Aparasu RR**. Anticholinergic Medication Use and Risk of Fracture in Elderly Adults with Depression. J Am Geriatr Soc. 2016 Jul;64(7):1492-7. PMID: 27294403.

6. Chatterjee S, Bali V, Carnahan RM, Johnson ML, Chen H, **Aparasu RR**. Anticholinergic Medication Use and Risk of Dementia Among Elderly Nursing Home Residents with Depression. Am J Geriatr Psychiatry. 2016 Jun;24(6):485-95. PMID: 26976294.

7. Bali V, Chatterjee S, Carnahan RM, Chen H, Johnson ML, **Aparasu RR**. Risk of Dementia Among Elderly Nursing Home Patients Using Paroxetine and Other Selective Serotonin Reuptake Inhibitors. Psychiatr Serv. 2015 Dec 1;66(12):1333-40.PMID: 26234334.

PRESENTATIONS

1. Bali V, **Aparasu RR**, Carnahan R, Chen H, Johnson ML. Characteristics of elderly nursing home residents with depression in the United States. Value in Health 17 (3): A211-A211. ISPOR 19th Annual International Meeting Research Abstracts, May 2014.

2. Bali V, **Aparasu RR**, Carnahan R, Chen H, Johnson ML. Risk of dementia associated with the use of paroxetine among the elderly nursing home patients with depression. Value in Health 17 (3), A209-A209. ISPOR 19th Annual International Meeting Research Abstracts, May 2014.

3. Chatterjee S, **Aparasu RR**, Carnahan R, Chen H, Johnson ML. Prevalence of anticholinergic medication use among elderly nursing home residents with depression. Value in Health 17 (3), A211-A211. ISPOR 19th Annual International Meeting Research Abstracts, May 2014.

4. **Aparasu RR**, Chatterjee S, Carnahan R, Chen H, Johnson ML. Anticholinergic medication use and risk of dementia among elderly nursing home residents with depression. Value in Health 17 (3), A208-A208. ISPOR 19th Annual International Meeting Research Abstracts, May 2014.

5. Chatterjee S, **Aparasu RR**, Carnahan R, Chen H, Johnson ML. Anticholinergic Medication use and risk of incident Fractures in the elderly with Depression. Value in Health 18; 3: A114–A115. ISPOR 20th Annual International Meeting Research Abstracts, May 2015.

6. Bali V, **Aparasu RR**, Chen H, Johnson ML, Carnahan R, Chatterjee S. Paroxetine use and Cognition in elderly nursing Home Patients with Depression. Value in Health 18; 3: A116. ISPOR 20th Annual International Meeting Research Abstracts, May 2015. **Finalist Poster Award**

7. Bali V, **Aparasu RR,** Johnson ML, Chen H, Carnahan RM. Comparative Safety Of Paroxetine And Other Ssris For The Risk Of Hip Fracture In Elderly Nursing Home Residents With Depression. Value in Health 19 (3), A183-A184. ISPOR 21st Annual International Meeting Research Abstracts, May 2016.

8. Bali V, **Aparasu RR**, Johnson ML, Chen H, Carnahan RM. Risk Of Mortality Associated With Use Of Anticholinergic Medications In Elderly Nursing Home Residents With Depression: A Nested Case-Control Study. Value in Health 19 (3): A183. ISPOR 21st Annual International Meeting Research Abstracts, May 2016.

9. **Aparasu RR**, Chatterjee S, Johnson ML, Chen H, Carnahan RM. Cognitive Decline with Anticholinergic Medication Use Among Elderly Nursing Home Residents with Depression. Value in Health 21: S8. ISPOR 23rd Annual International Meeting Research Abstracts, May 2018.