Bladder antimuscarinics use in the veterans affairs community living centers: description of medication use and evaluation of risks and benefits.

Moga, Daniela Claudia

BLADDER ANTIMUSCARINICS USE IN THE VETERANS AFFAIRS COMMUNITY LIVING CENTERS: DESCRIPTION OF MEDICATION USE AND EVALUATION OF RISKS AND BENEFITS

by

Daniela Claudia Moga

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Epidemiology
in the Graduate College of
The University of Iowa

May 2012

Thesis Supervisor: Professor Elizabeth Chrischilles

ABSTRACT

Urinary incontinence, one of the most prevalent conditions in elderly living in nursing homes (NH) was shown to significantly impact patient's quality of life (QOL) and health outcomes. Bladder antimuscarinics (BAM), the main drug class to treat urinary incontinence, have limited effects in managing the condition; however, given their anticholinergic properties and the characteristics of those living in NH, BAM could potentially lead to serious health consequences in this population.

We conducted a retrospective cohort study with a new-users design by linking existing Veterans Affairs (VA) data (inpatient, outpatient, pharmacy administrative files, and Minimum Data Set- MDS) between fiscal years 2003 and 2009. Potential risks (i.e. fractures and negative impact on cognitive performance) and benefits (i.e. improvement in urinary incontinence, social engagement and overall QOL) associated with initiation of a BAM were assessed in elderly (65+) admitted for long-term care in the VA Community Living Centers.

Descriptive statistics were used to compare BAM new-users and non-users at baseline; in addition, logistic regression was used to identify important predictors of BAM initiation. Treatment selection bias was addressed by using the propensity score matching method. After balancing the groups on baseline characteristics, the risk of fractures (hip fracture, any fracture) in relationship with BAM initiation was evaluated using Cox proportional hazard analysis. BAM impact on the cognitive status measured by the MDS-Cognitive Performance Scale (CPS) was evaluated through generalized estimated equations (GEE) method. Similarly, possible benefits measured through MDS were assessed via GEE.

The final cohort included 1195 BAM new-users (with the majority being prescribed Oxybutynin immediate-release) and 22,987 non-users. Predictors of

BAM initiation included demographic characteristics, bladder and bowel continence status, comorbidities, medication use, cognitive performance and functional status.

Our study showed that BAM improved urinary continence (OR=1.27, 95%CI: 1.07-1.50) in those treated; social engagement as measured by MDS-Index of Social Engagement also improved in users, although at a level that is not clinically significant (difference in mean MDS-ISE=0.2074, 95%CI: 0.0550-0.3598). However, BAM initiation increased the risk of fractures (hip: HR=3.69, 95% CI: 1.46 - 9.34, p=0.0059; any fracture: HR=2.64. 95% CI: 1.37 - 5.10, p=0.0039). Our results showed no difference between new-users and non-users with regard to mean CPS and overall QOL.

The purpose of the study was to clarify the proper role of medication use in the management of urinary incontinence in elderly in the VA CLC. The results raise questions about the continued use of Oxybutynin IR, the main BAM prescribed in this population. Given the increased risk for fractures in the context of potential improvement in urinary continence with no clinically significant improvement in social engagement, a wiser step might be to investigate the safety profile for newer BAM for situations when an addition to non-pharmacologic management for urinary incontinence is desired for elderly in long-term care.

Abstract Approved: _____
Thesis Supervisor

_____
Title and Department

_____
Date

BLADDER ANTIMUSCARINICS USE IN THE VETERANS AFFAIRS COMMUNITY LIVING CENTERS: DESCRIPTION OF MEDICATION USE AND EVALUATION OF RISKS AND BENEFITS

by

Daniela Claudia Moga

A thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Epidemiology
in the Graduate College of
The University of Iowa

May 2012

Thesis Supervisor: Professor Elizabeth Chrischilles

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

PH.D THESIS

This is to certify that the Ph.D. thesis of

Daniela Claudia Moga

has been approved by the Examining Committee for the thesis requirement for the Doctor of Philosophy degree in Epidemiology at the May 2012 graduation.

Thesis Committee: _____
Elizabeth Chrischilles, Thesis Supervisor

_____
Ryan Carnahan

_____
Yue Li

_____
Brian Lund

_____
Jane Pendergast

_____
James Torner

_____
Robert Wallace

To Ionut

ACKNOWLEDGEMENTS

This research would not have been possible without the support I received from the Center for Comprehensive Access & Delivery Research and Evaluation (CADRE) at the Iowa City VA Medical Center. I would like to particularly thank Brian Lund who helped me tremendously to obtain access to the data used in this analysis. Without his help, this work would have been impossible to conduct.

I would like to thank all my dissertation committee members for their support and guidance during this process. I especially thank Betsy Chrischilles not only for her help with my dissertation work, but also for her exceptional mentorship throughout my journey to become a pharmacoepidemiologist. I would like to thank Jim Torner for believing in me, for helping me throughout my academic education and for all the opportunities he offered in the past 5 years. I greatly appreciate the help and advice I received from Jane Pendergast, Bob Wallace and Ryan Carnahan with my dissertation and during my training.
I would also like to thank Kara Wright who helped me develop my SAS skills that were essential for this work. I want to thank Marilyn Anderson and Amy Sayer for all the help and moral support.

I would also like to acknowledge Dr. Ted Johnson from Birmingham/Atlanta VA Geriatrics Research Education Clinical Center (GRECC) who provided useful information related to my project, Dr. Christa Hojlo, Director, VA Community Living Centers for the support on getting the Minimum Data Set, and Dr. Walter Wodchis for sharing the SAS code for the Health Status Index.

I would like to thank my family and my friends for their ongoing support and love that kept me going. I would not have done it without you!

ABSTRACT

Urinary incontinence, one of the most prevalent conditions in elderly living in nursing homes (NH) was shown to significantly impact patient's quality of life (QOL) and health outcomes. Bladder antimuscarinics (BAM), the main drug class to treat urinary incontinence, have limited effects in managing the condition; however, given their anticholinergic properties and the characteristics of those living in NH, BAM could potentially lead to serious health consequences in this population.

We conducted a retrospective cohort study with a new-users design by linking existing Veterans Affairs (VA) data (inpatient, outpatient, pharmacy administrative files, and Minimum Data Set- MDS) between fiscal years 2003 and 2009. Potential risks (i.e. fractures and negative impact on cognitive performance) and benefits (i.e. improvement in urinary incontinence, social engagement and overall QOL) associated with initiation of a BAM were assessed in elderly (65+) admitted for long-term care in the VA Community Living Centers.

Descriptive statistics were used to compare BAM new-users and non-users at baseline; in addition, logistic regression was used to identify important predictors of BAM initiation. Treatment selection bias was addressed by using the propensity score matching method. After balancing the groups on baseline characteristics, the risk of fractures (hip fracture, any fracture) in relationship with BAM initiation was evaluated using Cox proportional hazard analysis. BAM impact on the cognitive status measured by the MDS-Cognitive Performance Scale (CPS) was evaluated through generalized estimated equations (GEE) method. Similarly, possible benefits measured through MDS were assessed via GEE.

The final cohort included 1195 BAM new-users (with the majority being prescribed Oxybutynin immediate-release) and 22,987 non-users. Predictors of

BAM initiation included demographic characteristics, bladder and bowel continence status, comorbidities, medication use, cognitive performance and functional status.

Our study showed that BAM improved urinary continence (OR=1.27, 95%CI: 1.07-1.50) in those treated; social engagement as measured by MDS-Index of Social Engagement also improved in users, although at a level that is not clinically significant (difference in mean MDS-ISE=0.2074, 95%CI: 0.0550-0.3598). However, BAM initiation increased the risk of fractures (hip: HR=3.69, 95% CI: 1.46 - 9.34, p=0.0059; any fracture: HR=2.64. 95% CI: 1.37- 5.10, p=0.0039). Our results showed no difference between new-users and non-users with regard to mean CPS and overall QOL.

The purpose of the study was to clarify the proper role of medication use in the management of urinary incontinence in elderly in the VA CLC. The results raise questions about the continued use of Oxybutynin IR, the main BAM prescribed in this population. Given the increased risk for fractures in the context of potential improvement in urinary continence with no clinically significant improvement in social engagement, a wiser step might be to investigate the safety profile for newer BAM for situations when an addition to non-pharmacologic management for urinary incontinence is desired for elderly in long-term care.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
ADL	Activities of Daily Living
ADS	Anticholinergic Drug Scale
BAM	Bladder antimuscarinic
BBB	Blood-brain barrier
BMI	Body mass index
BZD	Benzodiazepines
CADRE	Center for Comprehensive Access & Delivery Research and Evaluation
CHESS	Changes in Health, End-Stage Disease and Symptoms and Signs
CI	Confidence interval
CLC	Community Living Centers
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COGS	Cognition scale
CPS	Cognitive Performance Scale
DHHS	Department of Health and Human Services
DOD	Date of death
DSS	Decision Support System
ER	Extended release
FY	Fiscal year
GEE	Generalized estimating equations
HR	Hazard ratio
HRQOL	Health-related quality of life
HSI	Health Index Score
HUI	Health Utility Index

ICD-9-CM	International Classification of Diseases, 9th Clinical Medication
IEN	Internal Entry Number
IR	Immediate release
ISE	Index of Social Engagement
LTC	Long term care
MDS	Minimum Data Set
MMSE	Mini-mental state examination
NDE	National Data Extract
NH	Nursing homes
OR	Odds ratio
PBM	Pharmacy Benefits Management
PS	Propensity score
RCT	Randomized clinical trial
SA	Slow-acting
VA	Veterans Affairs
VAMC	Veterans Affairs Medical Center
VISN	Veterans Integrated Service Network
VistA	Veterans Health Information Systems and Technologies Architecture

CHAPTER I- INTRODUCTION

The elderly who reside in nursing homes (NH) suffer from multiple health conditions; they have a high chance of being prescribed multiple drugs and a high risk of experiencing medication-related adverse events. Urinary incontinence is one of the most frequent conditions in this population, with a prevalence of approximately 55% in NH worldwide (Hunskaar et al., 2005). In the United States, the prevalence has been estimated to be 65% (Newman, 2006) with an associated $5.32 billion (2000 dollars) in estimated total direct costs (Hu et al., 2004). Urinary incontinence has also been found to have a negative impact on different health-related outcomes (falls and fractures, urinary tract and skin infections, depression, chronic constipation), as well as on the emotional well-being and the quality of life (QOL) of older adults.

Current approaches for treating urinary incontinence include behavioral interventions and/or pharmacological treatment, and the use of absorbent products. The pharmacological treatment is mainly represented by bladder antimuscarinics (BAM), drugs with anticholinergic properties through their action on the muscarinic receptors, a type of cholinergic receptors. These drugs were mainly evaluated in younger populations or in community-dwelling elderly. A recent review of 14 randomized clinical trials (RCT) that were conducted between 1985 and 2008 and included NH residents evaluated the combination of behavioral interventions and medication and showed limited improvement in the number of incontinence episodes while reporting common adverse events (Fink et al., 2008). However, only one of these trials evaluated/reported falls and did not show a significant difference between Oxybutynin extended-release (ER) and placebo during the short, four-week follow-up (Lackner et al, 2008). In addition, given their short follow-up, these clinical trials could not evaluate the long-term

effectiveness or adverse outcomes potentially associated with BAM in this frail population.

Side effects described in RCT, such as loss in coordination, pupil dilatation, and double-vision can increase the risk of falls and fall-related fractures elderly in relationship to BAM use (Mustard et al., 1997; Ray et al., 1987; Ray et al., 2000). Anticholinergic burden was shown to increase the risk for falls (Aizenberg et al, 2002) and cause cognitive impairment as measured by the Mini-Mental State Examination (MMSE) (Fox et al, 2011). However, to our knowledge, no study evaluated the long term effects, both in terms of risks and benefits, associated with BAM use in institutionalized elderly; moreover, to our knowledge, no study evaluated BAM impact on cognitive performance in the NH setting and with a long follow-up. Studies conducted in this population, either (1) evaluated only improvement in urinary incontinence with the addition of BAM to behavioral interventions, or (2) compared Oxybutynin to another BAM in terms of risks and had a short follow-up, a small sample size, and/or did not include fall-related fractures as primary outcome of interest.

Specific Aims

The purpose of this research was to harness a unique data resource to investigate the balance between benefits and risks from antimuscarinic agents in a large population of NH residents with urinary incontinence. This healthcare database also offers the opportunity to study the characteristics that may be associated with use of these drugs. Although a well-design randomized clinical trial would be ideal to evaluate the risks and the benefits of BAM in the NH population, this option is not as feasible for assessing long-term effects.

We conducted a retrospective cohort study within a rich dataset that includes prescription and non-prescription drug use as well as clinical, functional, and quality of life outcomes. This project employed the linkage of Long Term Care Minimum Data Set (LTC MDS) assessments data with Veteran Affairs (VA) medical and pharmacy records, and enrollment files for residents in the VA Community Living Centers (CLC) (former VA Nursing Homes). MDS assessment data provided functional, behavioral, and symptom and syndrome data. VA administrative files were the source of drug exposure data needed to identify BAM users and also allowed for identification of diagnosis codes for outcomes and comorbidities assessment.

The specific aims of this study were to:

Aim 1: Describe the characteristics of those receiving different BAM (including demographics, baseline disease history, standardized measures of resident cognitive, behavioral, functional and medical stability status, and facility characteristics) and to identify predictors of medication initiation for managing urinary incontinence in NH.

Aim 2: Determine whether initiation of BAM is associated with increased risk of fractures and impaired cognition.

Hypothesis 2a: BAM will increase the risk of fractures in NH residents

Hypothesis 2b: BAM will negatively affect cognitive status as measured by MDS-Cognitive Performance Scale (CPS)

Aim 3: Determine whether BAM initiation is associated with improvement in incontinence and QOL.

Hypothesis 3a: BAM will improve incontinence as measured by MDS

Hypothesis 3b: BAM will improve social engagement and overall QOL

CHAPTER II- LITERATURE REVIEW

In 2003, it was estimated that 1.5 million adults over 65 years were living in NH in the US; today, as the population is aging, the number is now probably larger (National Center for Health Statistics, 2005; Sahyoun et al., 2001). An important proportion of this population would also fit the description of a frail elderly suffering from impaired physical activity, cognition, nutrition, and high medication use and a high risk of intercurrent disease, increased disability, hospitalization, and death (Ferrucci et al., 2004).

Urinary continence and falls are two very problematic conditions in NH. The treatment of one may adversely affect the other. The balance between risks and benefits is unknown in this vulnerable population. In this chapter, we first briefly review the burden of these health conditions and the characteristics of the vulnerable NH population. We next explain the pharmacologic properties of BAM followed by the evidence on BAM effects on health outcomes. The final section describes the data resource and summarizes previous research using the VA MDS.

Urinary Incontinence and Its Treatment

Urinary incontinence is a highly prevalent and costly condition that requires significant resources for care in NH worldwide. Despite the need for effective treatment options, the current pharmacologic management for the condition shows limited effectiveness (i.e. medication alleviates symptoms, but is not curative) and potential for bothersome and, sometimes, serious adverse effects. The prevalence of urinary incontinence among NH residents was estimated between 40% and 70% and it has been demonstrated that this condition seriously impacts QOL and functionality (Charalambous et al., 2009). It

is associated with substantial morbidity-predisposes to skin irritation, interferes with the healing of pressure ulcers, and results in symptomatic urinary tract infections. Additional serious consequences include depression, inactivity, and social isolation. Moreover, nocturia and urge incontinence may lead to falls among residents with impaired mobility (Ouslander et al, 2005). The economic costs of incontinence were estimated at a level of $5.32 billion (2000 dollars) (Hu et al., 2004). Moreover, urinary incontinence increased the risk of admission to a NH by 6 - 10%, thus creating an additional $6 billion annualized cost (2004 dollars) (Morrison & Levy, 2006).

Today, its management may involve various combinations of behavioral, surgical, and pharmacological interventions; however, most often, incontinence is controlled by catheters, diapers, and pads. Behavioral and pharmacological interventions are usually the treatment of choice for urge incontinence, whereas surgery is less common and is sought in stress incontinence if non-pharmacologic interventions fail.

In NH, residents newly diagnosed with urinary incontinence should be evaluated and behavioral interventions should be attempted before medication is initiated. Figure 2.1 below describes the stepwise approach in the management of urinary incontinence in the NH settings. Behavioral therapy (see Figure 2.2 below) in NH includes scheduled voiding or caregiver-dependent techniques like habit training (assisting residents with voiding according to their own schedules) and prompted voiding (usually using a 2-hour schedule).

BAM are the first-line pharmacological treatment in urinary incontinence, specifically for urge and mixed incontinence. These drugs depress both voluntary and involuntary bladder contractions. Some of the drugs have antimuscarinic effect exclusively, but some also exert other types of effects. The level of

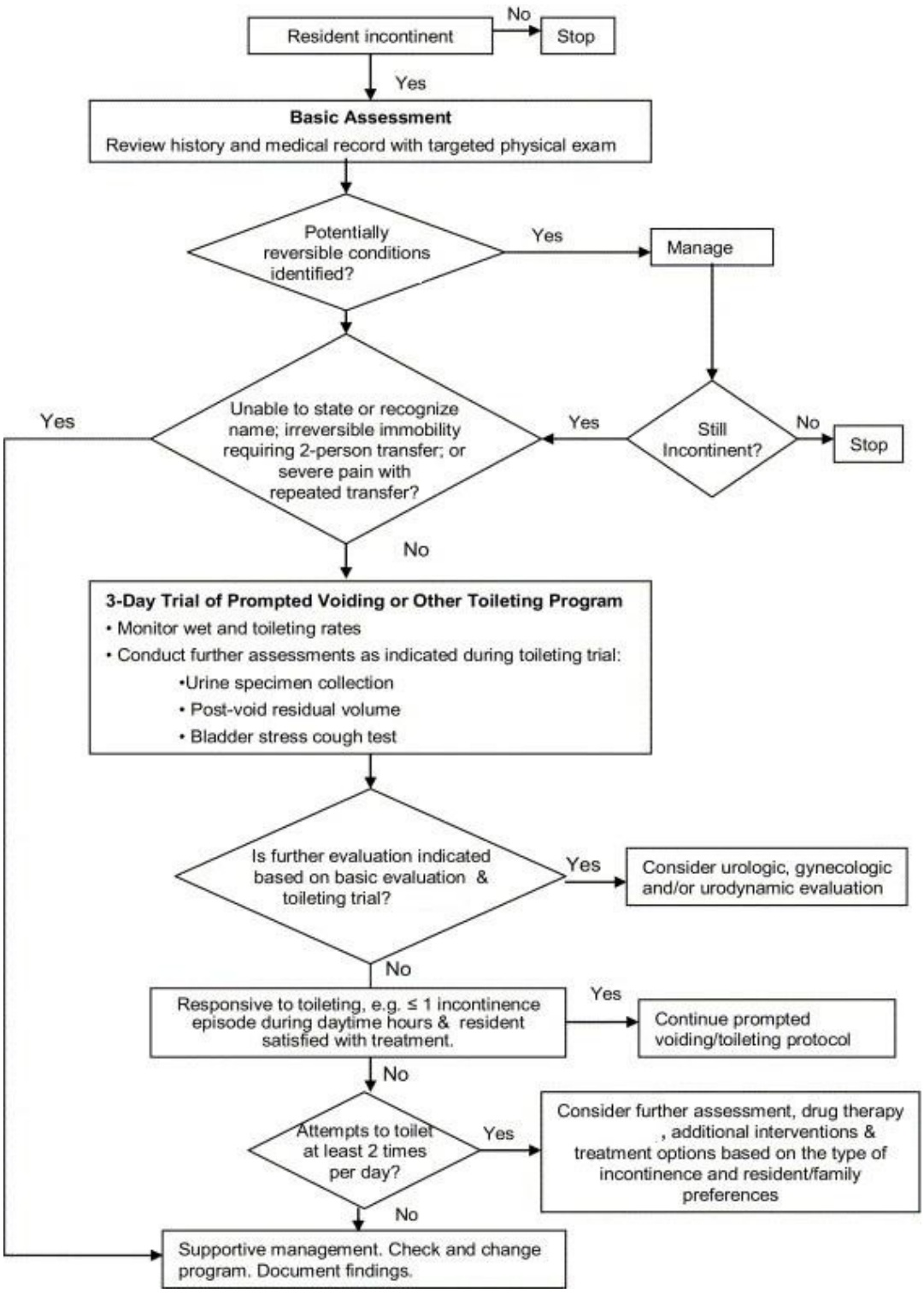


Figure 2.1: Urinary incontinence management in nursing homes

Source: Zarowitz, B., & Ouslander, J. (2007). The application of evidence-based principles of care in older persons (issue 6): Urinary incontinence. *Journal of the American Medical Directors Association, 8*(1), 35-45.

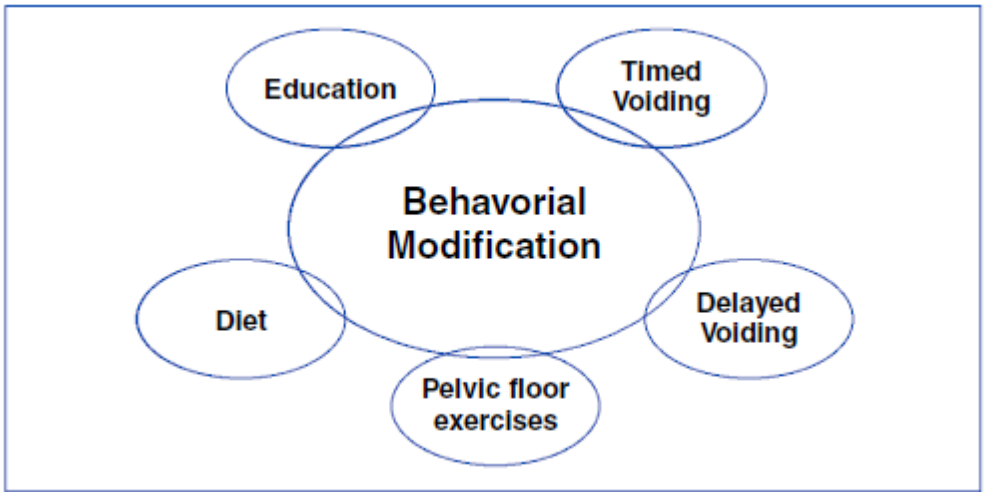


Figure 2.2 Behavioral interventions for urinary incontinence management

Source: Newman, D.K., and Wein, A.J.: Managing and Treating Urinary Incontinence. 2nd ed. Baltimore, MD. Health Professions Press, 2009.

Table 2.1: List of bladder antimuscarinics and level of evidence in urinary incontinence management

Drug	Level of evidence	Grade of recommendation
Antimuscarinic drugs		
Tolterodine	Randomized controlled clinical trials	Based on level-1 evidence (highly recommended)
Trospium	Randomized controlled clinical trials	Based on level-1 evidence (highly recommended)
Propantheline	Good-quality prospective studies	Consistent level-2 or level-3 evidence (recommended)
Atropine, hyoscyamine	Good-quality prospective studies	Evidence inconsistent/inconclusive (not recommended)
Darifenacin	Under investigation	..
Solifenacin	Under investigation	..
Drugs with mixed actions		
Oxybutynin	Randomized controlled clinical trials	Based on level-1 evidence (highly recommended)
Propiverine	Randomized controlled clinical trials	Based on level-1 evidence (highly recommended)
Dicyclomine	Case series	Level-4 studies or “majority evidence” (recommended with reservation)
Flavoxate	Case series	Evidence inconsistent/inconclusive (not recommended)

Note: Assessments according to the Oxford system, modified

Source: Andersson, K. (2004). Antimuscarinics for treatment of overactive bladder. Lancet Neurology, 3(1), 46.

evidence with regard to their use as part of the urinary incontinence management also varies greatly (see Table 2.1 below).

A study conducted in 1999 within the Veteran Affairs Medical Centers (VAMC) identified Oxybutynin Chloride, followed by Dicyclomine as the most commonly used BAM in the VA population (Malone et al, 1999). The existent information on the prevalence of BAM use is contradictory. The aforementioned study reported a high prevalence of BAM use- 72.9% of the patients identified with urinary incontinence received medication as part of their disease management (Malone, 1999). However, a more recent study conducted in NH showed a significantly lower prevalence of medication use (7.49%) among those identified with urinary incontinence through MDS. This study concluded that only a small proportion of the NH residents with adequate mobility and cognitive function received medication (Narayanan et al., 2007); however, the authors could not evaluate whether BAM were indeed under-prescribed, or these practices were appropriate, based on the multiple and interacting factors that influence decisions on drug therapy in the NH population.

A review of the literature on the clinical trials assessing the efficacy of different treatment options for urinary incontinence is summarized in Table 2.2 below. Various randomized clinical trials assessing behavioral interventions and/or BAM efficacy shown reduction in the number of incontinence episodes with either treatment option; the combination of the two was shown to be superior to the treatment with one alone (Ouslander et al., 1995; Ouslander et al., 2001; Schnelle et al., 1995).

Table 2.2: Summary of evidence for urinary incontinence management

Ouslander et al (1995)	75 nursing home residents with predominantly urge incontinence, whose incontinence did not respond well to a trial of prompted voiding	Randomized, placebo-controlled, double-blind dose-adjusted, crossover trial	Oxybutynin added along with prompted voiding in 7 nursing homes	63 (84%) of the residents completed the study and, in those, the percentage of wet checks went from 26.5% to 23.7% on placebo and to 20.2% on active drug. These changes were statistically significant but not clinically meaningful. A clinically significant decrease in the frequency of incontinence, defined as relative reduction in the percentage of wet checks of > 33%, occurred in 20 subjects (32%) while on active drug and in 12 subjects (19%) while on placebo, P = .48. Twenty-five subjects (40%) met the incontinence criteria of an average of 1 or less wet per day while on active drug and 11 subjects (18%) achieve this goal on placebo, P = .005.
Drutz et al (1999)	277 patients over 18 years (mean age 62 years) with detrusor over-activity on cystometry and symptoms of urge incontinence and urinary frequency	Multicenter randomized controlled trial in the United States and Canada	Tolterodine 2 mg twice daily or Oxybutynin 5 mg thrice daily, or placebo thrice daily	At least a 50% reduction in frequency was observed (63% tolterodine vs 65% oxybutynin,(, but the difference was not significant between the treated groups
Birns et al (2000)	128 men and women (68%), mean age 56, range 18-76, 81% urge or stress/urge incontinence	Multicenter randomized controlled trial in the United Kingdom	Oxybutynin ER* 10 mg daily or Oxybutynin IR 5 mg twice daily for 6 weeks	No significant differences were found in daytime incontinence (ER 53% vs IR 58%), nighttime continence, median change in the number of voluntary daytime or nighttime voids, daytime or nighttime episodes of incontinence. Seventy-eight (60%) of patients reported adverse events: Dry mouth (ER, 55%; IR 67%); Dizziness (ER, 2%; IR 9%); Vision abnormality (ER, 7%; IR, 5%); Cough (ER, 3%; IR, 5%); Headache (ER, 0; IR, 5%)

*Note: ER= extended-release; IR= immediate-release

Table 2.2 continued

Malone-Lee et al (2001)	378 patients with overactive bladder Age = 50 years, mean age 65, range 49-90	Randomized controlled comparative trial	Tolterodine IR 2 mg twice daily; Oxybutynin IR 2.5-5 mg twice daily	Tolterodine better tolerated with fewer adverse drug events than oxybutynin (69% vs 81%, *P* = .01). Incidence of dry mouth significantly lower in the tolterodine group vs the oxybutynin group (37% vs 61%, P < .0001). Both agents were effective, significantly decreasing mean number of voids per 24 hours, increasing mean voided volume, decreasing mean number of incontinence pads used, and decreasing mean number of urge incontinence episodes per 24 hours.
Ouslander et al (2001)	151 nursing home residents with urinary incontinence	Prospective field trial incorporating practice guidelines and principles of continuous quality improvement in 5 nursing facilities	Nursing home staff were trained in incontinence program and assumed responsibility for implementing it in their facilities. The program consisted of a clinical assessment, toileting protocols, and the addition of tolterodine in selected patients.	A total of 645 residents were evaluated, 58% of whom were incontinent of urine, 40% (n = 151) of whom received toileting and 48 of whom received tolterodine. The initial dryness rate was 57%, and for the group as a whole remained essentially unchanged (increase in dryness 1%, P = .50). Among 50 clinically stable on a toileting program alone, the increase in the dryness rate was 16% (P = .001), and for 31 clinically stable residents prescribed tolterodine, the increase in the dryness rate was 29% (P = .012).
Zinner et al (2002)	1015 men and women (43.1% ≥ 65 years) with urge incontinence and urinary frequency	Multicenter, international, double-blind, placebo-controlled study at 167 medical centers	Tolterodine ER 4 mg daily or placebo daily for 12 weeks	There were no differences in micturition efficacy endpoints in older (74 years, range 65-93) and younger patients (51 years, range 20-64). Overall, a greater % of patients irrespective of age perceived any benefit with tolterodine ER than with placebo, P < .001. Less than 2% of tolterodine ER-treated patients had dry mouth. There were no CNS, visual, cardiac, or laboratory concerns. The withdrawal rate was similar in both age cohorts: < 65 years, 5.5%; ≥ 65 years, 5.1%; P = .87.

Note: CNS= Central Nervous System; ER= extended-release; IR= immediate-release

Table 2.2 continued

Diokno et al (2003)	790 women with overactive bladder. Mean age 60, range 18-92	Multicenter randomized double-blind, controlled trial	Oxybutynin ER 10 mg daily or Tolterodine ER 4 mg daily	No significant differences in the number of final average weekly urge incontinence episodes between the 2 groups. Micturition frequency decreased significantly more with oxybutynin than with tolterodine. More oxybutynin-treated patients were incontinence-free during the last week of study than those taking tolterodine (23% on oxybutynin vs 16.8% on tolterodine, P = .03). Dry mouth was more common with oxybutynin (29.7% with oxybutynin vs 22.3% with tolterodine,P = .02).
Halaska et al (2003)	357 patients with urge syndrome or incontinence; Mean age 53.7, 86% female	Multicenter randomized controlled trial in Europe	Oxybutynin 5 mg twice daily or Trospium 20 mg twice daily	Treatment in both arms resulted in diminished frequency of incontinence episodes by about 1 episode at each follow-up evaluation. No differences were reported between groups. Adverse events occurred in both groups.
Chapple et al (2005)	1200 patients with overactive bladder; mean age 56.5 years in the solifenacin groups and 56.4 years in the tolterodine groups	Randomized controlled trial in Europe	Solifenacin 5 mg/day or Tolterodine ER 4 mg/day with option of dosage increase after 5 weeks	Solifenacin showed greater efficacy than tolterodine for some endpoints but differences were modest. The products produced a comparable incidence of dry mouth, constipation, and blurred vision. The drug withdrawal rates were similar (3.5% solifenacin vs 3% tolterodine ER).
Wagg et al (2006)	1045 patients aged 71.9 years with symptoms of overactive bladder	Pooled data from four 12-week randomized, placebo-controlled trials and one 40-week open label extension trial	Solifenacin 5 mg or 10 mg placebo once daily.	Similar effects for the two doses; superiority as compared to placebo.

Note: ER= extended-release

Table 2.2 continued

Song et al (2006)	139 women with overactive bladder	Randomized trial	Randomized to treatment with bladder training, tolterodine (2 mg twice daily) or both for 12 weeks.	Although bladder training, tolterodine and their combination were all effective in controlling overactive bladder symptoms, combination therapy was more effective than either method alone.
Burgio et al (2011)	143 men aged 42 to 88 who continued to have urgency and more than eight voids per day, with or without incontinence, after run-in	Randomized, controlled, equivalence trial with 4-week alpha-blocker run-in	Randomized to 8 weeks of behavioral treatment (pelvic floor muscle exercises, urge suppression techniques, delayed voiding) or drug therapy (individually titrated, extended-release oxybutynin, 5-30 mg/d)	Mean voids per day decreased from 11.3 to 9.1 (-18.8%) with behavioral treatment and 11.5 to 9.5 (-16.9%) with drug therapy. Equivalence analysis indicated that post-treatment means were equivalent ($P < .01$). After treatment, 85% of participants rated themselves as much better or better; more than 90% were completely or somewhat satisfied, with no between-group differences. The behavioral group showed greater reductions in nocturia (mean = -0.70 vs -0.32 episodes/night; $P = .05$). The drug group showed greater reductions in maximum urgency scores (mean = -0.44 vs -0.12; $P = .02$). Other between-group differences were non-significant.
Lee et all (2011)	Of a total of 558 patients who took the study medication, 173 were randomized and 108 (A: 40, B: 40, C: 28) were included in the analysis.	Randomized, open-label, multicenter trial	Women who showed successful response to 1 month of Tolterodine 4 mg were randomly assigned to: (A) discontinue medication, (B) 2-month additional medication and (C) 5-month additional medication. Symptom relapse and retreatment rates were evaluated.	Discontinuation of antimuscarinic therapy resulted in high symptom relapse and retreatment rates regardless of treatment duration.

Although previous research showed that a combined approach in the urinary incontinence management is superior to either behavioral interventions or medication alone, there are many factors that could interfere with the actual success of a management plan in NH, in terms of adherence. Some of these factors could be driven by patient characteristics, but some of them could be the result of the increased burden with the addition of non-pharmacological interventions, both in terms of costs as well as in terms of staffing.

Behavioral change is the underlying theory for toileting interventions; this theory mainly focuses on individual behaviors of the individual who is incontinent and those of the caregiver. In this regard, preferences related to treatment choices differ between patients, their family, and caregivers. A study conducted in 2001 showed that patients preferred medication and considered prompted voiding embarrassing and “fostering dependence” (Johnson et al., 2001). In addition, behaviors are also influenced by organizational and regulatory factors like staffing turnover, training, resource allocation, and organizational culture. All these have been associated with patient outcomes in those with urinary incontinence (DuBeau, 2005).

Different studies attempted to identify barriers to the initiation of and adherence to behavioral treatment guidelines; these barriers include incomplete knowledge, time, resources, lack of authority to change practice, lack of support from administration, physicians, and other staff, poor communication among staff, lack of financial incentives to keep individuals dry, and a sense of uselessness and hopelessness among providers, families, and residents with regard to improving urinary function (Rutledge et al, 1998; Bowers et al, 2000; Resnick et al, 2006).

To summarize, urinary incontinence is a highly prevalent condition in the NH population and its management is complex and not curative.

Pharmacological treatment options exist and provide benefits when used in combination with behavioral interventions; however, they also add the potential for side effects.

Pharmacologic Properties of Bladder Antimuscarinics

BAM, the main pharmacological treatment for urinary incontinence, exert their effects through drug-binding to muscarinic receptors, a type of cholinergic receptor. By blocking these receptors, BAM exhibit anticholinergic effects (including blurred vision and dizziness) to an extent related to receptor specificity. There are five types of muscarinic receptors (M1-M5) widely distributed throughout the human body (see Table 2.3), from the bladder detrusor muscle to the central nervous system (CNS) (Eglen, 2006). Their role is mediated by acetylcholine, a neurotransmitter found extensively in the brain and autonomic nervous system, and also the neurotransmitter used to cause cardiac and smooth muscle contractions.

Table 2.3: Muscarinic Receptors Distribution

M_1	Abundant in cerebral cortex, hippocampus, and neostriatum; constitute 40–50% of total acetylcholine receptors	Salivary glands, sympathetic ganglia
M_2	Located throughout brain	Smooth muscle, cardiac muscle
M_3	Low levels throughout brain	Smooth muscle, salivary glands, eyes
M_4	Abundant in neostriatum, cortex, and hippocampus	Salivary glands
M_5	Projection neurons of substantia nigra pars, compacta and ventral tegmental area, and hippocampus	Eyes (ciliary muscle)

Note: CNS= Central Nervous System

The muscarinic receptors important to target for the treatment of urinary incontinence are those found in the bladder's detrusor muscle- M2 and M3; the latter are mainly responsible for normal micturition contraction (Hegde et al.,

1999; Chess-Williams et al., 2001; Fetscher et al., 2002; Yamanishi et al., 2002). M1 and M2 receptors are considered important for cognitive functioning. Animal models showed that M1 receptors are necessary for cognitive processing, while M2 receptors are required for behavioral flexibility and learning (Abrams et al., 2006; Yamada et al., 2001).

Non-selective muscarinic-receptor blockers (as most of the BAM are) targeting bladder receptors would interact not only with the detrusor muscle receptors, but also with other muscarinic receptors distributed throughout the body, including the CNS receptors. Through this pathway, non-selective drugs would potentially impact cognitive functions, especially in elderly where cognitive impairment is amplified through the gradual loss of cholinergic function caused by aging (Schliebs et al, 2011) and concomitant medication. A review of the literature regarding receptor-associated mechanisms leading to CNS adverse events and their impact in geriatric patients suggests that nonselective antimuscarinic agents that bind to M1 receptors would be most likely to cause significant cognitive adverse events as compared to bladder-selective agents (Kay, 2005).

In addition to the muscarinic receptors selectivity, antimuscarinics' effect on the CNS also depends on their physicochemical characteristics. Based on this criterion, BAM are either tertiary or quaternary amines. Tertiary amines are well absorbed from the gastrointestinal tract and can pass into the CNS; quaternary amines are not well absorbed and pass into the CNS to a limited extent.

Risks Factors for Falls and Fractures in Institutionalized Elderly

Falls and fractures are among the conditions with a higher incidence in institutionalized elderly as compared to other populations. It has been estimated that between half and three-quarters of NH residents fall each, twice the rate of

falls for older adults living in the community (Rubinstein et al, 1994; Messinger-Rappaport et al., 2009). Similarly, a study comparing the incidence of fractures in NH residents and in community indwelling elderly estimated that hip fractures were 2.8 to 5.8 times more frequent in those institutionalized than in age- and sex-matched elderly living independently (Ooms et al., 1994).
Approximately 50% of the fallers fall repeatedly and are at risk for serious injuries. According to Center for Disease Control and Prevention, about 10% to 20% of nursing home falls cause serious injuries, and about 1,800 older adults living in NHs die each year from fall-related injuries (CDC, 2011). A prospective study assessing staff-reported falls estimated that about 30% of these falls resulted in some injury, with 6.5% requiring physician care, 3% needing treatment for a fracture other than of the hip, 1.4% needing treatment for a hip fracture and 19.3% for a head injury. (Nurmi et al., 2002).

Risk factors for falls include advanced age, cognitive status, sex (women are at higher risk), past history of falls, walking, gait and balance problems, medications, health conditions such as arthritis and Parkinson's disease, low blood pressure, problems with hearing or vision (CDC, 2011). Fracture mechanisms are different for different age groups. In elderly, osteoporosis is an important risk factor for fractures and it helps explaining the increase in incidence with age; however osteoporosis is not a sufficient or even necessary factor for fracture. Research showed that falls are the main injury mechanism for fractures in elderly people (Bell et al., 2000; Bergstrom et al., 2008), especially hip, spine, forearm, leg, ankle, pelvis, upper arm, and hand fractures (Scott, 1990).Usually, the fall resulting in fracture is a seemingly insignificant fall. A Swedish study evaluated the importance of falls in causing fractures in elderly in the community (see Figure 2.3). They found that, with increasing age, the role of low energy falls

became more and more important and is the dominating injury mechanism behind fractures among the oldest (75+) (Bergstrom et al., 2008).

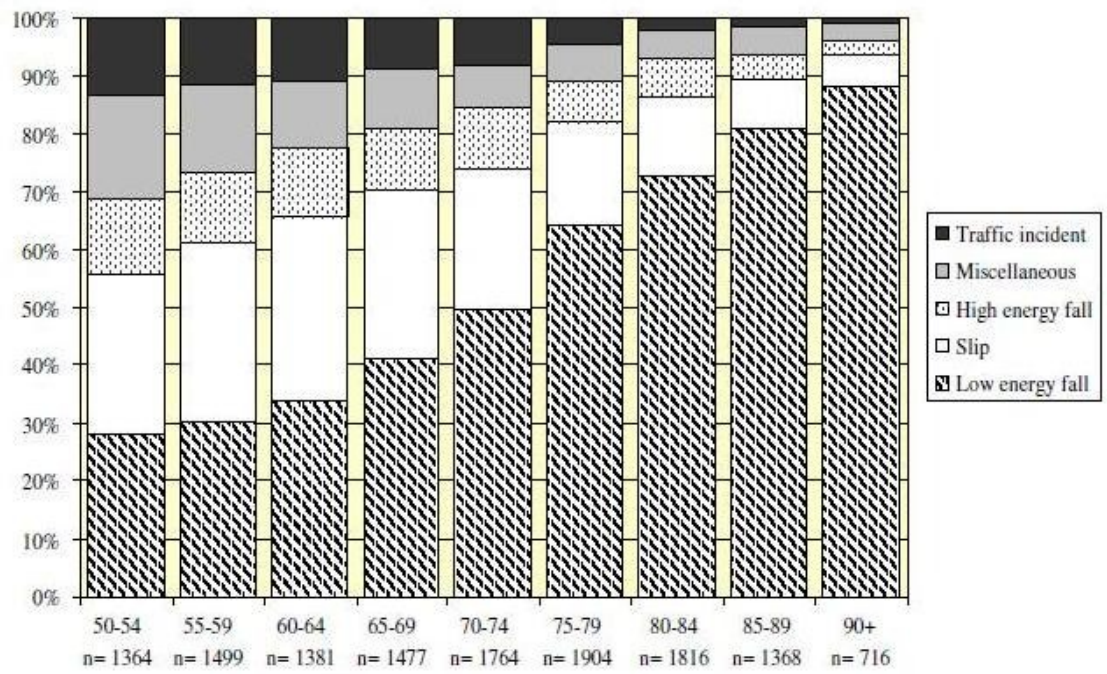


Figure 2.3. The main causes for fractures in adults 50+

With regard to medication as a risk factor, there are multiple mechanisms involved in elevating the risk of fall-related fractures in elderly. These include age-related reduction in bone density, declines in liver metabolic capacity and reduced renal function (which may contribute to extending the duration of drug action), psychomotor impairment through CNS effects, medication induced orthostatic hypotension, dizziness, or blurred vision, effects on patient ambulation, and the occurrence of multiple effects caused by polypharmacy. In addition, another mechanism that could play a role in mediating the risk for fractures associated with medication use is represented by the potential effects

on the autonomic nervous system that regulates bone density (Maser et al, 2009). Several studies and meta-analyses have shown an increased fall risk in elderly users of diuretics, type 1a antiarrhythmics, digoxin and psychotropic agents (Leipzig et al., 1999).

Medication with anticholinergic properties when used in geriatric population can cause falls, dizziness, and confusion in a significant proportion of patients (Rudolph et al., 2008). This study enrolled 117 male subjects, 65 years or older, treated in primary care clinics at the VA Boston Healthcare System between September 1, 2005, and June 30, 2006). They evaluated the risks associated with use of medication classified on a 0 to 3 scale according to their anticholinergic potential (0- limited or none; 1- moderate; 2-strong; and 3- very strong).

A randomized trial confirmed that gradual withdrawal of psychotropic drugs reduces the risk of falling by 66% in elderly (65+) (Campbell et al., 1999). Studies showed that risk is increased significantly if a person is on more than four medications, irrespective of type (Feder et al., 2000). The use of four or more medications is associated with a nine-fold increased risk of cognitive impairment (Koski et al., 1996; Koski et al., 1998) and fear of falling (Friedman et al., 2002) and cognitive impairment adds to the increased risk for falls (Formiga et al., 2008).

Table 2.4 below summarizes findings from studies evaluating the role of medication use in increasing the risk of falls and fractures; these studies describe medication associated side effects that could play an important role in increasing the risk of falls and, consequently, fractures.

Table.2.4 Summary of evidence for the risk of falls and fractures in relationship to medication use

Study	Study design	Main results	Possible mechanism for fractures
Mustard et al., 1997	Case-control study in NH residents in Canada	Antipsychotics and anxiolytics/sedatives/hypnotics use increase the odds of injurious falls	Increased risk of injurious falls including fractures due to psychomotor impairment produced by sedative action of psychotropic medications.
Liu et al., 1998	Population-based case control, ≥65 years	Antidepressants (SSRI, TCA*) increase the risk of hip fractures	Fall-related hip fractures due to medication adverse effects: sedation, orthostatic hypotension, arrhythmias, and confusion
Wang et al., 2001	Population-based case-control, ≥65 years	Zolpidem (BZD*)≥3mg/d increase the risk of hip fractures	Medication causing impaired cognition, impaired balance, and falls.
Neutel et al., 2002	Case-crossover design, elderly	Increase risk of falls in those receiving many drugs, or in those starting a new prescription of BZD* or antipsychotics	N/A
Aizenberg et al., 2002	Hospital-based case control, elderly psychiatric patients	Anticholinergic burden increases the risk of falls	N/A
Chrischilles et al., 2001	Retrospective cohort using claims from a large pension-plan database	Initiation of nonselective alpha-antagonist therapy increases the risk of hypotension-related adverse events, including fractures	Hypotension induced by medication initiation can lead to falls that can, consequently lead to fractures
Souverein et al., 2003	Population-based case-control, adults ≥40 years	Alpha-blockers increase the risk of hip/femur fractures	Falls due to vasodilator effects of the drugs: dizziness, weakness, headache, postural hypotension, syncope
Kallin et al., 2004	Prospective, NH residents	Antidepressants and antipsychotics increase the risk of falls	N/A
Hartikainen et al., 2007	Systematic review of drugs with effects on the CNS* as risk factors for falls	Psychotropic medication is associated with increased risk of falling	N/A
Mamun et al., 2009	Hospital-based case-control, ≥65 years	Risk of falls in hospitalized patients was increased by medication use (hypnotics, cough preparations, anti-platelets)	N/A
Nanda et al, 2011	Hospital-based case-control, elderly in psychiatric care	A falls risk tool, Fall Risk Assessment in Geriatric-psychiatric Inpatients to Lower Events, was developed for assessment and risk stratification with new diagnoses or medications. BAM included in this risk score as they predicted falls.	N/A

Note: SSRI= serotonin reuptake inhibitors; TCA= tricyclic antidepressants; BZD= benzodiazepine; CNS= central nervous system;

Falls and fall-related fractures are important problems in elderly as they can lead to serious health-consequences and even death. They bring additional burden by increasing the level of dependency and the costs associated with care for the patient (Stevens et al. 2005). Several risk factors have been identified and medication was shown to be an important one in elderly. To our knowledge, there hss been no large study to evaluate the risk of fall-related fractures in relationship to BAM use. Two studies compared Oxybutynin and Tolterodine and included falls as secondary outcomes, but did not show any difference between the groups (Jumadilova et al, 2006; Gomes et al, 2011). Given the existing evidence that suggests an increased risk for falls associated with drugs with anticholinergic properties, the addition of a BAM for managing urinary incontinence could cause more harm than good if the anticholinergic burden combined with the additive polymedication effect puts the patient at risk for falls and fall-related fractures.

Factors Influencing Cognitive Function- The Possible Role of BAM

Recently published research suggests that drugs with anticholinergic properties might result in cognitive decline and even precipitate dementia in elderly (Carriere et al., 2009; Cancelli et al., 2009) since the cholinergic system in the brain plays an important role in attention, awareness, and selection of relevant stimuli from the environment. Possible anticholinergic effects include ataxia, loss of coordination, pupil dilation, double-vision and blurred vision, disorientation, agitation, and confusion.

The direct effect on the CNS depends on the ability of the drug to cross the BBB, an important protective mechanism. Factors that impact drugs' ability to penetrate this physiologic barrier include lipophilicity, polarity, and molecular size. BAM are highly lipophilic, have a neutral charge or a low degree of ionization,

and are small in size; all these characteristics increase their ability to pass the BBB and exert an effect on the CNS (Cornford et al., 1999; Pak et al., 2003). Advanced age and different comorbidities (diabetes mellitus, Alzheimer's disease, vascular dementia) can increase the BBB permeability and can inflate the risk of CNS adverse effects (Blennow et al., 1990; Starr et al., 2003; de Ridder, 2006). The potential BAM effect on the cognitive function is linked to their ability to bind to muscarinic receptors in the brain. Although all five muscarinic receptors have been identified in brain tissue, M1 receptors appear to play an important role in cognitive functioning, including attention, learning, memory (Kay et al., 2005; Abrams et al., 2006).

Several factors can influence cognitive function in elderly. In elderly, factors like an increased BBB permeability, the additive anticholinergic burden, and coexisting conditions, could synergistically interact and result in an increased CNS risk from non-selective BAM.

Different studies evaluated cognitive outcomes based on the ability of different BAM to cross the blood-brain barrier (BBB) and to exert effects on the muscarinic receptors in the CNS. A single-blind crossover design study on nine patients with Alzheimer disease showed that urinary incontinence medication produces cognitive, behavioral, and physiological changes as measured by the cognitive subscale of the Alzheimer's Disease Assessment Scale, the Mini-Mental State Examination, the Neuropsychiatric Inventory and the Memory and Behavior Problems Checklist (Jewart et al., 2005). Similarly, a randomized clinical trial on 150 healthy volunteers found effects of BAM impact on cognitive functions (delayed recall) and suggested differences in effects for different BAM depending on their selectivity for different muscarinic receptors; specifically, the study identified significantly more important impairment associated with the non-

selective BAM (Oxybutynin) as compared to the bladder-selective one (Darifenacin) (Kay et al., 2006). A recent retrospective cohort study conducted in a NH population evaluated the long-term functional and cognitive outcomes in elderly that received antimuscarinics concomitant to cholinesterase inhibitors; the authors concluded that those taking both medications had greater rates of functional decline as compared to those who only received cholinesterase inhibitors alone (Sink, 2008). To our knowledge, no large observational studies were conducted with the purpose of evaluating BAM impact on cognitive performance in elderly with urinary incontinence.

Urinary Incontinence and its Impact on Health-related Quality of Life

The effect of urinary incontinence on health-related quality of life (HRQOL) has been described for community-dwelling older adults (Naughton et al., 1997) as well as for NH residents (Dubeau et al., 2006). Urinary incontinence was shown to reduce social interaction and physical activities, and to produce a feeling of guilt/depression, loss of self-esteem, fear of being a burden, fear of odor and lack of control (Milsom et al., 2001). As a consequence, generic and disease-specific HRQOL measurements were included as outcomes in observational studies on lower urinary tract dysfunctions including urinary incontinence, as well as primary or secondary end-points in randomized clinical trials assessing BAM (Diokno et al., 2002; Kelleher, 2002; Robinson et al., 2007; Zinner et al., 2009). These RCT showed significant improvement in QOL in those taking a BAM.

Disease-specific instruments like Kings Health Questionnaire, Overactive Bladder Questionnaire, or Urogenital Distress Inventory, as compared to generic instruments, have the advantage of assessing the impact on different QOL

domains in direct relationship with lower urinary tract dysfunctions. However, they were sometimes criticized for being too specific, thus potentially missing important aspects related to disease's impact on QOL (Hannestad et al., 2000). Some studies used generic HRQOL measures with demonstrated reliability and validity in several settings, the SF-36 (Ware et al., 1992), the EuroQol (EQ-5D) (EuroQoL Group, 1990), and the Health Utility Index 2 (HUI2) (Torrance et al., 1996) in clinical research on patients with urinary incontinence and showed significantly negative impact on QOL across all domains (Mo et al., 2004; Currie et al., 2006).

The majority of these studies were conducted in adults living in the communities and their results are unlikely to fully apply to the institutionalized elderly. The effects of urinary incontinence and its management on QOL is likely different in community-dwelling elderly as compared to the NH population. There are significant differences between these two populations with regard to functional and cognitive abilities, social and role functions, and the burden of comorbid disease, differences that could confound the QOL assessment. In order to address QOL in evaluating urinary incontinence's impact it is important to have valid assessment instruments for NH residents. The aforementioned disease-specific QOL instruments (e.g., the Incontinence Impact Questionnaire, the Kings Health Questionnaire) are not yet validated in frail or functionally and cognitively impaired populations (Dubeau, 2006). Recently, the MDS-derived Index of Social Engagement scale was used to evaluate the impact of urinary incontinence on QOL in NH residents. Social engagement is defined as the ability to initiate social interaction and to be receptive to social overtures from others, including the formation of social ties, contact, and interactions. It is distinct from depression/anxiety, conflicted relationships, and problematic behaviors (Mor et

al., 1995) and was shown to be considerably influenced by urinary incontinence in adults living in the community (Milsom et al., 2001). Similarly, Dubeau et al. showed that change in continence status was strongly correlated with a change in the MDS measure of social engagement as a measure of QOL, independent of cognitive and functional decline (i.e. improvement in urinary incontinence resulted in improvement in social engagement as measured by MDS-ISE). However, the study did not incorporate information on the type of urinary incontinence management (i.e. pharmacologic and/or behavioral interventions).

In a study by Mo et al., HUI was used to measure the quality of life for individuals living with various chronic conditions (including urinary incontinence) and showed that urinary incontinence had a negative impact on QOL. In 2003, Wodchis and collaborators developed MDS-Health Status Index (MDS-HSI), a generic HRQOL instrument using elements from MDS and mapping them to the HUI2. In a recent study conducted among NH residents, MDS-HSI was directly compared to the classic HUI2 and was shown to provide analogous group-level results (Wodchis et al., 2007). Considering these results, it seems reasonable to use MDS-HSI as a substitute for the HUI2 in group-level comparisons when HUI2 survey data are not available.

Previous research showed that urinary incontinence has a significant impact on the HRQOL as measured by disease- specific or generic instruments. In addition, there is an indication of a positive impact on QOL with improvement in urinary incontinence. The availability of MDS derived instruments that were validated as measures of QOL provides a good opportunity to evaluate the potential BAM effect on the QOL in NH residents.

Previous Research Using MDS Assessments in the VA NH Population

Previous studies used MDS assessments and MDS derived instruments for large retrospective studies addressing different healthcare issues and health-related outcomes in the VA NH population. Important findings from these studies are summarized below to support design-related decision process for this research.

MDS assessments were the source used to identify cohorts of NH residents admitted for long-term care. For example, French et al. conducted a series of studies involving 6554 long-stay nursing home residents in the VA CLC (French et al., 2007a; French et al., 2007b; French et al., 2008a; French et al., 2008b). These veterans were identified using the MDS assessments; residents were defined as long-term and were included in the analysis if they had an annual assessment during FY 2005. By linking MDS with other VA data sources, they were able to combine the information from the various sources and use them in the data analysis. In one study, they developed a multivariate fall risk assessment model based on the information from the MDS assessments; the model empirically confirmed the relative importance of certain risk factors for falls in long-term care settings. In other studies, they linked MDS to other sources of data from the VA system (i.e. inpatient pharmacy records, the national Veteran Health Administration discharge dataset). They estimated drug costs and use by drug classes, and described hospital admissions for long-stay NH residents. The longitudinal follow-up with periodic evaluations enables the use of MDS to identify large range of ‘new events’. In a recent study, MDS variables (cognitive impairment, mood, behavior problems, activities of daily living and wandering) recorded at admission and a minimum of two other time points at quarterly intervals were used to explore the extent of and factors associated with male

residents who change wandering status post NH admission (King-Kallimanis et al., 2010). With the advantage of this longitudinal evaluation of NH residents, the authors concluded that a resident's change from non-wandering to wandering status may reflect an undetected medical event that affects cognition, but spares mobility.

Another important aspect in using MDS comes from the ability to construct various instruments to reflect more complex domains than the individual MDS items are capable to measure. Van der Steen et al. included VA and Dutch NH residents diagnosed with moderate to severe dementia and used MDS items to create a MDS-derived definition for severe dementia (Van der Steen et al., 2006). They proposed a definition combining the evaluation of cognitive performance with activities of daily living: a resident would be considered severely demented if he/she had a Cognitive Performance Scale score of 5 or 6 with a minimum score of at least 10 points on the MDS Activities of Daily Living-Short Form.

The MDS was used and validated in previous research and provided us with the opportunity to evaluate outcomes and potential confounders not available from administrative data sources. Moreover, the addition of the MDS helped address one of the potential limitations of using VA administrative data sources exclusively in secondary studies- the out-of-system care.

Summary

To date, the management for urinary incontinence consists in a combined approach (drug therapy and behavioral interventions); an accurate estimate for the prevalence of medication use in long-term care facilities is yet to be established. These frail elderly living in NH are likely on multiple drugs regimens possibly including many drugs with anticholinergic effects, thus at increased risk

for medication-related adverse effects. The addition of a medication regimen (i.e. BAM) could provide individuals with the benefit of a better urinary incontinence management and QOL, but it could also increase their risk for undesirable health outcomes. Despite the indisputable importance of a proper disease management, safety should also be considered. The question whether more NH residents could benefit from a better disease management for urinary incontinence by increasing medication use does not have an easy answer. Previous research suggested that BAM pharmacologic properties combined with age and comorbidities induced changes in the BBB have the potential to determine cognitive functioning impairments. Along with the recognized anticholinergic side effects (e.g. blurred vision and dizziness) these could lead to an increase risk for falls and fall-related fractures. In contrast, studies also showed the negative impact of urinary incontinence on QOL and suggest that medication would play a positive role in improving these outcomes.

CHAPTER III- METHODS

Study overview

In 2002, the Centers for Medicare and Medicaid Services (CMS) NH Quality Initiative included urinary incontinence as a NH care quality indicator with an emphasis on prevention and proper management (U.S. Department of Health and Human Services [DHHS] CMS, 2006). However, this condition does not benefit from any curative intervention and there are no well-defined guidelines for pharmacological treatment in institutionalized elderly.

This research was conducted with a threefold purpose: (1) to describe the patterns of BAM use in VA CLC, (2) to quantify beneficial and (3) to quantify harmful outcomes of BAM use in an attempt to clarify the proper role of medication use in management of urinary incontinence in the NH setting.

The study was conducted by assembling a retrospective cohort of residents admitted for long-term care in the VA CLC and residing in these facilities between FY 2003 and FY 2009. For each patient an index date defined the cohort start date; this was either the first date of BAM use in the NH or a date matched for fiscal year at admission and assessment type among non-users. Data were collected from the MDS, as well as from VA enrollment, medical reimbursement and pharmacy records. As described previously, the quality and completeness of the VA MDS data improved over time; the first year of mandatory MDS data collection in the VA CLC was 2001, but data is considered of appropriate quality for research purposes starting with fiscal year (FY) 2003. Considering all these, we focused on a study period from FY 2003 through FY 2009. The year prior to the index date was used for construction of disease and medication histories; therefore, medical and pharmacy files from FY 2002 were

also included to evaluate medical history for subjects admitted in the nursing home during FY 2003.

For aim 1, in this population we described the important predictors of receiving different BAM, including demographics, baseline disease history, standardized measures of resident's cognitive, behavioral, functional, and medical stability status, and facility characteristics. Prevalent and incident BAM were identified, and the aforementioned characteristics were evaluated as predictors of BAM initiation in the NH.

For aim 2, new BAM users were compared with propensity score matched non-users for subsequent fracture risk; In addition, cognitive status was assessed throughout the follow-up period and generalized estimating equations (GEE) were used to evaluate cognitive decline in relationship to BAM use.

For aim 3 we determined the effect of BAM on improving the frequency of urinary incontinence episodes and QOL through measurements derived from MDS and evaluated using the GEE method.

Database Description

Of all the long term care programs and services, VA CLC has one of the richest databases available for research. This project utilized data from VA enrollment files, inpatient and outpatient administrative medical files, inpatient and outpatient pharmacy records, and MDS. Medical and pharmacy records one year prior to the index date were used for construction of disease and medication histories; as a consequence, for those subjects in the nursing home during FY 2003, data from FY 2002 was included, although the study follow-up started during FY 2003. Except for MDS, the administrative records datasets were readily available from the Center for Comprehensive Access & Delivery

Research and Evaluation (CADRE) at the Iowa City VAMC (formerly known as Center for Research in the Implementation of Innovative Strategies in Practice-CRIISP). The MDS data were obtained after approval within the VA Office of Patient Care Services system through a standardized data request process. This study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Affairs Research and Development Committee.

Assessment Data: The Minimum Data Set

The Long Term Care MDS represent a rich source of information that can complement medical and pharmacy records. MDS is a standardized tool developed for comprehensive assessment of residents of long-term care facilities and is mandatory in all of the VA CLC. MDS items are completed within 7 days of NH admission and repeated quarterly thereafter and at discharge. Significant changes in the residents' health status also require additional assessments. The MDS collects information on each resident's physical, psychological, cognitive and psycho-social functioning as well as assessment of end-stage disease (6 months or less to live), geriatric problems (e.g. falls and balance performance test, delirium, urinary incontinence and catheter use, pressure sores, height, weight, weight loss, weight gain), and demographic characteristics (education, life occupation) that are not well-identified in administrative files data (see Table 3.1).

Table 3.1: Minimum Data Set assessment sections

1. Demographic Information	10. Health Conditions
2. Cognitive Patterns	11. Oral/Nutritional Status
3. Communication/Hearing Patterns	12. Oral/Dental Status
4. Vision Patterns	13.Skin Condition
5. Mood and Behavior Patterns	14. Activity Pursuit Patterns
6. Psychological Well-being	15. Medications
7. Physical Functioning and Structural Problems	16. Special Treatments and Procedures
8. Continence in last 14 days	17. Discharge Potential and Overall Status
9. Disease Diagnosis	18. Assessment information

Administrative Files

Medical- Inpatient and Outpatient Files: Patient Treatment File- Extended files

This data source includes information on all VA hospitalizations and outpatient care. Key data elements include: demographic and socioeconomic information, military service-related disabilities, primary and secondary diagnoses and procedures, as defined by International Classification of Diseases, 9th Clinical Medication (ICD-9-CM) codes, admission source (e.g., transfer from another hospital), admission and discharge dates, and discharge disposition.

Pharmacy Records

VA pharmacy prescription and dispensing information is available for researchers from three main sources: (1) Veterans Health Information Systems and Technologies Architecture (VistA), (2) Pharmacy Benefits Management (PBM) Database, and (3) Decision Support System (DSS) National Data Extract (NDE) Pharmacy SAS® Datasets. While all prescription orders are captured at the local level in VistA, PBM and DSS originate from VistA extracts (See Figure 3.1). PBM and DSS pull data from all facilities to create national files.

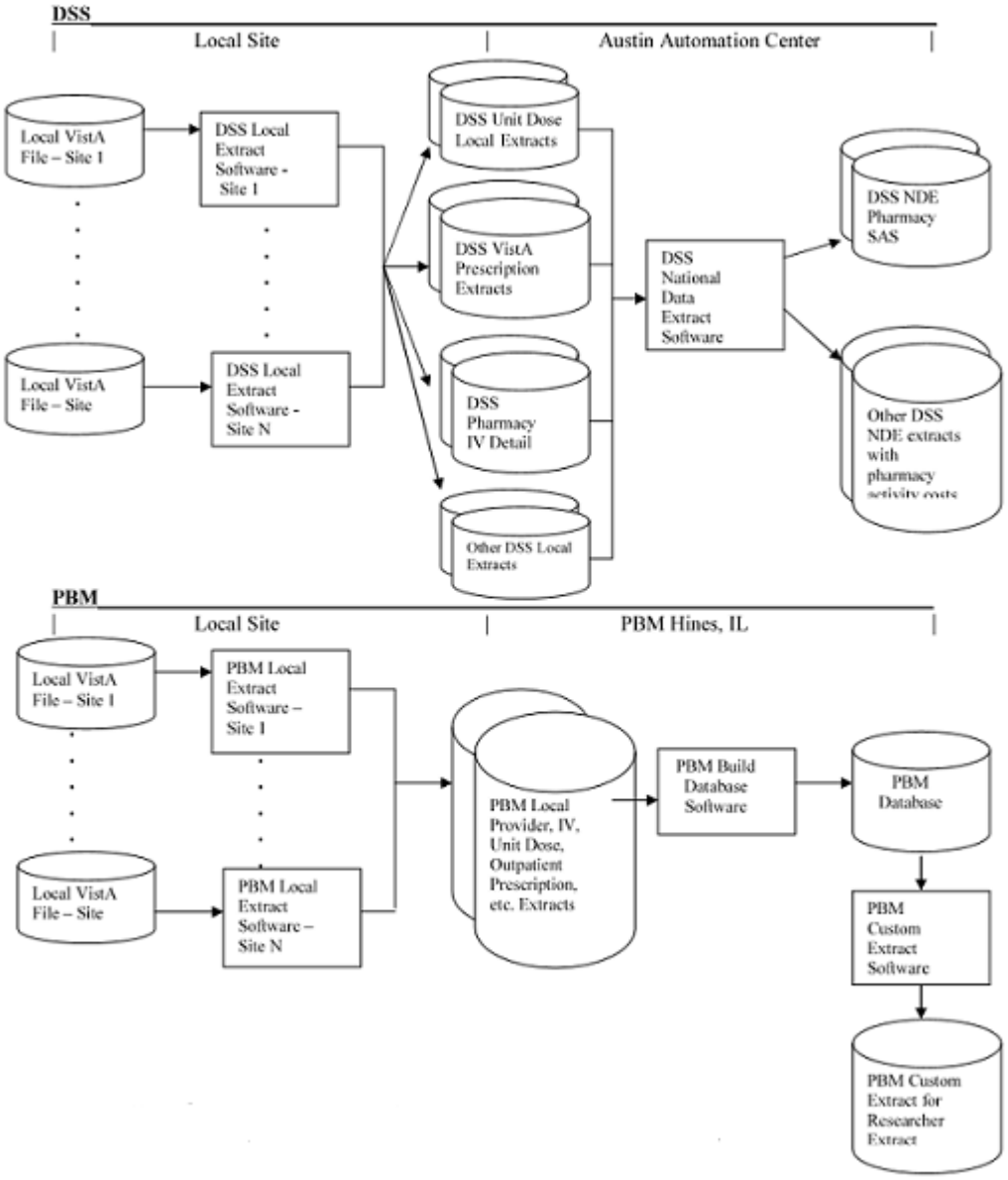


Figure 3.1: Flow of Pharmacy Prescription Data from Vista to Researcher Accessible Decision Support System and Pharmacy Benefits Management Data

For this research we used DSS-NDE datasets which are comprehensive, recording all aspects of prescription drug therapy across inpatient and outpatient settings (Smith et al., 2003). Prescription data include limited patient information, details about the condition being treated, and an indicator linkable to National Drug File records, thus allowing for richer medication description (Arnold et al., 2003). The drug codes in VA Pharmacy Database have an estimated accuracy of 97.1% (Arnold et al., 2006).

These records represented the source of information for determining exposure to BAM, including detailed description of the drug dispensed (generic name: Oxybutynin, Tolterodine, or other type; slow-acting vs immediate-release) and exposure-time. They were also used to construct medication covariates.

Table 3.2: Data elements in pharmacy databases

Category	Available information
Medication	National Drug Code Product Name VA Drug Class National formulary indicator National Formulary Restrictions
Dispensing details	Fill Date Prescription Number Total Quantity Dispensed Dispensing Unit Day SupplyNew Fill/Refill/Partial Dosing Instructions

Source Population

Our study population was identified using MDS assessments data from the VA operated nursing homes between FY 2003 and FY 2009. According to a VA report, from 2000 through 2004, the average daily census across all VA NH

ranged from 11,000 to more than 12,000 residents; VA guidelines required admission assessments on all residents admitted for 14 days or more (VA Long Term Care GAO Report 2004, 2006).

Figure 3.2 below maps the distribution of the Veterans integrated service network (VISN) Regions. Each region operates one or more Community Living Centers.

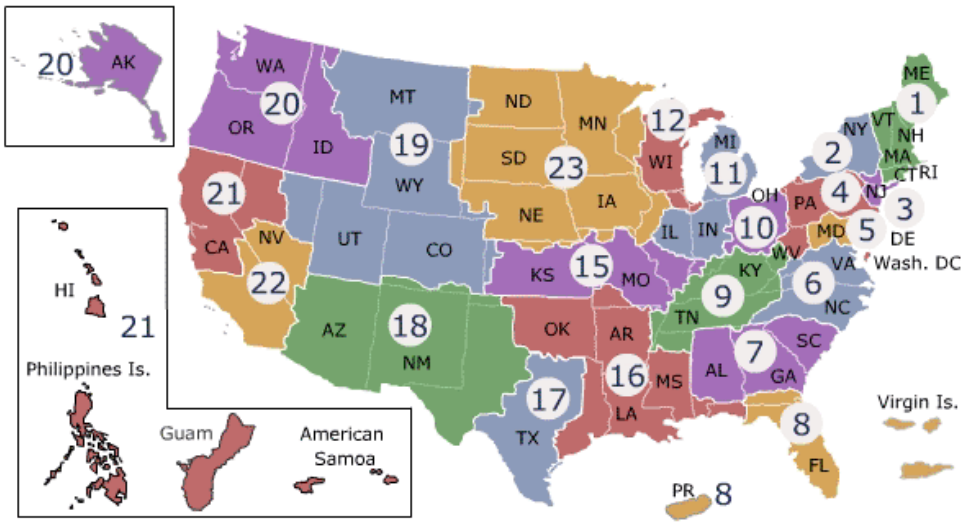


Figure 3.2: Distribution of Veterans Integrated Service Network Regions

Study Design

We designed a retrospective cohort study using the new-user approach.

Index date definition and baseline selection

For new-users, the index date was identified as the first date a BAM was prescribed during their NH stay. In this group, the baseline characteristics were measured from the last MDS assessment conducted before the index date and from administrative data in the one year before the index date.

In order to assure comparability of baseline data source and time spent in the nursing home, for those identified in the nonusers group, index dates were chosen such that the distribution of baseline assessment type (admission versus periodic) was matched to that among BAM new-users. In order to accomplish this, based on the distribution of new-users, for each FY, non-users were first randomly assigned to have their baseline evaluation based as either their admission or a periodic assessment. Next, an index date was randomly chosen such that the baseline assessment type was the one assigned earlier.

Subject Selection

For our study, inclusion criteria were the following: (1) veteran residing in a VA CLC facility and admitted during FY 2003-2009; (2) age 65 and older at admission; (3) admitted for long-term care. Residents were excluded if they (1) were comatose at admission in the NH; or (2) were confined to bed. In addition, those identified with important risk factors (.e.g. bone cancer) were excluded from the fracture risk analysis.

We included in the long-term care pool only those residents who had been in a VA CLC facility for a minimum of 90 days (operationally defined as having at least one quarterly assessment following the admission assessment). We are aware that this definition resulted in the exclusion of residents who were admitted with the intention for long-term care but who died or were transferred before residing in the facilities for the required minimum time. However, the MDS data does not provide a better method to identify intent for long-term versus rehabilitation care. The approach was based on previous research and it ensured that the sample included only long-term care.

Measures

Exposure to Bladder Antimuscarinics

Exposure to the drugs of interest was assessed using the VA class list and a variable in the DSS (feeder key) pharmacy prescription records. The first five digits in in the feeder key contain an Internal Entry Number (IEN) which points to the entry in the VistA VA Product File for the drug dispensed and the last 12 digits contain the 12-digit version of the National Drug Code. The IEN was used to identify all of the drugs containing a certain active ingredient. The list of drugs included in the BAM group along with their corresponding IENs is listed in Appendix 1. Both immediate-release (IR) and slow-acting (SA) drugs were included.

Medication was considered active from the first prescription after admission in the NH and the date on the first BAM prescription record was defined as the index date for the exposed group. Exposed person-time was determined from the dispensing dates and gaps between two consecutive records, as documented in the automated pharmacy records. Exposure to medication started on the initial date a BAM was dispensed and extended until the earliest of: (1) discontinuation of therapy, calculated as 7 days following the last prescription record; (2) death; (3) discharge from the NH; (4) the end of the study period.

For patients included in the comparison group of BAM non-users, follow-up person-time started on the assigned index date and was extended until the earliest of 1) death; 2) the end of follow-up; 3) the end of the study period. Since this was a new-users design the following criteria were considered when deciding our new-user definition:

a. The urinary incontinence management guidelines for NH patients require a combination of behavioral approaches with or without pharmacological interventions; the implementation of these guidelines is evaluated through NH care quality indicators. If a NH resident becomes urinary incontinent, medication should be initiated only after a 3 days trial of prompted-voiding/behavioral interventions.
b. The medication administered to a VA CLC resident during the NH stay is prescribed and dispensed similarly to an inpatient setting. Patients are not permitted to bring and use medication from home. Any chronic medication prescribed before a NH admission is continued and a NH inpatient prescription order is placed within 12 hours after entering the facility.

Based on the information above, we defined the following users' categories (see Figure 3.3 below):

1. New user: an individual who's first dispensing of a BAM occurred more than 3 days after being admitted in a VA NH and who did not have any BAM prescription one year prior to this first prescription date. Since out-of-system care would not be observable using VA data, in order to assure the accuracy of this definition, we required pharmacy prescriptions, outpatient visits, and/or hospital admission in a VA facility in the year before the NH admission.
2. Prevalent user: an individual who is using BAM immediately after NH admission (first prescription ≤ 3 days after admission) or who had prescriptions in the year prior to the NH admission and during the NH stay included in the study.
3. Former user: an individual with at least one BAM prescription in the year prior to the NH admission. These users were excluded from the analysis.

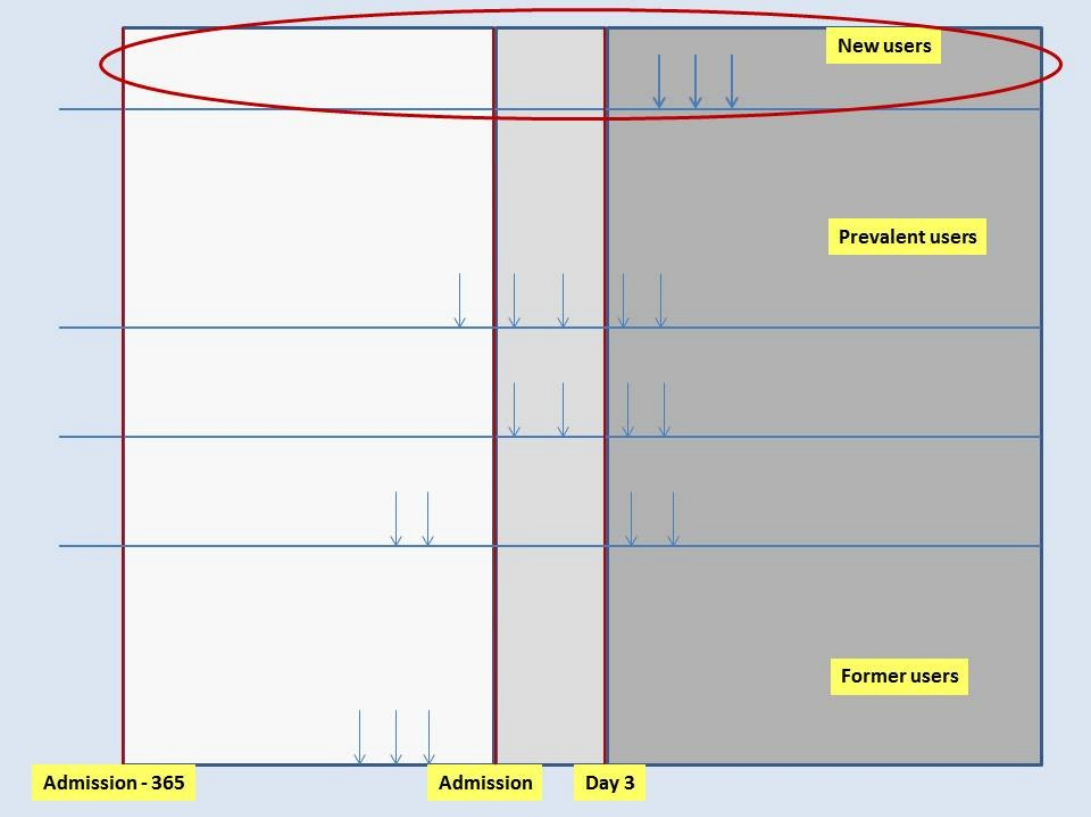


Figure 3.3: Definition of bladder antimuscarinics users

Outcomes

Hip Fracture

New hip fractures during follow-up time were identified by combining the information from three VA data sources: hospital discharges, outpatient visits, and MDS assessments as described below.

In the inpatient discharges records we looked for specific ICD9 codes for hip fractures (808.xx, 820.xx, or 821.xx) in any diagnostic field (Chrischilles et al., 2001; van Lenthe et al., 2011) and the date of the event date was considered as the date of the hospital admission date.

Similarly, in the outpatient visits records we looked for the aforementioned ICD9 codes in any diagnostic field and the event date was assigned as the date of the outpatient visit.

The MDS assessments reported whether the individual had sustained a hip fracture in the 180 days before the assessment. If the answer was ‘yes’, a new fracture was considered to have happened only if the previous assessment did not have any indication of a hip fracture.

After hip fractures were identified from all the sources, we evaluated their overlap.

For hip fractures identified from outpatient visits exclusively we verified further before deciding whether that was a new event; specifically, we looked in the year before the visit date for any hospitalizations with a hip fracture code listed in any of the diagnosis fields; if inpatient data was identified, the hip fracture was considered an ‘old’ fracture and was excluded from the analysis. Similarly, for the fractures identified from MDS only, we evaluated inpatient and outpatient data sources looking for hip fracture ICD9 codes in the year prior to the MDS assessment date.

A hospital discharge provides a more precise hip fracture ascertainment; however, the potential for out of the system care for VA beneficiaries is a known issue. Based on this and considering the fact that hip fractures are rare events, we decided to include all of the fractures we identified, regardless of their identification source. About 1/3 of the new fractures identified in our cohort did not have any inpatient and/or outpatient record.

When combining the information from the three sources of data, the final hip fracture definition was as follows:

- If the fracture was identified through a hospital discharge or an outpatient visit, the date of the event was considered the earliest date of the two.
- If the fracture was identified from MDS exclusively, the midpoint date between the two MDS assessments dates described above was assigned as the event date.

The follow-up time for the fracture analysis was calculated from the index date; the 'end' date was considered for the exposed and control group as follows:

- New-users: the earliest of:
    - Discontinuation of therapy defined as seven days after the last prescription of a BAM during the NH stay. This approach allowed for gaps in exposure; however, given the random assignment for the fracture date for those fractures identified from MDS exclusively and the small number of fractures, a more precise measure of exposure could have led to outcome misclassification. In order to account for these gaps, each follow-up day was classified as exposed or unexposed and an indicator for the exposed time relative to the total follow-up time was included in the analysis.
    - Outcome (hip fracture)
    - The end of the NH follow-up:
        - Admission to a non-VA acute care facility- Identification of a NH discharge code 'discharge, return anticipated' without identifying an admission to a VA acute care facility- the individual was censored at the time of the NH discharge because of the discontinuation in follow-up;
        - Identification of a MDS reentry assessment without a discharge code on a prior assessment and without

identifying an admission to a VA acute care facility- the individual was censored at the time of the last MDS assessment before reentry

- A gap of more than 100 days between two consecutive periodic assessments without identifying an admission to a VA acute care facility sometime between the two assessments- the individual was censored at the time of the first periodic assessment of the two
- Discharge from the NH (discharge code 'discharge, return not anticipated')
- Death
- The end of the study period

- Non-users:
  - Outcome (hip fracture)
  - The end of the NH follow-up (see above)
  - Death
  - The end of the study period.

Any Fracture

This outcome was defined using an algorithm that was similar to the one used for identifying hip fractures by combining the information from three VA data sources: hospital discharges, outpatient visits, and MDS assessments.
The ICD9-CM codes included all fractures code (800.xx-829.xx); from MDS two items were included: 'Hip fracture in last 180 days' and 'Other fracture in last 180 days'. For those that experienced multiple fractures, only the first one was included in this analysis.

Cognitive Status

Cognitive status in NH residents can be evaluated through different instruments that were developed using MDS elements. The most frequently used scales are the Cognitive Performance Scale (CPS) and the MDS- Cognition Scale (MDS-COGS). Both scales are calculated from a set of 10 cognitive items and one functional item, but CPS is hierarchical, whereas MDS-COGS is additive. CPS was developed using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Test of Severe Impairment (TSI) (Albert et al., 1992) as criterion measures, whereas MDS-COGS was constructed from the Global Deterioration Scale (Hartmaier et al., 1994). Both instruments have high internal consistency and moderate construct validity when compared with the Mini-Mental State Examination and the staff rating on the Psychogeriatric Dependency Rating Scale (Hartmaier et al., 1995; Morris et al., 1994). The CPS is not as sensitive as MDS-COGS in capturing the severe cognitive decline (Hartmaier et al., 1994). However, CPS can be calculated from items required on all assessments but MDS-COGS require items present only on full MDS assessment form. Moreover, the internal consistency for CPS was shown to be higher without the comatose item, one of our study's exclusion criteria (Gruber-Baldini et al., 2000). Considering all these, in this study we used CPS as the measure for the cognitive status for our study population.
Figures 3.4 and 3.5 illustrate the scoring mechanism for CPS (Morris et al., 1994) and the algorithm used in calculating the score.

CPS combines information on memory impairment, level of consciousness, and executive function, with scores ranging from 0 (intact) to 6 (very severe impairment). The CPS has been shown to be highly correlated with

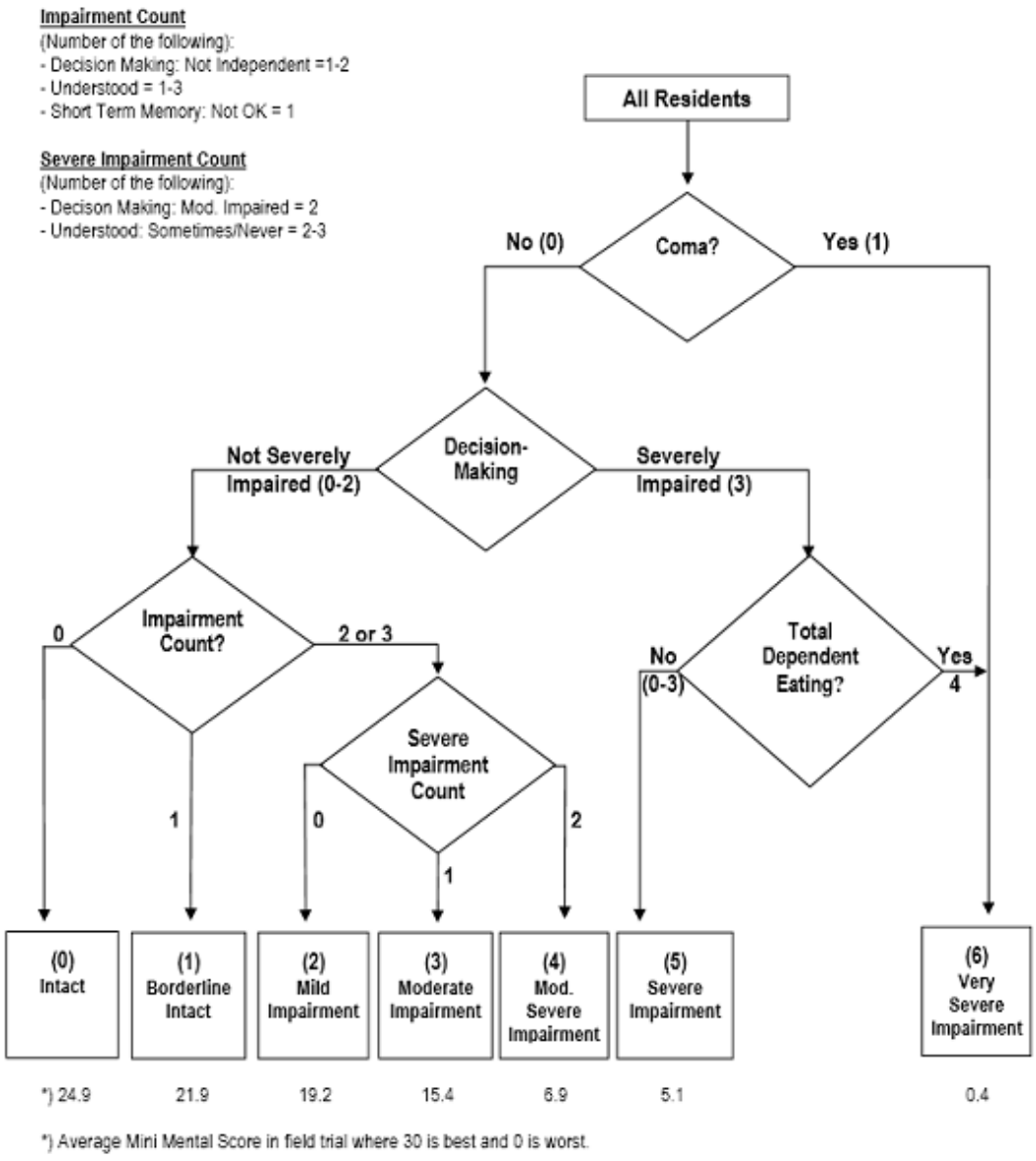
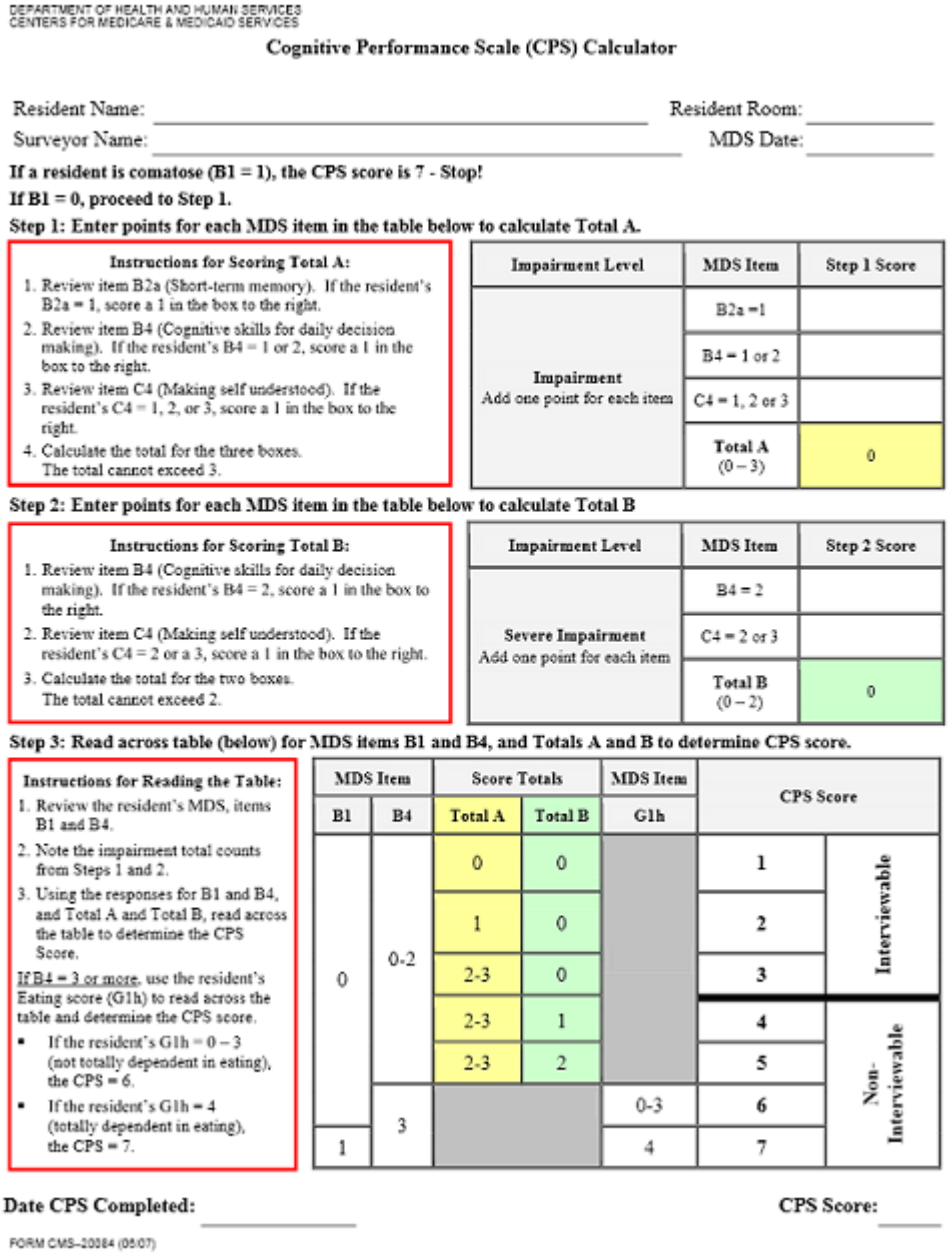


Figure 3.4 Construction of Cognitive Performance Score



DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICES

Cognitive Performance Scale (CPS) Calculator

Resident Name: _____ Resident Room: _____

Surveyor Name: _____ MDS Date: _____

If a resident is comatose (B1 = 1), the CPS score is 7 - Stop!

If B1 = 0, proceed to Step 1.

Step 1: Enter points for each MDS item in the table below to calculate Total A.

Instructions for Scoring Total A:

1. Review item B2a (Short-term memory). If the resident's B2a = 1, score a 1 in the box to the right.
2. Review item B4 (Cognitive skills for daily decision making). If the resident's B4 = 1 or 2, score a 1 in the box to the right.
3. Review item C4 (Making self understood). If the resident's C4 = 1, 2, or 3, score a 1 in the box to the right.
4. Calculate the total for the three boxes. The total cannot exceed 3.

Impairment Level	MDS Item	Step 1 Score
Impairment Add one point for each item	B2a =1	
	B4 = 1 or 2	
	C4 = 1, 2 or 3	
	Total A (0 – 3)	0

Step 2: Enter points for each MDS item in the table below to calculate Total B

Instructions for Scoring Total B:

1. Review item B4 (Cognitive skills for daily decision making). If the resident's B4 = 2, score a 1 in the box to the right.
2. Review item C4 (Making self understood). If the resident's C4 = 2 or a 3, score a 1 in the box to the right.
3. Calculate the total for the two boxes. The total cannot exceed 2.

Impairment Level	MDS Item	Step 2 Score
Severe Impairment Add one point for each item	B4 = 2	
	C4 = 2 or 3	
	Total B (0 – 2)	0

Step 3: Read across table (below) for MDS items B1 and B4, and Totals A and B to determine CPS score.

Instructions for Reading the Table:

1. Review the resident's MDS, items B1 and B4.
2. Note the impairment total counts from Steps 1 and 2.
3. Using the responses for B1 and B4, and Total A and Total B, read across the table to determine the CPS Score.

If B4 = 3 or more, use the resident's Eating score (G1h) to read across the table and determine the CPS score.

- If the resident's G1h = 0 – 3 (not totally dependent in eating), the CPS = 6.
- If the resident's G1h = 4 (totally dependent in eating), the CPS = 7.

MDS Item		Score Totals		MDS Item	CPS Score	
B1	B4	Total A	Total B	G1h		
0	0-2	0	0		1	Interviewable
		1	0		2	
		2-3	0		3	
		2-3	1		4	Non-Interviewable
		2-3	2		5	
	3			0-3	6	
1				4	7	

Date CPS Completed: _____ **CPS Score:** _____

FORM CMS–20084 (05/07)

Figure 3.5: Cognitive Performance Scale Scoring Algorithm

the MMSE in a number of validation studies. The MDS parameters included are as follows:

(1) Comatose (item B1) – this is part of exclusion criteria and was not considered for calculating our outcome variable

(2) Problem with short-term memory (item B2a)

(3) Cognitive skills for daily decision making (item B4)

(4) Being understood by others (item C4)

(5) Activities of daily living (ADL) self-performance in eating (item G1ha).

Improvement of the Urinary Incontinence Symptoms

This outcome was measured by combining two elements from the MDS assessments- the bladder control rating and the 'change in urinary incontinence' variable (Table 3.3). The MDS bladder control rating instrument (see below) evaluates urinary incontinence on a 5-point scale from 0 (complete control) to 4 (inadequate control with multiple daily episodes of urinary incontinence). This measure is reliable (inter-rater reliability = 0.90) and valid (good correlation with research staff wet checks) (Hawes et al., 1991; Hawes et al., 1995; Crooks et al., 1995; Resnick et al.,1996). We evaluate improvement by constructing a dichotomized variable (improvement yes/no) based on the information available. Specifically, improvement was defined as when either improvement was checked on the 'change in urinary incontinence' variable and/or the score on the bladder control rating improved between two MDS assessments.

Table 3.3. Minimum Data Set elements for defining improvement in urinary incontinence

SECTION H: CONTINENCE IN LAST 14 DAYS		
H1	**CONTINENCE SELF-CONTROL CATEGORIES**	
	(Code for resident's PERFORMANCE OVER ALL SHIFTS) 0. CONTINENT- Complete control (includes use of indwelling catheter that does not leak urine) 1. USUALLY CONTINENT- BLADDER incontinent episodes once a week or less 2. OCCASIONALLY INCONTINENT- BLADDER 2 or more times per week, but not daily 3. FREQUENTLY INCONTINENT- BLADDER tended to be incontinent daily, but some control present 4. INCONTINENT- Had inadequate control BLADDER, multiple daily episodes	
H4	**CHANGE IN URINARY CONTINENCE**	Resident's urinary continence has changed as compared to status of 90 days ago (or since last assessment if less than 90 days) 0. No change 1. Improved 2. Deteriorated

Quality of Life Outcomes

Medication use may influence quality of life (QOL) by both tolerability of an agent (side effects) and the extent to which it relieves urinary symptoms. The balance of these effects determines whether an agent improves an individual's ability to function physically, emotionally, and socially.

Social engagement, the extent to which an individual is active and embedded in a social context, was shown to be an important predictor for psychosocial well-being, an important QOL domain (Mor et al., 1995; Gerritsen et al., 2004). In elderly admitted for long-term care in NH, higher levels of social engagement were shown to decrease mortality (Kiely et al., 2003). A recent study by Dubeau et al. evaluated QOL in NH residents with urinary incontinence using a measure of social engagement derived from the MDS (Dubeau et al., 2006). This scale is reliable and valid and emphasizes positive social behavior and assesses a resident's willingness to participate in social opportunities and to initiate actions that engage the resident in the life of the NH (Dubeau et al., 2006).

In this research we examined indicators of quality of life from MDS ratings. From the periodic MDS assessments we constructed the MDS-QOL index for psychosocial well-being (MDS-Index of Social Engagement; MDS-ISE) (Mor et al., 1995); in addition, a MDS-based generic scale, the MDS-Health Status Index (MDS-HSI), was considered to evaluate the overall QOL.

The ***MDS-Index of Social Engagement***, MDS-ISE describes the individual's sense of initiative and involvement in social activities (Table 3.4). The scale was validated in a nursing home population by comparing its scores with actual time spent in activity programs. MDS-ISE was calculated from six MDS items scored dichotomously as positive versus absent and ranges from 0 (severe withdrawal) to 6 (high level of participation and initiative). Intraclass reliability between research and facility nurses for the items ranges from 0.51 to 0.64 (Hawes et al., 1995) and the instrument is internally consistent (Cronbach α= 0.79) (Mor et al., 1995). MDS-ISE is in accordance with the World Health Organization definition of QOL ‘‘incorporating . . . physical health, psychosocial state, level of independence, social relationship, personal benefits and relationships to salient features in the environment’’ (Health Promotion Glossary, 1998). Social engagement is directly related to important QOL domains specified for NH residents (including those with dementia): autonomy (taking of initiatives), individuality (expression of preferences and pursuance of interests), and enjoyment (verbal and nonverbal expressions), meaningful activity (partake in discretionary behaviors that are interesting, stimulating, and worthwhile), relationships, and functional competence (independent function in keeping with abilities and preferences) (Kane et al., 1999).

Table 3.4. Minimum Data Set -Index of Social Engagement

At ease interacting with others (item F1a)	Consider how the resident behaves during the time you are together and reports of how the resident behaves with other residents, staff, and visitors. Residents who try to shield themselves from being with others, spend most of their time alone, or become agitated when visited are not “at ease with others.”
At ease doing planned or structured activities (item F1b)	Consider how the resident responds to organized social or recreational activities. Residents who feel comfortable with the structure or not restricted by it are “at ease with doing planned or structured activities.” Residents who are unable to sit still in organized group activities and act disruptive or make attempts to leave or refuse to attend such activities are not “at ease with doing planned or structured activities.”
At ease doing self-initiated activities (item F1c)	These include leisure activities (e.g., reading, watching TV, talking with friends) and work activities (e.g., folding personal laundry, organizing belongings). Residents who spend most of their time alone and unoccupied or who are always looking for someone to find something for them to do are not “at ease doing self-initiated activities.”
Establishes own goals (item F1d)	Consider statements the resident makes, such as “I hope I am able to walk again,” or “I would like to get up early and visit the beauty parlor.” Goals can be as traditional as wanting to learn how to walk again after hip replacement or wanting to live to say goodbye to a loved one. Some goals may not be verbalized by the resident but may be inferred in that the resident is observed to have an individual way of living at the facility (e.g., organizing own activities or setting own pace).
Pursues involvement in life of facility (item F1e)	Consider whether the resident partakes of facility events, socializes with peers, and discusses activities as if he or she is part of things. Residents who convey a sense of belong to the community represented by the nursing home or the particular nursing unit are “involved in the life of the facility.”
Accepts invitations into most group activities (item F1f)	Residents who are willing to try group activities even if they later decide the activity is not suitable and leave or who do not regularly refuse to attend group programs “accept invitations into most group activities.”

For the overall assessment of the HRQOL as one of our outcomes variables we used a generic QOL instrument derived from the MDS - the ***MDS-Health Status Index*** (MDS-HSI). This instrument was originally constructed by mapping the Health Utilities Index Mark 2 (HUI2) with elements from MDS. The HUI2 attributes range from severely impaired to no impairment/normal on a four or five levels scale. This scale uses standard gamble-based Canadian community preference weights to obtain a cardinal index of HRQOL with a range of -0.02 through 1.0, where a score of 0 represents dead and 1.0 represents the best possible health one could expect to achieve (Furlong et al., 2001; Torrance et al., 1996). A negative score implies health states worse than dead. A difference of 0.03 or more on an overall score is considered clinically important based on cross-sectional and longitudinal comparisons of known groups (Drummond, 2001).

The MDS-HSI instrument encompasses six attributes to define health states: cognition, self-care, mobility, sensation (vision, hearing, and speech), emotion, and pain (Furlong et al., 2001; Torrance et al., 1996). After mapping specific MDS elements to each attribute of the HUI2 classification system, scores are assigned using the HUI2 preference weights (Phillips et al., 1997). Previous studies have shown a good relationship between the HUI2 and the MDS-HSI in older community dwelling and institutional long-term care residents (Wodchis et al., 2003). Also, MDS-HSI has good construct and convergent validity; MDS-HSI scores and related summary functioning scores are highly correlated (Wodchis et al., 2003 and 2007). Table 3.5 below presents the mapping system that Wodchis et al. used for creating MDS-HSI (Wodchis et al., 2003).

Table 3.5. Minimum Data Set -Health Status Index mapping to Health Utility Index 2

Attribute	MDS variable	HUI2 level, description, and preference weight[a]	
Sensation (vision, hearing, speech)	No vision, hearing, or communication difficulty	1. Able to see, hear, and speak normally for age	1.00
	Minimal impairment (with or without aids)	2. Requires equipment to see or hear or speak	0.95
	Highly impaired (with or without aids)	3. Sees, hears, or speaks with limitations, even with equipment	0.86
	Severely impaired (with or without aids)	4. Blind, deaf, or mute	0.61
Mobility	Independent in locomotion	1. Able to walk, bend, lift, jump and run normally for age	1.00
	Supervision but no physical help from others & no devices	2. Walks, bends, lifts, or jumps with some limitations; no help required	0.97
	No physical help & self-supporting devices (cane, walker, self-wheel)	3. Requires mechanical equipment (such as canes, crutches, braces or wheelchair) to walk or get around independently	0.84
	Physical help from others & use of devices	4. Requires the help of another person to walk or get around and requires equipment	0.73
	Total dependence on others	5. Unable to control or use arms and legs	0.58
Emotion	No negative mood indication in last 30 days (5 indicators)	1. Generally happy and free from worry	1.00
	Up to two indications exhibited 1–5 days per week	2. Occasionally fretful, angry, irritable, anxious, depressed, or suffering "night terrors"	0.93
	Any one daily or at least three exhibited 1 to 5 days per week	3. Often fretful, angry, irritable, anxious, or depressed	0.81
	Two or three indicators exhibited daily	4. Almost always fretful, angry, irritable, anxious, or depressed	0.70
	Four or five indicators exhibited daily	5. Extremely fretful, angry, irritable, anxious, or depressed usually requiring hospital or psychiatric care	0.53
Cognition	No problem with memory or decision-making	1. Learns and remembers normally for age	1.00
	Memory problem or mild impairment in decisionmaking	2. Learns and remembers more slowly than peers	0.95
	Moderate impairment in decision-making	3. Learns and remembers very slowly	0.88
	Severe impairment in decision-making	4. Unable to learn and remember	0.65
Self-care	Independence in all these activities	1. Eats, bathes, dresses, and uses toilet normally for age	1.00
	Supervision by others but no assistance for any of these activities	2. Eats, bathes, dresses, or uses the toilet independently with difficulty	0.97
	Limited assistance in any of these activities	3. Requires equipment to eat, bathe, dress, or use the toilet independently	0.91
	Extensive assistance or total dependence in any of these activities	4. Requires help of another person to eat, bathe, dress, or use the toilet	0.80
Pain	No pain	1. Free from pain and discomfort	1.00
	Pain less than daily, not requiring prescribed medications	2. Occasional pain. Discomfort relieved by nonprescription drugs or self control without activity disruption	0.97
	Pain daily, not intense, disrupts activities, and relieved by medication	3. Frequent pain. Discomfort relieved by oral medicines with occasional disruption of normal activities	0.85
	Pain daily, intense, disrupts activities, and relieved by medication	4. Frequent pain; frequent disruption of normal activities. Discomfort requires prescription narcotics for relief	0.64
	Pain daily, intense, disrupts activities, and not relieved by medication	5. Severe pain; pain not relieved by drugs and constantly disrupts normal activities	0.38

Exploratory Outcomes

In an attempt to have a better understanding of the potential effects of BAM in this population, additional outcomes were explored. Mortality and bowel effects (constipation and fecal impaction) were evaluated in relationship to BAM initiation. Cardiovascular outcomes (arrhythmia) were also considered, but not included in the analyses based on data availability. Specifically, MDS does not allow for identification of a new arrhythmia case; the only available option was to define the outcome based on ICD-9 codes (427.1, 427.4, 427.41, 427.42, 427.5, 798.1, and 798.2). However, as discussed earlier in the hip fracture definition, using ICD-9 codes will likely introduce outcome misclassification due to a low sensitivity.

Mortality

The date of death (DOD) was available from multiple sources and all-cause mortality was evaluated as part of the exploratory analyses. Data from the following sources was combined to identify DOD for those included in our cohort:

a. MDS- if item r3a (discharge status) = 8 (deceased) then DOD=date of discharge (item r4)
b. Inpatient, long-term care – type of discharge=death, with autopsy (distype=6) or type of discharge=death, without autopsy (distype=7) then DOD= date of discharge (disday)
c. Inpatient, acute care- DOD variable

In the situation when DOD was available from multiple sources without perfect overlap, the earliest date was adjudicated as the final DOD.

Bowel Effects

These outcomes were explored as potential parasympathetic BAM adverse event and were measured using the MDS items H2b (constipation- yes/no) and H2d (fecal impaction- yes/no).

Covariates

Demographics

The demographic section on the full MDS assessments provided information on demographic characteristics for all the subjects included in our study.

Age was calculated based on the date of birth and the index date and was evaluated as both continuous and categorical variable (as described in the statistical analysis section below). Since our study population only included subjects 65 or older, the following age categories were created: (1) 65 to 69, (2) 70 to 74, (3) 75 to 79, (4) 80 to 84, and (5) 85 and older.

Gender was coded as “Male” or “Female”.

Race and ethnicity variables were available and were originally coded as: (1) American Indian/Alaskan Native, (2) Asian/Pacific Islander, (3) Black, not of Hispanic origin, (4) Hispanic, (5) White, not of Hispanic origin. For the purposes of this investigation, White, Black, and other (including American Indian/Alaskan Native, Asian/Pacific Islander, and Hispanic) were the main categories considered.

When discrepancies were found (different values assigned to the same unique scrambled SSN), the discrepancy was resolved by noting which value was coded on the bulk of the MDS assessments.

In addition to these personal demographic characteristics, information on the VISN where the CLC was located and information on the FY at admission in the nursing home were incorporated in our analyses.

Baseline Conditions and Comorbidities Measures

Selection bias may result in differences in comorbidity at baseline. As different treatment decisions may be influenced by underlying comorbidities these need to be measured as accurately as possible. In this analysis, baseline conditions and comorbidities were measured from data collected during the routine MDS assessments and also from inpatient and outpatient administrative files.

The Elixhauser modified by Quan algorithm (Elixhauser et al., 1998; Quan et al., 2005) was used to identify important confounding conditions. This diagnosis-based algorithm originally consisted of 30 conditions, each marked with a dichotomous indicator variable using ICD-9-CM codes from the available inpatient administrative data (Elixhauser et al., 1998; Quan et al., 2005). The algorithm was modified to also include outpatient administrative data (Groeneveld et al., 2009; Weinhandl et al., 2009; Li et al., 2010). A full list of the Quan modified Elixhauser conditions and associated ICD-9 codes are included in Table 3.6.

Conditions that have been reported to be potential risk factors for the study outcomes or with unknown relationship to the outcome(s) but likely to be associated with exposure to BAM were included (see Table 3.6). In addition, we created a variable indicating the number of comorbidities identified through the Elixhauser algorithm, and an indicator of whether the person had any hospitalizations and/or outpatient visits for a comorbidity included in this algorithm.

Table 3.6: List of comorbidities (Quan-Elixhauser and Minimum Data Set)

Condition	ICD-9 codes	MDS assessment	Included in the analysis (source)
Quan modified Elixhauser algorithm			
Congestive heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0-428.9	Item I1f	Yes (ICD-9 combined with MDS)
Cardiac arrhythmias	426.10, 426.11, 426.13, 426.2-426.53, 426.6-426.89, 427.0, 427.2, 427.31, 427.60,427.9, 785.0, V45.0, V53.3	Item I1e	Yes (MDS)
Valvular disease	093.20-093.24, 394.0-397.1, 424.0-424.91, 746.3-746.6, V42.2, V43.3		No
Pulmonary circulation disorders	416.0-416.9, 417.9		No
Peripheral vascular disorders	440.0-440.9, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1,557.9, V43.4		No
Hypertension, uncomplicated	401.1, 401.9	Item I1h (Hypertension)	Yes (ICD-9 combined with MDS)
Hypertension, complicated	402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99		
Paralysis	342.0-342.12, 342.9-344.9		Yes (ICD-9)
Other neurological disorders	331.9, 332.0, 333.4,333.5, 334.0-335.9,340, 341.1-341.9, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1, 348.3, 780.3, 784.3		No
Chronic pulmonary disease	490-492.8, 493.00-493.91, 494, 495.0-505, 506.4		Yes (ICD-9)
Diabetes, uncomplicated	250.00-250.33	Item I1a (Diabetes mellitus)	Yes (ICD-9 combined with MDS)
Diabetes, complicated	250.40-250.73, 250.90-250.93		
Hypothyroidism	243-244.2, 244.8, 244.9		No
Renal failure	300- 403.11, 403.91, 404.12, 404.92, 585, 586, V42.0,V45.1,V56.0,V56.8		No
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9,572.3,572.8, V42.7		No

Table 3.6 continued

Peptic ulcer disease excluding bleeding	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70,534.90, V12.71		No
AIDS	042-044.9		No
Lymphoma	200.00-202.38, 202.50-203.01,203.8-203.81, 238.6, 273.3,V10.71,V10.72,V10.79		No
Metastatic cancer	196.0-199.1		Yes (ICD-9)
Solid tumor without metastasis	140.0-172.9,174.0-175.9,179-195.8, V10.00-V10.9		No
Rheumatoid arthritis/collagen vascular diseases	701.0, 710.0-710.9, 714.0-714.9, 720.0-720.9, 725		No
Coagulopathy	286.0-286.9, 287.1, 287.3-287.5		No
Obesity	278	calculated based on item K2a and item K2b	Yes (MDS)
Weight loss	260-263.9		No
Fluid and electrolyte disorders	276.0-276.9		No
Blood loss anemia	280		No
Deficiency anemias	280.1-281.9, 285.9		No
Alcohol abuse	291.1, 291.2, 291.5, 291.8, 291.9, 303.90-303.93,305.00-305.03, V113		No
Drug abuse	292.0, 292.82-292.89,292.9,304.00-304.93, 305.20-305.93		No
Psychoses	295.00-298.9, 299.10-299.11		Yes (ICD-9)
Depression	300.4, 301.12, 309.0, 309.1, 311	Item I1ee	Yes (ICD-9)
Other conditions			
Hypotension		Item I1i	Yes (MDS)
Hip fracture before index date	808, 820, 821	Item J4c and Item I1m	Yes (ICD-9 combined with MDS)
Osteoporosis	733.0	Item I1o	Yes (ICD-9 combined with MDS)
Pathological Bone fracture	170, 198.5	Item I1p	Yes (ICD-9 combined with MDS)

We evaluated whether inpatient only, or a combination of inpatient and outpatient administrative data sources should be used to identify comorbidities in our study population and a final decision was made based on the data.
In addition, Section I from the MDS assessment (Disease Diagnoses) form was evaluated as possible source of active comorbidities (see Table 3.6). For the conditions that were identified with both algorithms (i.e. Elixhauser and MDS), new variables were created and evaluated; these new variables considered the condition if either source indicated it.

Medication Covariates

Exposure to drugs that could confound the relationship between our exposure of interest and the study outcomes was identified using a similar approach to the one we used to evaluate exposure to BAM. Specifically, we evaluated the complete listing of drugs used in our cohort using the VA drug classes and the unique IENs. For each class of interest, we compiled the list of IENs that were then used to create indicators of specific medications use prior to the index date. The following classes of drugs were evaluated: (1) Alpha-blockers; (2) Beta-blockers; (3) Calcium channel blockers; (4) Angiotensin-converting-enzyme (ACE) inhibitors; (5) Diuretics; (6) Cognitive enhancers; (7) Benzodiazepines (BZD); (8) Antipsychotics; (9) Antidepressants; (10) Antivertigo agents; (11) Anti-Parkinson agents; (12) Anticonvulsants. Appendices 2 through 13 include the complete list of drugs with their corresponding IENs and VA drug class.

Exposure to medication was also evaluated through two additional variables. The first one was measured using the MDS item O1 (Number of medication in the last 7 days) and was categorized as ≤ 3 drugs, 3 – 10, and ≥ 10 drugs. The second measurement combined the information on the anticholinergic

properties exerted by various drugs and allowed us to summarize the anticholinergic burden through the Anticholinergic Drug Scale (ASD) (Carnahan et al., 2006).

Other Characteristics

Body Mass Index (BMI) was calculated on the height and weight recorded on the MDS assessment at baseline (items K2a and K2b). For the analyses, BMI was categorized into six categories: (1) Underweight (BMI<18.5); (2) Normal weight (BMI=18.5 – 24.9); (3) Overweight (BMI=25 – 29.9); (4) Obese (BMI=30 – 39.9); (5) Morbidly obese (BMI≥40); and (6) Missing or extreme values (extreme values were considered based on the BMI distribution).

Bladder and bowel continence (MDS section H- item H1a for bladder continence and item H1b for bowel continence) were evaluated based on the 'Continence self-control categories' that measures continence in last 14 days. This is a 5 point rating scale:

0. CONTINENT— complete control [includes use of indwelling urinary catheter or ostomy device that does not leak urine or stool]
1. USUALLY CONTINENT— BLADDER, incontinent episodes once a week or less; BOWEL, less than weekly
2. OCCASIONALLY INCONTINENT— BLADDER, 2 or more times a week but not daily; BOWEL, once a week
3. FREQUENTLY INCONTINENT— BLADDER, tended to be incontinent daily, but some control present (e.g., on day shift); BOWEL, 2-3 times a week
4. INCONTINENT— had inadequate control BLADDER, multiple daily episodes; BOWEL, all (or almost all) of the time

As part of the bladder control management measures we included the following items collected in the MDS as dichotomous variables (yes/no):

- Any scheduled toileting plan (item H3a)
- Bladder retraining program (item H3b)
- External catheter (item H3c)
- Indwelling catheter (item H3d)
- Intermittent catheter (item H3e)
- Pads/briefs used (item H3g)
- No appliance or program (item H3j)

Urinary tract infections at baseline were measured as a dichotomous variable using the corresponding item on the MDS assessments (item I2j- Urinary tract infection in last 30 days yes/no)

Bowel elimination pattern was measured through four MDS items (yes/no):

- Regular bowel elimination pattern (item H2a)
- Constipation (item H2b)
- Diarrhea (item H2c)
- Fecal impaction (item H2d).

The MDS Behavioral Symptoms scale was used to measure the extent to which the NH resident exhibited problematic behaviors. This scale includes questions on 5 categories of behavioral symptoms, including wandering (item E4a), verbally abusive behavior (item E4b), physically abusive behavior (item E4c), socially inappropriate or disruptive behavioral symptoms (item E4d), and resistance to care (item E4e) (Bharucha et al., 2008). Every item is measured on a scale from 0 (behavior not present in past 7 days) to 3 (behavior of this type occurred daily), with a total score range of 0-15 points.

The MDS Activities of Daily Living-Long Form (MDS ADL-Long Form) that was used in our study is a validated instrument that includes all seven MDS activities of daily living (ADL) items (dressing- item G1ga, personal hygiene- item G1ja, toilet use- item G1ia, locomotion on unit- item G1ea, transfer- item G1ba, bed mobility- item G1aa, eating- item G1ha); they are scored on a 0 (independent) to 4 (total dependence) scale for possible scores ranging from 0 to 28 points.

The MDS Changes in Health, End-Stage Disease and Symptoms and Signs (MDS-CHESS) Scale is a score that measures instability of health status and has been shown to predict mortality among nursing home residents (Hirdes et al., 2003). MDS-CHESS was used in our study to measure frailty at baseline and was also evaluated as covariate in the analysis (see Statistical analyses section). The following MDS items are included in CHESS:

- Item B6- Change in cognitive status (decline)
- Item G9- Change in ADL function (decline)
- Item J1c- Dehydrated; output exceeds input (yes/no)
- Item J1d- Insufficient fluid; did not consume all/almost all liquids provided during last 3 days (yes/no)
- Item J1g- Edema (yes/no)
- Item J1l- Shortness of breath (yes/no)
- Item J1o- Vomiting (yes/no)
- Item J5c- End-stage disease, 6 or fewer months to live (yes/no)
- Item K3a- Weight loss- 5% or more in last 30 days; or 10% or more in last 180 days (yes/no)

Vision as possible confounder was measured on a five point scale using the information collected as part of section D in the MDS (0= adequate to 4=severely

impaired). The scale measures the ability of the NH resident to see when the light is adequate and (s)he is using glasses if normally needed.

Balance was evaluated using two different measures from MDS. The first one, the test for balance (item G3) uses a four point scale (0=adequate to 3=not able to attempt test without physical support) to test for both- balance while standing (G3a) and 'balance while sitting' (G3b). The second measurement is represented by the dichotomous variable- unsteady gait (item J1n).

Falls and fractures– in addition to identifying hip/other fractures during the NH stay included in our study, item J4 (Accidents) was used to identify residents that experienced falls and/or fractures before their baseline assessment. The four indicators were evaluated as possible predictors of BAM initiation and were further included in the propensity score model. More specifically, MDS measures the following:

J4a- Fell in past 30 days (yes/no)

J4b- Fell in past 31-180 days (yes/no)

J4c- Hip fracture in last 180 days (yes/no)

J4d- Other fracture in last 180 days (yes/no)

Some of the characteristics were only available from a full MDS assessment. For those that did not have a full assessment as their baseline assessment, the last full assessment before the index date was identified and used. NH are required to conduct a full assessment not only as part of the periodic evaluation but also whenever a significant change occurs in the resident's health status. The list of characteristics evaluated as part of the full assessment exclusively is presented in Table 3.7.

Table 3.7. List of conditions available from a full Minimum Data Set assessments exclusively

MDS comorbidities	
	Diabetes
	Cardiac dysrhythmias
	Congestive Heart Failure
	Hypertension
	Hypotension
	Hip fracture
	Osteoporosis
	Pathological bone fracture
	Cerebrovascular accident (stroke)
	Cancer
	No active comorbidity
Body Mass Index	
Bladder continence management	
	Intermittent catheter
	Pads/Briefs Used
Bowel elimination pattern	
	Regular
	Constipation
	Diarrhea
CHESS	
Vision	
Balance while sitting	
Balance while standing	
Unsteady gait	

CHESS= Changes in Health, End-Stage Disease and Symptoms and Signs

Statistical Analyses

Aim 1

In an initial step, we identified all the BAM users (prevalent users and new users) in our cohort. Descriptive statistics (mean, proportion, frequency, standard deviation) were performed to compare new users and non-users with regard to residents' characteristics prior to the index date (demographics, comorbidities at baseline, and existence of other conditions at baseline). For continuous patient covariates (e.g. behavioral and functional scales) the mean (with SD) and median (with IQR) values were also be calculated. The

possible statistical association between study groups and continuous variables were tested using a t-test (or Mann-Whitney test if normality assumptions were not met).The chi-square statistic was used to document the statistical association between the dependent variable (BAM use) and categorical independent variables such as sex.

We used unconditional logistic regression to determine factors predicting BAM initiation after NH admission. Demographic characteristics, baseline disease history, MDS derived measures of resident cognitive, behavioral, functional, and medical stability status, and VISN indicator were considered for inclusion in this model. In an initial step, we ran simple logistic models for each of the individual characteristics described above; the subsequent step selected the final pool of variables considered for the prediction model and only included those variables with a p-value ≤ 0.20 in the first step. In the final step we constructed the final prediction model using a backward elimination approach.

Aim 2

To address endogeneity from treatment selection bias and to balance observed covariates between the study groups, we used a propensity score method. Propensity scores reflect the probability that a patient will receive a treatment based on his/her observed pretreatment covariates.

The score for each resident was the estimated probability that he or she started treatment with a BAM during their NH stay, based on his or her baseline characteristics. We used logistic regression to calculate propensity scores with the dependent variable in the regression being the BAM use status (new user vs non-user). The predictors used in the PS logistic regression included variables not only related to the BAM initiation and included in the final predictive model we

constructed, but also variables for which there is empirical evidence to support their relationship with any of the study's outcomes (Brookhart et al, 2006; Westreich et al, 2011).

In a subsequent step, we individually matched new-users with up to five non-users based on their propensity scores using a SAS greedy matching technique that performs the matching procedure based on the distance (D_{ij}) between a BAM user and a non-user in terms of matching variable (i.e. propensity score) (Parsons, 2001; http://mayoresearch.mayo.edu/mayo/research/biostat/upload/gmatch.sas). In our study, the maximum difference in propensity score between a new-user and his matched non-users (D_{ij}) was set as 0.01, This approach of allowing for a variable number of untreated subjects to be matched to each BAM new-user was shown to improve bias reduction compared to matching with a fixed number of controls (Ming et al, 2000).

From all the possible ways of incorporating PS in the analysis, if the distribution of scores for the study groups allows, matching seems to result in a better balance between groups (Austin, 2009). In addition, matching on PS is an efficient method to control for confounders under certain situations that were true for our study. Specifically, these included the following: (1) the number of treated patients is limited and there is a larger pool of controls, (2) the outcome is rare, (3) the number of potential confounders is large, and/or (4) multiple outcomes are evaluated for the study groups (Austin, 2009).

For the final matched groups we conducted all of the descriptive analysis described above (see Statistical analyses- Aim 1) to verify if we reached a balance between new-users and non-users.

Hypothesis 2a: BAM will increase the risk of fractures in NH residents

Time to event analysis was conducted to evaluate risk of fractures (hip fractures and any fracture) in relationship to BAM use using a Cox proportional hazard model. At the moment, there are no clear guidelines with regard to accounting for matching in the analysis when matching is done by PS. Two individuals with the same PS can have different baseline characteristics; when balance between the matched groups is achieved on those variables, matching on PS can be seen as frequency matching. In addition, simulation studies showed that unconditional analysis performs better than conditional analysis when the true effect is different than the null and conditional analysis can lead to loss in power (Rubin et al, 2000; Hill, 2008). Considering these, we did not conduct the analysis as conditional time to event. Since the baseline covariates were included in the PS calculation, measures of exposure were the only variables considered for inclusion in the Cox proportional hazard model. Exposure to BAM was measured by two variables; the first one was an indicator of use (BAM new-user yes/no) and the other one indicated the number of BAM-exposed days out of the total follow-up time. The maximum follow-up time was identified as described under outcome (fracture) definition; in summary, the end of the follow-up was the earliest of:

- Discontinuation of therapy
- Outcome (fracture)
- The end of the NH follow-up

Hypothesis 2b: BAM will negatively affect cognitive status as measured by MDS-CPS

Generalized estimating equations (GEE) were used to estimate the average treatment effect of BAM use on the cognitive performance; GEE allows population level interpretation of the regression coefficients (Fitzmaurice et al.,

2004). We modeled mean CPS for the groups at each time as a function of person-level covariates, using the PROC GENMOD procedure (SAS Institute Inc., 1999) in SAS (distribution=normal, link=identity, correlation matrix=exchangeable). Interaction between baseline CPS and BAM use along with time-varying covariates (i.e. important characteristics measured through MDS assessments that were included in the PS model, but were allowed to change during follow-up and were measured at the each time CPS was calculated) were assessed for inclusion in the final model using the Quasi-Information Criterion (QIC) (Pan, 2001). QIC is similar to the Akaike's Information Criterion used in model selection for regression based on maximum likelihood estimation. The list of time-varying covariates considered for inclusion was created a priori based on the empirical evidence on potential risk factors for the outcome; final model was selected using a manual backward elimination technique. Some of the variables that could change over time and could impact cognitive performance (e.g. antipsychotics use, dementia) were not included as time-varying in our model based on their potential mediator role for the relationship between BAM use and CPS.

Time-stationary covariates were included in the PS model and were not further considered for the model selection.

Aim 3

Hypothesis 3a: BAM will improve incontinence as measured by MDS

Hypothesis 3b: BAM will improve social engagement and overall QOL

Improvement in urinary incontinence and change in QOL (overall QOL measured by MDS-HSI, and social engagement measured by MDS-ISE) were evaluated using the GEE method. Similarly to the CPS analysis, these

evaluations also included time-varying covariates based on the list created a priori, with the final model being selected based on QIC.

Improvement in urinary incontinence was modeled as a binary response; odds ratio estimates were calculated to evaluate the relationship between BAM use and improvement in urinary incontinence while adjusting for time-varying confounders (PROC GENMOD with distribution=binomial, link=logit, correlation matrix=exchangeable).

Similarly to the cognitive performance analysis, the effect of BAM use on QOL was assessed by modeling the mean score at each time point using the GEE approach (distribution=normal, link=identity, correlation matrix=exchangeable).

Exploratory analyses

Two exploratory outcomes were included in the analysis plan: overall mortality and bowel effects (constipation and fecal impaction).

Mortality was evaluated through a time-to-event analysis using a Cox proportionate hazard model. The follow-up time was extended until the earliest of the following: (1) outcome (death); (2) the end of the NH follow-up; (3) the end of the study period; and for new-users (4) treatment discontinuation. Censoring at treatment discontinuation was done in two ways: (1) censoring on the date of the last BAM prescription, and (2) censoring 30 days after the last BAM prescription. The latter was considered since treatment modifications (in this case discontinuation of a BAM use) can be the result of a change in care for those close to death and assuming that medication's impact on mortality would most likely go beyond the end of exposure.

Constipation and bowel impaction as potential parasympathetic effects determined by BAM use were modeled as a binary response; odds ratio estimates were calculated to evaluate this relationship using the GEE method (distribution=binomial, link=logit, correlation matrix=exchangeable).

CHAPTER IV- RESULTS

Aim 1

Aim 1: Describe the characteristics of those receiving different BAM (including demographics, baseline disease history, standardized measures of resident cognitive, behavioral, functional and medical stability status, and facility characteristics) and to identify predictors of medication initiation for managing urinary incontinence in NH.

From the 208,946 unique subjects identified from the MDS data available, about 25% (48,631) were admitted in a VA CLC for a long-term stay based on the definition described in the Methods section. Of these, and after applying our exclusion criteria, 2739 were identified as BAM users during their NH stay. About 44% (1195) of the users started a BAM during their NH stay and were included in the new-users group. The flow diagram describing this identification process is depicted in Figure 4.1 below.

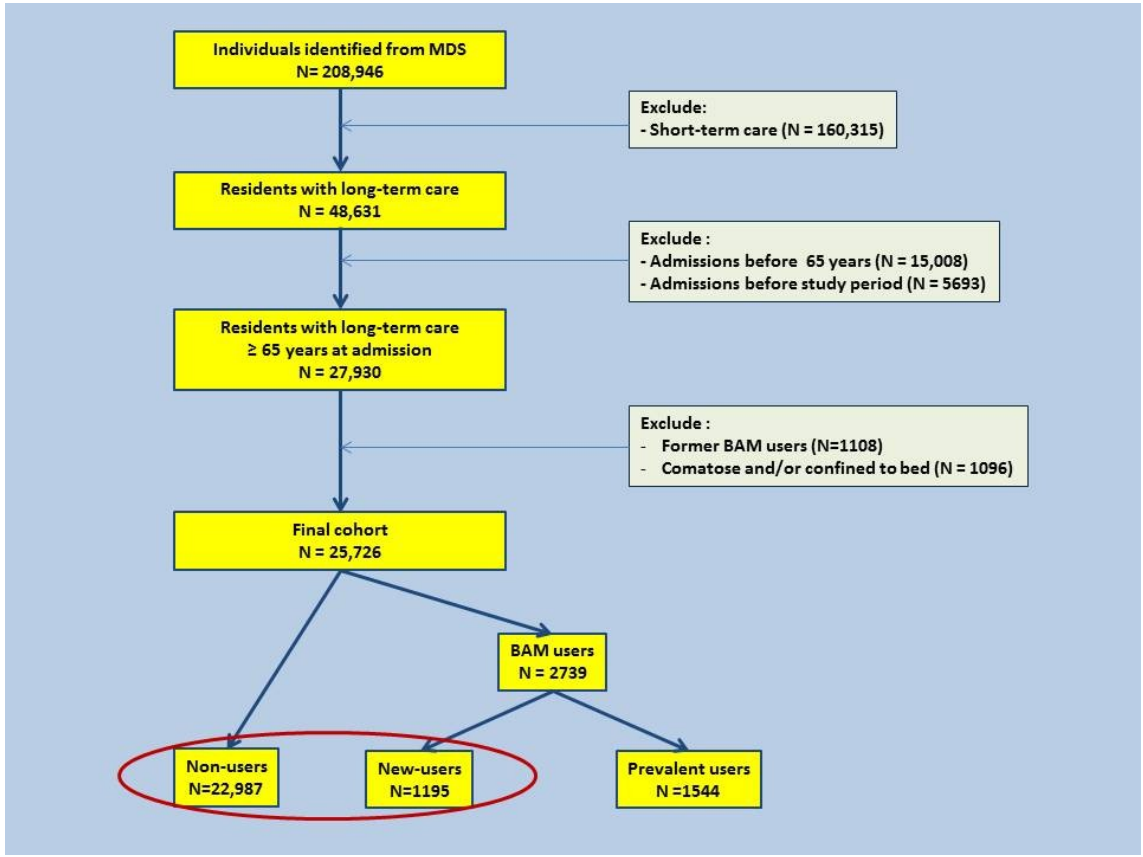


Figure 4.1 Flow diagram- Identification of study groups

Among the 1195 new-users, about three quarters (74.9%) were treated with IR Oxybutinin Chloride, either from the moment a BAM was initiated, or after using another drug. Of the remaining 25.1%, the majority (84.67%) was treated with an IR BAM; the following IR BAM were initiated: Hyoscyamine (N=142), Dicyclomine (N=89), Tolterodine (N=30), Flavoxate (N=8), and Trospium (N=2). The ER formulations used were: Oxybutynin (N=30), Tolterodine (N=19), and Hyoscyamine (N=4).

The comparison between new-users and non-users on baseline characteristics is presented in Tables 4.1 through 4.4.

Baseline demographic characteristics are reported in Table 4.1. Baseline comorbidities identified through the Quan-Elixhauser algorithm and included in the MDS assessments are included in Table 4.2. Table 4.3 presents data on medication covariates at baseline. Table 4.4 shows the distribution on other important variables, including bladder and bowel continence, continence management, cognitive performance, activities of daily living, behavioral score, frailty (CHESS), balance, and accidents.

BAM new-users and non-users differed significantly on baseline demographic characteristics (Table 4.1). New-users were older and admitted in the earlier years. The BAM users group had a larger white majority and more women than the non-users group. BAM were prescribed at a different rate in different VA regions (VISN).

Table 4.1 Distribution of demographic characteristics at baseline

Variable		New users (N=1195)	Non-users (N=22,985)	p-value
Age				
	Age at index date- Mean ±SD	79.56 (6.74)	79.42 (6.95)	0.5858
	Age categories- no (%)			0.0281
	65 to 69	110 (9.21)	2564 (11.16)	
	70 to 74	219 (18.33)	3896 (16.95)	
	75 to 79	257 (21.51)	5132 (22.33)	
	80 to 84	359 (30.04)	6200 (26.97)	
	85+	250 (20.92)	5193 (22.59)	
Gender- n (%)				0.0003
	Male	1147 (95.98)	22,446 (97.65)	
	Female	48 (4.02)	539 (2.35)	
Race- no (%)				0.0361
	White	969 (81.09)	17,911 (77.92)	
	Black	139 (11.63)	3115 (13.55)	
	Other	87 (7.28)	1959 (8.52)	
Fiscal year at admission- no (%)				0.0002
	2003	243 (20.33)	4449 (19.36)	
	2004	230 (19.25)	3920 (17.05)	
	2005	191 (15.98)	3357 (14.61)	
	2006	175 (14.64)	3104 (13.50)	
	2007	147 (12.30)	3062 (13.32)	
	2008	143 (11.97)	2929 (12.74)	
	2009	66 (5.52)	2164 (9.41)	

Table 4.1 continued

Variable	New users (N=1195)	Non-users (N=22,985)	p-value
Veteran Integrated Service Network- no (%)			<.0001
VISN 1: VA New England Healthcare System	49 (4.10)	1077 (4.69)	
VISN 2: VA Health Care Upstate New York	35 (2.93)	951 (4.14)	
VISN 3: VA NY/NJ Veterans Healthcare Network	56 (4.69)	1335 (5.81)	
VISN 4: VA Healthcare	126 (10.54)	1890 (8.22)	
VISN 5: VA Capitol Health Care Network	51 (4.27)	1139 (4.96)	
VISN 6: VA Mid-Atlantic Health Care Network	70 (5.86)	1353 (5.89)	
VISN7: VA Southeast Network	42 (3.51)	1153 (5.02)	
VISN 8: VA Sunshine Healthcare Network	91 (7.62)	1830 (7.96)	
VISN 9: VA Mid South Healthcare Network	42 (3.51)	640 (2.78)	
VISN 10: VA Healthcare System of Ohio	47 (3.93)	1212 (5.27)	
VISN 11: Veterans In Partnership	91 (7.62)	1245 (5.42)	
VISN 12: VA Great Lakes Health Care System	46 (3.85)	934 (4.06)	
VISN 15: VA Heartland Network	44 (3.68)	581 (2.53)	
VISN 16: South Central VA Health Care Network	71 (5.94)	1062 (4.62)	
VISN 17: VA Heart of Texas Health Care Network	54 (4.52)	1243 (5.41)	
VISN 18: VA Southwest Health Care Network	69 (5.77)	755 (3.28)	
VISN 19: Rocky Mountain Network	24 (2.01)	383 (1.67)	
VISN 20: Northwest Network	30 (2.51)	551 (2.40)	
VISN 21: Sierra Pacific Network	54 (4.52)	1494 (6.50)	
VISN 22: Desert Pacific Healthcare Network	20 (1.67)	756 (3.29)	
VISN 23: VA Midwest Health Care Network	83 (6.95)	1401 (6.10)	

VISN= Veteran Integrated Service Network

BAM users were heavier, had fewer comorbidities and hospitalizations and/or outpatient visits for a comorbid condition identified through the Elixhauser algorithm. In addition, they had complicated diabetes and psychosis less frequently then the non-users. However, more new-users had paralysis at baseline and suffered from depression. Cardiac dysrhythmia, hypertension, stroke, and bone pathology were more frequent in BAM users (Table 4.2). New-users were taking more drugs before a BAM was initiated and they had a higher anticholinergic burden; they were more likely to use an alpha-blocker, an antidepressant, or an anticonvulsant at baseline. In contrast, they were less likely to use a diuretic, an antipsychotic, or a cognitive enhancer (Table 4.3).

Table 4.2 Distribution of baseline comorbidities

Variable	New users (N=1195)	Non-users (N=22,985)	p-value
Elixhauser Comorbidities- hospital admissions			
Number of Elixhauser Comorbidities- Mean (SD)	2.75 (2.65)	2.74 (2.65)	0.9344
Congestive Heart Failure	185 (15.48)	3872 (16.85)	0.2184
Cardiac Arrhythmia	244 (20.42)	4736 (20.60)	0.8766
Hypertension- not complicated	502 (42.01)	9252 (40.25)	0.2277
Hypertension- complicated	101 (8.45)	2196 (9.55)	0.2052
Paralysis	47 (3.93)	538 (2.34)	0.0005
Chronic Obstructive Pulmonary Disease	272 (22.76)	5056 (22.00)	0.5341
Diabetes- not complicated	250 (20.92)	4937 (21.48)	0.6464
Diabetes- complicated	101 (8.45)	2224 (9.68)	0.1617
Tumor with metastasis	62 (5.19)	1016 (4.42)	0.2098
Obesity	31 (2.59)	534 (2.32)	0.5456
Depression	158 (13.22)	2458 (10.69)	0.0061
Psychosis	60 (5.02)	1642 (7.14)	0.0052
Hospitalization indicator	793 (66.36)	15,560 (67.70)	0.3357
Elixhauser Comorbidities- hospital and/or outpatient			
Number of Elixhauser Comorbidities- Mean (SD)	3.99 (2.82)	4.10 (2.86)	0.2474
Congestive Heart Failure	255 (21.34)	5053 (21.98)	0.5995
Cardiac Arrhythmia	340 (28.45)	6370 (27.71)	0.5785
Hypertension- not complicated	735 (61.51)	14,134 (61.49)	0.9923
Hypertension- complicated	108 (9.04)	2442 (10.62)	0.0817
Paralysis	69 (5.77)	834 (3.63)	0.0001
Chronic Obstructive Pulmonary Disease	372 (31.13)	6863 (29.86)	0.3495
Diabetes- not complicated	371 (31.05)	7439 (32.36)	0.3419
Diabetes- complicated	158 (13.22)	3598 (15.65)	0.0236
Tumor with metastasis	76 (6.36)	1258 (5.47)	0.1905
Obesity	86 (7.20)	1391 (6.05)	0.1071
Depression	292 (24.44)	5195 (22.60)	0.1401
Psychosis	146 (12.22)	3955 (17.21)	<.0001
Hospitalization and/or outpatient visits indicator	1064 (89.04)	21,091 (91.76)	0.0009
Comorbidities- MDS identified			
Diabetes	456 (38.16)	8464 (36.82)	0.3511
Cardiac dysrhythmias	205 (17.15)	3474 (15.11)	0.0555
Congestive Heart Failure	220 (18.41)	4130 (17.97)	0.6983
Hypertension	820 (68.62)	15,073 (65.58)	0.0308
Hypotension	16 (1.34)	451 (1.96)	0.1269
Hip fracture	57 (4.77)	1092 (4.75)	0.8333
Osteoporosis	68 (5.69)	1314 (5.72)	0.9694
Pathological bone fracture	17 (1.42)	174 (0.76)	0.0113

MDS= Minimum Data Set

Table 4.2 continued

Variable	New users (N=1195)	Non-users (N=22,985)	p-value
Comorbidities- MDS identified			
Cerebrovascular accident (stroke)	242 (20.25)	4052 (17.63)	0.0207
Cancer	317 (26.53)	4935 (21.47)	<.0001
No active comorbidity	146 (12.22)	3200 (13.92)	0.0235
Comorbidities- inpatient/outpatient/MDS combined			
Diabetes	477 (39.92)	9014 (39.22)	0.6293
Congestive Heart Failure	298 (24.94)	5706 (24.82)	0.9302
Cardiac dysrhythmias	343 (28.70)	6255 (27.21)	0.2597
Hypertension	928 (77.66)	17,119 (74.48)	0.0138
Osteoporosis	95 (7.95)	1807 (7.86)	0.9121
Bone cancer/Bone metastasis/ Pathological bone fracture	49 (4.10)	634 (2.76)	0.0063
Hip fracture before index date	78 (6.53)	1594 (6.93)	0.588
Body Mass Index: BMI categories- no (%)			<.0001
Underweight	75 (6.28)	1985 (8.64)	
Normal weight	509 (42.59)	10,598 (46.11)	
Overweight	361 (30.21)	6422 (27.94)	
Obese	202 (16.90)	3080 (13.40)	
Morbidly obese	13 (1.09)	148 (0.64)	
Missing or extreme value	35 (2.93)	752 (3.27)	

MDS= Minimum Data Set

Table 4.3 Distribution of baseline medication covariates

Variable	New users	Non-users	p-value
Medication use- number of medications (last 7			
Mean (SD)	13.29 (5.36)	12.02 (5.10)	<.0001
Range	0 - 36	0 - 77	
≤ 3	21 (1.76)	578 (2.51)	<.0001
3 - 10	363 (30.38)	8973 (39.04)	
>10	811 (67.87)	13,434 (58.45)	
Medication use 30 days before index date			
Alpha-blockers	471 (39.41)	6626 (28.83)	<.0001
Beta-blockers	562 (47.03)	10,260 (44.64)	0.105
Calcium channel blockers	245 (20.50)	4601 (20.02)	0.6832
ACE inhibitors	415 (34.73)	7728 (33.62)	0.4302
Diuretics	474 (39.67)	8533 (37.12)	0.0765
Antidepressants	637 (53.31)	10,928 (47.54)	0.0001
Antipsychotics	280 (23.43)	6279 (27.32)	0.0032
Anticonvulsants	322 (26.95)	4917 (21.39)	<.0001
Cognitive enhancers	167 (13.97)	4137 (18.00)	0.0004
Antiparkinson	64 (5.36)	1243 (5.41)	0.938
Antivertigo	18 (1.51)	267 (1.16)	0.2818
Benzodiazepines	52 (4.35)	1036 (4.51)	0.8
Anticholinergic burden (ADS score)- Mean (SD)	3.43 (3.23)	2.94 (3.01)	<.0001
Anticholinergic burden (ADS score)- Range	0 - 23	0 - 27	
Medication use 90 days before index date			
Alpha-blockers	512 (42.85)	7372 (32.07)	<.0001
Beta-blockers	613 (51.30)	11,472 (49.91)	0.3501
Calcium channel blockers	302 (25.27)	5617 (24.44)	0.5131
ACE inhibitors	495 (41.42)	9253 (40.26)	0.4231
Diuretics	582 (48.70)	10,612 (46.17)	0.0868
Antidepressants	690 (57.74)	12,125 (52.75)	0.0008
Antipsychotics	343 (28.70)	7510 (32.67)	0.0043
Anticonvulsants	351 (29.37)	5660 (24.62)	0.0002
Cognitive enhancers	192 (16.07)	4645 (20.21)	0.0005
Antiparkinson	70 (5.86)	1350 (5.87)	0.9821
Antivertigo	28 (2.34)	433 (1.88)	0.2577
Benzodiazepines	127 (10.63)	2413 (10.50)	0.8868
Anticholinergic burden (ADS score)- Mean (SD)	5.62 (4.84)	5.09 (4.75)	<.0001
Anticholinergic burden (ADS score)- Range	0 - 35	0 - 43	

ADS= Anticholinergic Drug Scale

More BAM users were classified as ‘continent’ or ‘usually continent’ in the bladder and bowel continence ratings at baseline. They had more frequently an indwelling catheter in place and they were more likely to have experienced urinary tract infections in the 30 days before the baseline assessment. In addition, BAM users had an irregular bowel elimination pattern; they experienced constipation or diarrhea more often than the non-users did.

BAM users had better cognitive performance, better functional status, and less ‘problematic’ behaviors at baseline. The groups did not differ significantly with regard to vision and balance at baseline, falls and fractures before the index date (Table 4.4).

Table 4.4 Distribution of other characteristics at baseline

Variable	New users (N=1195)	Non-users (N=22,985)	p-value
Bladder Continence			<.0001
Continent	731 (61.17)	13,065 (56.84)	
Usually Continent	116 (9.71)	2057 (8.95)	
Occasionally Incontinent	80 (6.69)	1507 (6.56)	
Frequently Incontinent	74 (6.19)	1516 (6.60)	
Incontinent	188 (15.73)	4800 (20.88)	
Unknown (missing or out of range value)	6 (0.50)	40 (0.17)	
Bladder Continence Management			
Scheduled toileting plan	267 (22.34)	5646 (24.56)	0.0816
Bladder retraining program	24 (2.01)	500 (2.18)	0.6991
External catheter	94 (7.87)	2128 (9.26)	0.1043
Indwelling catheter	352 (29.46)	3342 (14.54)	<.0001
Intermittent catheter	26 (2.18)	466 (2.03)	0.7233
Pads/Briefs Used	412 (34.48)	8454 (36.78)	0.1072
No appliance or program	405 (33.89)	9107 (39.62)	<.0001
UTI in last 30 days- no (%)	183 (15.31)	2266 (9.86)	<.0001
Bowel Continence			0.0013
Continent	704 (58.91)	12,720 (55.34)	
Usually Continent	131 (10.96)	2036 (8.86)	
Occasionally Incontinent	67 (5.61)	1353 (5.89)	
Frequently Incontinent	54 (4.52)	1170 (5.09)	
Incontinent	238 (19.92)	5688 (24.75)	
Unknown (missing or out of range value)	1 (0.08)	18 (0.08)	
Bowel Elimination Pattern- no (%)			
Regular	483 (40.42)	10,186 (44.32)	0.0082
Constipation	200 (16.74)	3027 (13.17)	0.0004
Diarrhea	81 (6.78)	1052 (4.58)	0.0004
Fecal Impaction	3 (0.25)	54 (0.23)	0.7599

UTI= Urinary tract infections

Table 4.4 continued

Variable	New users	Non-users	p-value
Cognitive Performance Score (CPS)			<.0001
Intact: CPS=0	228 (19.08)	3365 (14.64)	
Borderline intact: CPS=1	148 (12.38)	2588 (11.26)	
Mild impairment: CPS=2	177 (14.81)	4718 (20.53)	
Moderate impairment: CPS=3	24 (2.01)	588 (2.56)	
Moderate severe impairment: CPS=4	73 (6.11)	2261 (9.84)	
Severe impairment: CPS=5	33 (2.76)	951 (4.14)	
Very severe impairment: CPS=6	3 (0.25)	62 (0.27)	
Activities of Daily Living (ADL score)			0.0621
Mean ±SD	11.28 (8.24)	11.79 (8.49)	
Fully independent (ADL=0)- no (%)	146 (12.22)	2674 (11.63)	0.0775
Total dependence (ADL=28)- no (%)	38 (3.18)	877 (3.82)	
CHESS			0.2812
CHESS=0	378 (31.63)	7413 (32.25)	
CHESS=1	345 (28.87)	6753 (29.38)	
CHESS=2	260 (21.76)	4531 (19.71)	
CHESS=3	108 (9.04)	2194 (9.55)	
CHESS=4	34 (2.85)	518 (2.25)	
CHESS=5	4 (0.33)	51 (0.22)	
Missing	66 (5.52)	1525 (6.63)	
MDS Behavioral Score			<.0001
Mean ±SD	0.53 (1.47)	0.81 (1.98)	
None of the behaviors: score=0- no (%)	979 (81.92)	17,618 (76.65)	0.017
Score=10 to 15- no (%)	3 (0.25)	216 (0.92)	
Vision			0.4665
Adequate	838 (70.13)	16,211 (70.53)	
Impaired	252 (21.09)	4563 (19.85)	
Moderately impaired	63 (5.27)	1140 (4.96)	
Highly impaired	23 (1.92)	632 (2.75)	
Severely impaired	14 (1.17)	329 (1.43)	
Unknown (missing or out of range value)	5 (0.42)	110 (0.48)	

CHESS= Changes in Health, End-stage disease and Symptoms and Signs;
MDS= Minimum Data Set

Table 4.4 continued

Variable	New users	Non-users	p-value
Balance while standing			0.5578
Maintained position as required in test	229 (19.16)	4736 (20.60)	
Unsteady, but able to rebalance w/o physical	221 (18.49)	4221 (18.36)	
Partial physical support during test or stands but	248 (20.75)	4746 (20.65)	
Not able to attempt test w/o physical help	449 (37.57)	8524 (37.09)	
Unknown (missing or out of range value)	48 (4.02)	758 (3.30)	
Balance while sitting			0.4143
Maintained position as required in test	877 (73.39)	16,757 (72.90)	
Unsteady, but able to rebalance w/o physical	96 (8.03)	2141 (9.31)	
Partial physical support during test or stands but	95 (7.95)	1875 (8.16)	
Not able to attempt test w/o physical help	120 (10.04)	2050 (8.92)	
Unknown (missing or out of range value)	7 (0.59)	162 (0.70)	
Unsteady Gait	537 (44.94)	10,221 (44.47)	0.7504
Fell in past 30 days	226 (18.91)	4496 (19.56)	0.5814
Fell in past 31-180 days	281 (23.51)	5076 (22.08)	0.2456
Hip fracture in last 180 days	24 (2.01)	682 (2.97)	0.0549
Other fracture in past 180 days	36 (3.01)	618 (2.69)	0.5011

Unadjusted odds ratios for all the variables included in Tables 4.1 through 4.4 in relationship with BAM use were calculated using simple logistic regression and are included in Table 4.5. The variables with a p-value<0.2 at this point were included in the backward elimination process that resulted in selecting the final model that best predicted BAM initiation in our study population. Table 4.6 lists the variables included in the predictive model and Table 4.7 shows the adjusted odds ratios for each of the variables and every category within the individual covariate.

Table 4.5 Unadjusted odds ratio estimates for bladder antimuscarinics initiation

Effect		Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Age							
	Age at index date	0.00288	0.00427	1.003	0.995	1.011	0.5002
	Age categories						0.0286
	65 to 69	Reference					
	70 to 74	0.2701	0.1196	1.31	1.036	1.656	
	75 to 79	0.1546	0.1165	1.167	0.929	1.466	
	80 to 84	0.2998	0.1115	1.35	1.085	1.679	
	85+	0.1151	0.1169	1.122	0.892	1.411	
Gender							
	Male	Reference					
	Female	0.5555	0.1536	1.743	1.29	2.355	0.0003
Race							0.0365
	White	Reference					
	Black	-0.1926	0.0928	0.825	0.688	0.989	
	Other	-0.1973	0.1144	0.821	0.656	1.027	
Fiscal Year at admission							0.0002
	2003	Reference					
	2004	0.0716	0.0946	1.074	0.892	1.293	
	2005	0.0408	0.0994	1.042	0.857	1.266	
	2006	0.0317	0.1019	1.032	0.845	1.26	
	2007	-0.129	0.1071	0.879	0.713	1.084	
	2008	-0.1122	0.108	0.894	0.723	1.105	
	2009	-0.5827	0.1413	0.558	0.423	0.737	

Table 4.5 continued

Effect	Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Veteran Integrated Service Network						<.0001
VISN 1: VA New England Healthcare System	Reference					
VISN 2: VA Health Care Upstate New York	-0.2121	0.2257	0.809	0.52	1.259	
VISN 3: VA NY/NJ Veterans Healthcare Network	-0.0812	0.1999	0.922	0.623	1.364	
VISN 4: VA Healthcare	0.3821	0.1726	1.465	1.045	2.055	
VISN 5: VA Capitol Health Care Network	-0.016	0.2045	0.984	0.659	1.469	
VISN 6: VA Mid-Atlantic Health Care Network	0.1285	0.1907	1.137	0.783	1.652	
VISN 9: VA Mid South Healthcare Network	0.3663	0.2161	1.442	0.944	2.203	
VISN 10: VA Healthcare System of Ohio	-0.1598	0.2084	0.852	0.567	1.282	
VISN 11: Veterans In Partnership	0.4741	0.182	1.607	1.125	2.295	
VISN 12: VA Great Lakes Health Care System	0.0793	0.2101	1.083	0.717	1.634	
VISN 15: VA Heartland Network	0.5096	0.214	1.665	1.094	2.532	
VISN 16: South Central VA Health Care Network	0.3849	0.1907	1.469	1.011	2.135	
VISN 19: Rocky Mountain Network	0.3201	0.2562	1.377	0.834	2.275	
VISN 20: Northwest Network	0.1796	0.2377	1.197	0.751	1.907	
VISN 21: Sierra Pacific Network	-0.2301	0.2013	0.794	0.535	1.179	
VISN 22: Desert Pacific Healthcare Network	-0.5421	0.2695	0.582	0.343	0.986	
VISN 23: VA Midwest Health Care Network	0.264	0.1847	1.302	0.907	1.87	

VISN= Veteran Integrated Service Network

Table 4.5 continued

Effect	Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Elixhauser Comorbidities- hospital admissions						
Number of Elixhauser Comorbidities	0.000942	0.0112	1.001	0.979	1.023	0.9329
Congestive Heart Failure	-0.1007	0.0819	0.904	0.77	1.062	0.2186
Cardiac Arrhythmia	-0.0114	0.0736	0.989	0.856	1.142	0.877
Hypertension- not complicated	0.0725	0.0601	1.075	0.956	1.21	0.2277
Hypertension- complicated	-0.1347	0.1064	0.874	0.71	1.077	0.2056
Paralysis	0.5354	0.1551	1.708	1.26	2.315	0.0006
Chronic Obstructive Pulmonary Disease	0.044	0.0708	1.045	0.91	1.201	0.5342
Diabetes- not complicated	-0.0332	0.0729	0.967	0.839	1.116	0.6492
Diabetes- complicated	-0.1487	0.1064	0.862	0.7	1.062	0.1622
Tumor with metastasis	0.1683	0.1343	1.183	0.909	1.54	0.2101
Obesity	0.1131	0.1872	1.12	0.776	1.616	0.5458
Depression	0.2411	0.088	1.273	1.071	1.512	0.0062
Psychosis	-0.3752	0.1349	0.687	0.527	0.895	0.0054
Any hospitalization for an Elixhauser comorbidity	-0.0605	0.0628	0.941	0.832	1.065	0.3357
Elixhauser Comorbidities- hospital and/or outpatient						
Number of Elixhauser Comorbidities	-0.0141	0.0105	0.986	0.966	1.006	0.1771
Congestive Heart Failure	-0.0376	0.0724	0.963	0.836	1.11	0.6029
Cardiac Arrhythmia	0.0368	0.0658	1.038	0.912	1.18	0.5757
Hypertension- not complicated	0.000591	0.061	1.001	0.888	1.128	0.9923
Hypertension- complicated	-0.1793	0.1031	0.836	0.683	1.023	0.0822
Paralysis	0.4871	0.1289	1.628	1.264	2.096	0.0002
Chronic Obstructive Pulmonary Disease	0.06	0.0641	1.062	0.936	1.204	0.3496
Diabetes- not complicated	-0.0609	0.0641	0.941	0.83	1.067	0.342
Diabetes- complicated	-0.1972	0.0873	0.821	0.692	0.974	0.0239
Tumor with metastasis	0.1596	0.122	1.173	0.924	1.49	0.1909
Obesity	0.1856	0.1153	1.204	0.96	1.509	0.1074
Depression	0.102	0.0691	1.107	0.967	1.268	0.1403
Psychosis	-0.4009	0.09	0.67	0.561	0.799	<.0001
Any hospitalization or outpatient visit for an Elixhauser comorbidity	-0.3156	0.0956	0.729	0.605	0.88	0.001

Table 4.5 continued

Effect	Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Comorbidities- MDS identified						
Diabetes	0.057	0.0611	1.059	0.939	1.193	0.3511
Cardiac dysrhythmias	0.151	0.0789	1.163	0.996	1.358	0.0557
Congestive Heart Failure	0.0299	0.0766	1.03	0.887	1.197	0.6958
Hypertension	0.1378	0.0639	1.148	1.013	1.301	0.0309
Hypotension	-0.3869	0.256	0.679	0.411	1.122	0.1306
Hip fracture	-0.0396	0.1205	0.961	0.759	1.217	0.7423
Osteoporosis	-0.0049	0.1281	0.995	0.774	1.279	0.9695
Pathological bone fracture	0.6377	0.2558	1.892	1.146	3.124	0.0127
Cerebrovascular accident (stroke)	0.1711	0.074	1.187	1.026	1.372	0.0209
Cancer	0.2782	0.0675	1.321	1.157	1.508	<.0001
No current diagnosis	-0.2052	0.0908	0.814	0.682	0.973	0.0238
Comorbidities- inpatient/outpatient/MDS combined						
Diabetes	0.0293	0.0606	1.03	0.914	1.16	0.6283
Congestive Heart Failure	0.00602	0.0686	1.006	0.88	1.151	0.9301
Cardiac dysrhythmias	0.074	0.0656	1.077	0.947	1.225	0.2598
Hypertension	0.1747	0.0711	1.191	1.036	1.369	0.014
Osteoporosis	0.0122	0.1097	1.012	0.816	1.255	0.9117
Bone cancer/Bone metastasis/ Pathological bone fracture	0.4104	0.1513	1.507	1.12	2.028	0.0067
Hip fracture before index date	-0.065	0.12	0.937	0.741	1.185	0.5881
Body Mass Index						<.0001
Normal weight	Reference					
Underweight	-0.2399	0.1261	0.787	0.614	1.007	
Overweight	0.1574	0.0706	1.17	1.019	1.344	
Obese	0.3116	0.0856	1.366	1.155	1.615	
Morbidly obese	0.6037	0.2928	1.829	1.03	3.247	
Missing or extreme value	-0.0314	0.1788	0.969	0.683	1.376	

MDS= Minimum Data Set

Table 4.5 continued

Effect	Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Medication use- number of medications (last 7 days)						<.0001
<3	Reference					
3-10	0.1075	0.2285	1.113	0.711	1.743	
>10	0.5078	0.2251	1.662	1.069	2.583	
Medication use 30 days before index date						
Alpha-blockers	0.4738	0.061	1.606	1.425	1.81	<.0001
Beta-blockers	0.0963	0.0595	1.101	0.98	1.237	0.1051
Calcium channel blockers	0.0302	0.0735	1.031	0.892	1.19	0.6808
ACE inhibitors	0.0492	0.0623	1.05	0.93	1.187	0.4303
Diuretics	0.1075	0.0607	1.113	0.989	1.254	0.0766
Antidepressants	0.2307	0.0595	1.26	1.121	1.415	0.0001
Antipsychotics	-0.2055	0.0699	0.814	0.71	0.934	0.0033
Anticonvulsants	0.3043	0.0671	1.356	1.189	1.546	<.0001
Benzodiazepines	-0.0363	0.1453	0.964	0.725	1.282	0.8029
Cognitive enhancers	-0.3006	0.0852	0.74	0.627	0.875	0.0004
Antiparkinson agents	-0.0102	0.1318	0.99	0.765	1.281	0.9382
Antivertigo medication	0.2638	0.2453	1.302	0.805	2.105	0.2822
Anticholinergic burden (Anticholinergic Drug Scale score)	0.0478	0.0088	1.049	1.031	1.067	<.0001
Medication use 90 days before index date						
Alpha-blockers	0.4622	0.0601	1.588	1.411	1.786	<.0001
Beta-blockers	0.0555	0.0594	1.057	0.941	1.187	0.3501
Calcium channel blockers	0.0447	0.0683	1.046	0.915	1.195	0.5132
ACE inhibitors	0.0483	0.0602	1.049	0.933	1.181	0.4231
Diuretics	0.1016	0.0594	1.107	0.985	1.244	0.0869
Antidepressants	0.2019	0.06	1.224	1.088	1.377	0.0008
Antipsychotics	-0.1868	0.0655	0.83	0.73	0.943	0.0043
Anticonvulsants	0.2415	0.0653	1.273	1.12	1.447	0.0002
Benzodiazepines	0.0138	0.0963	1.014	0.839	1.224	0.8863
Cognitive enhancers	-0.2797	0.0805	0.756	0.646	0.885	0.0005
Antiparkinson agents	-0.00283	0.1263	0.997	0.778	1.277	0.9821
Antivertigo medication	0.2231	0.1973	1.25	0.849	1.84	0.2581
Anticholinergic burden (Anticholinergic Drug Scale score)	0.0219	0.0058	1.022	1.011	1.034	0.0002

Table 4.5 continued

Effect		Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Bladder Continence							0.0001
	Continent	Reference					
	Usually Continent	0.00787	0.1027	1.008	0.824	1.233	
	Occasionally Incontinent	-0.0526	0.1209	0.949	0.749	1.202	
	Frequently Incontinent	-0.1365	0.125	0.872	0.683	1.115	
	Incontinent	-0.3567	0.0835	0.7	0.594	0.824	
	Unknown (missing or out of range value)	0.9862	0.4394	2.681	1.133	6.344	
Bladder Continence Management							
	Scheduled toileting plan	-0.1238	0.0711	0.884	0.769	1.016	0.0818
	Bladder retraining program	-0.0816	0.2111	0.922	0.609	1.394	0.6992
	External catheter	-0.1781	0.1098	0.837	0.675	1.038	0.1049
	Indwelling catheter	0.8981	0.0662	2.455	2.156	2.795	<.0001
	Intermittent catheter	0.0721	0.2037	1.075	0.721	1.602	0.7233
	Pads/Briefs Used	-0.1005	0.0624	0.904	0.8	1.022	0.1073
	No appliance or program	-0.2468	0.0626	0.781	0.691	0.883	<.0001
UTI in last 30 days- no (%)		0.5028	0.0833	1.653	1.404	1.947	<.0001
Bowel Continence							0.0014
	Continent	Reference					
	Usually Continent	0.1508	0.0981	1.163	0.959	1.409	
	Occasionally Incontinent	-0.1112	0.131	0.895	0.692	1.157	
	Frequently Incontinent	-0.1816	0.1445	0.834	0.628	1.107	
	Incontinent	-0.2795	0.0767	0.756	0.651	0.879	
	Unknown (missing or out of range value)	0.00378	1.0281	1.004	0.134	7.53	
Bowel Elimination Pattern- no (%)							
	Regular	-0.1597	0.0604	0.852	0.757	0.96	0.0082
	Constipation	0.282	0.0799	1.326	1.134	1.55	0.0004
	Diarrhea	0.416	0.1193	1.516	1.2	1.915	0.0005
	Fecal Impaction	0.0685	0.5934	1.071	0.335	3.426	0.9081

Table 4.5 continued

Effect	Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Cognitive Performance Score						<.0001
Intact: CPS=0	Reference					
Borderline intact: CPS=1	0.1179	0.0823	1.125	0.958	1.322	
Mild impairment: CPS=2	-0.0517	0.0961	0.95	0.787	1.146	
Moderate impairment: CPS=3	-0.4733	0.0891	0.623	0.523	0.742	
Moderate severe impairment: CPS=4	-0.389	0.2132	0.678	0.446	1.029	
Severe impairment: CPS=5	-0.6234	0.1274	0.536	0.418	0.688	
Very severe impairment: CPS=6	-0.5513	0.1829	0.576	0.403	0.825	
Unknown	-0.2188	0.5929	0.803	0.251	2.568	
Activities of Daily Living (ADL score- 0=independent**)**	-0.00713	0.00353	0.993	0.986	1	0.0432
CHESS						0.2829
CHESS=0	Reference					
CHESS=1	0.0019	0.0763	1.002	0.863	1.164	
CHESS=2	0.1181	0.0827	1.125	0.957	1.323	
CHESS=3	-0.0353	0.1118	0.965	0.775	1.202	
CHESS=4	0.2528	0.1847	1.288	0.897	1.849	
CHESS=5	0.4335	0.5213	1.543	0.555	4.285	
Unknown	-0.1639	0.1363	0.849	0.65	1.109	
MDS Behavioral Score (0=no problem behavior)	-0.0977	0.0201	0.907	0.872	0.943	<.0001
Vision						0.4737
Adequate	Reference					
Impaired	0.0661	0.0738	1.068	0.925	1.235	
Moderately impaired	0.0668	0.1342	1.069	0.822	1.391	
Highly impaired	-0.3497	0.2151	0.705	0.462	1.074	
Severely impaired	-0.1944	0.2752	0.823	0.48	1.412	
Unknown (missing or out of range value)	-0.1286	0.4586	0.879	0.358	2.16	

Table 4.5 continued

Effect	Parameter Estimate	Standard Error	Odds Ratio	95% Wald Confidence Limits		p-value
Balance while standing						0.5586
Maintained position as required in test	Reference					
Unsteady, but able to rebalance w/o physical support	0.0796	0.0966	1.083	0.896	1.309	
Partial physical support during test or stands but does not follow directions for test	0.0776	0.0939	1.081	0.899	1.299	
Not able to attempt test w/o physical help	0.0856	0.0832	1.089	0.925	1.282	
Unknown (missing or out of range value)	0.2699	0.1635	1.31	0.951	1.805	
Balance while sitting						0.4157
Maintained position as required in test	Reference					
Unsteady, but able to rebalance w/o physical support	-0.1546	0.1099	0.857	0.691	1.063	
Partial physical support during test or stands but does not follow directions for test	-0.0324	0.1107	0.968	0.779	1.203	
Not able to attempt test w/o physical help	0.112	0.1001	1.118	0.919	1.361	
Unknown (missing or out of range value)	-0.1915	0.3876	0.826	0.386	1.765	
Unsteady Gait	0.019	0.0596	1.019	0.907	1.146	0.7501
Fell in past 30 days	-0.0417	0.0757	0.959	0.827	1.113	0.5814
Fell in past 31-180 days	0.0813	0.07	1.085	0.946	1.244	0.2457
Hip fracture in last 180 days	-0.4001	0.2098	0.67	0.444	1.011	0.0566
Other fracture in past 180 days	0.1171	0.1741	1.124	0.799	1.581	0.5012

The final predictive model had a C-statistic=0.705 and provided a good fit (p= 0.2047 for the Hosmer and Lemeshow Goodness-of-Fit test). It included age, FY at admission and VISN among other variables; variables that increased the chance of being initiated on a BAM included gender (female), urinary incontinence, indwelling catheter, urinary tract infections, some comorbidities (hypertension, stroke, cancer, paralysis, depression), increased body mass index, medication use (more than 3 drugs prescribed, alpha-blockers, anticonvulsants, and a higher anticholinergic score), and diarrhea. Hip fracture in the last 180 days, comorbidities (diabetes, psychosis, having multiple Elixhauser comorbidities), diuretics, bowel incontinence or having regular bowel movements, cognitive impairment, being dependent (high ADL score) or having a high behavioral score, all decreased the chance of starting a BAM.

Table 4.6 Final predictive model for bladder antimuscarinics initiation

Type 3 Analysis of Effects	DF	Wald Chi-Square	p-value
Age category	4	9.5579	0.0486
Gender	1	21.5301	<.0001
FY at admission	6	29.6001	<.0001
VISN	20	84.9317	<.0001
Hypertension	1	3.9024	0.0482
Stroke	1	4.0605	0.0439
Cancer	1	18.0563	<.0001
Paralysis	1	6.2757	0.0122
Diabetes complicated	1	5.5362	0.0186
Depression	1	10.8537	0.001
Psychosis	1	6.3875	0.0115
Number of Elixhauser comorbidities	1	8.5194	0.0035
Any hospitalizations and/or outpatient visit for an Elixhauser comorbidity	1	5.3713	0.0205
BMI category	5	17.4646	0.0037
Number of meds in last 7 days	2	12.1477	0.0023
Alpha-blockers in last 30 days	1	29.0134	<.0001
Anticonvulsants in last 30 days	1	23.7147	<.0001
Diuretics in last 30 days	1	3.9022	0.0482
ADS total in last 30 days	1	5.13	0.0235
Bladder continence	5	22.3464	0.0004
Indwelling catheter	1	171.0753	<.0001
UTI in last 30 days	1	6.1436	0.0132
Bowel continence	5	11.5664	0.0412
Regular bowel movements	1	4.886	0.0271
Diarrhea	1	4.3287	0.0375
Cognitive Performance Score	7	21.6646	0.0029
Activities of Daily Living	1	10.852	0.001
MDS Behavioral Score	1	4.7003	0.0302
Hip fracture in last 180 days	1	5.9253	0.0149

*FY= fiscal year; VISN= Veteran Integrated Service Network; BMI=Body Mass Index; UTI= urinary tract infection; ADS- Anticholinergic Drug Scale; MDS= Minimum Data Set

Table 4.7 Final predictive model for bladder antimuscarinics initiation - Adjusted odds ratio estimates

Parameter		Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
		Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Point Estimate	95% Wald Confidence Limits	
Intercept		-3.3876	0.3156	115.1915	<.0001			
Age category	**65 to 69**	Reference						
	70 to 74	0.2641	0.122	4.6834	0.0305	1.302	1.025	1.654
	75 to 79	0.1572	0.1199	1.7189	0.1898	1.17	0.925	1.48
	80 to 84	0.3251	0.1164	7.8035	0.0052	1.384	1.102	1.739
	85+	0.2131	0.124	2.9537	0.0857	1.237	0.971	1.578
Gender	**Male**	Reference						
	Female	0.7446	0.1605	21.5301	<.0001	2.106	1.537	2.884
FY at admission	**2003**	Reference						
	2004	0.0792	0.0966	0.6727	0.4121	1.082	0.896	1.308
	2005	0.0184	0.1019	0.0325	0.8570	1.019	0.834	1.244
	2006	-0.00044	0.1049	0.0000	0.9967	1.000	0.814	1.228
	2007	-0.1399	0.1104	1.6057	0.2051	0.869	0.700	1.080
	2008	-0.1486	0.1122	1.7546	0.1853	0.862	0.692	1.074
	2009	-0.6572	0.1453	20.4448	<.0001	0.518	0.390	0.689

FY= fiscal year

Table 4.7 continued

Parameter		Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
		Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Point Estimate	95% Wald Confidence Limits	
VISN	**1**	Reference						
	2	-0.2291	0.2304	0.9888	0.32	0.795	0.506	1.249
	3	-0.0252	0.2047	0.0151	0.9022	0.975	0.653	1.457
	4	0.3986	0.1762	5.1175	0.0237	1.49	1.055	2.104
	5	0.0344	0.2092	0.0271	0.8692	1.035	0.687	1.56
	6	0.1611	0.1948	0.684	0.4082	1.175	0.802	1.721
	7	-0.0965	0.2186	0.195	0.6588	0.908	0.592	1.394
	8	0.00903	0.1856	0.0024	0.9612	1.009	0.701	1.452
	9	0.3097	0.2217	1.9524	0.1623	1.363	0.883	2.105
	10	-0.1775	0.213	0.6945	0.4047	0.837	0.552	1.271
	11	0.5422	0.187	8.4059	0.0037	1.72	1.192	2.481
	12	0.00642	0.2149	0.0009	0.9762	1.006	0.66	1.534
	15	0.4459	0.2194	4.1295	0.0421	1.562	1.016	2.401
	16	0.3676	0.1958	3.5254	0.0604	1.444	0.984	2.12
	17	-0.0265	0.206	0.0166	0.8975	0.974	0.65	1.458
	18	0.6911	0.1976	12.226	0.0005	1.996	1.355	2.94
	19	0.3362	0.2622	1.6437	0.1998	1.4	0.837	2.34
	20	0.0327	0.2424	0.0182	0.8925	1.033	0.643	1.662
	21	-0.3388	0.2051	2.729	0.0985	0.713	0.477	1.065
	22	-0.5485	0.2741	4.0035	0.0454	0.578	0.338	0.989
	23	0.2242	0.1898	1.3955	0.2375	1.251	0.863	1.815

VISN= Veterans Integrated Service Network

Table 4.7 continued

Parameter		Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
		Estimate	Standard Error	Wald Chi-Square	p-value	Point Estimate	95% Wald Confidence Limits	
Hypertension		0.1519	0.0769	3.9024	0.0482	1.164	1.001	1.353
Stroke		0.1582	0.0785	4.0605	0.0439	1.171	1.004	1.366
Cancer		0.3028	0.0713	18.0563	<.0001	1.354	1.177	1.557
Paralysis		0.4105	0.1638	6.2757	0.0122	1.508	1.093	2.078
Diabetes complicated		-0.2337	0.0993	5.5362	0.0186	0.792	0.652	0.962
Depression		0.3111	0.0944	10.8537	0.001	1.365	1.134	1.642
Psychosis		-0.2445	0.0968	6.3875	0.0115	0.783	0.648	0.947
Number of Elixhauser comorbidities		-0.0436	0.0149	8.5194	0.0035	0.957	0.93	0.986
No hospitalizations and/or outpatient visit for an Elixhauser comorbidity		-0.2623	0.1132	5.3713	0.0205	0.769	0.616	0.96
BMI	**Normal weight**	Reference						
	Overweight	0.1349	0.0728	3.4358	0.0638	1.144	0.992	1.32
	Obese	0.2467	0.0908	7.387	0.0066	1.28	1.071	1.529
	Morbidly obese	0.6404	0.3009	4.5294	0.0333	1.897	1.052	3.422
	Underweight	-0.2242	0.1288	3.0292	0.0818	0.799	0.621	1.029
	Missing	0.0572	0.1833	0.0973	0.755	1.059	0.739	1.517
Number of meds in last 7 days	**<3**	Reference						
	3 - 10	-0.0454	0.2326	0.0381	0.8452	0.956	0.606	1.507
	>10	0.2036	0.2333	0.7617	0.3828	1.226	0.776	1.936
Alpha-blockers in last 30 days		0.3494	0.0649	29.0134	<.0001	1.418	1.249	1.61
Anticonvulsants in last 30 days		0.3435	0.0705	23.7147	<.0001	1.41	1.228	1.619
Diuretics in last 30 days		-0.1354	0.0686	3.9022	0.0482	0.873	0.764	0.999
ADS total in last 30 days		0.0235	0.0104	5.13	0.0235	1.024	1.003	1.045

BMI=Body Mass Index; ADS= Anticholinergic Drug Scale

Table 4.7 continued

Parameter		Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
		Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Point Estimate	95% Wald Confidence Limits	
Bladder continence	**Continent**	Reference						
	Usually Continent	0.3345	0.1161	8.299	0.004	1.397	1.113	1.754
	Occasionally Incontinent	0.3728	0.1355	7.5747	0.0059	1.452	1.113	1.893
	Frequently Incontinent	0.4264	0.146	8.528	0.0035	1.532	1.151	2.039
	Incontinent	0.4091	0.1154	12.5712	0.0004	1.505	1.201	1.887
	Missing	0.4551	0.4686	0.9434	0.3314	1.576	0.629	3.949
Indwelling catheter		1.0988	0.084	171.0753	<.0001	3	2.545	3.538
UTI in last 30 days		0.2215	0.0894	6.1436	0.0132	1.248	1.047	1.487
Bowel continence	**Continent**	Reference						
	Usually Continent	0.0395	0.1125	0.1231	0.7256	1.04	0.834	1.297
	Occasionally Incontinent	-0.2409	0.1473	2.6737	0.102	0.786	0.589	1.049
	Frequently Incontinent	-0.31	0.1658	3.4985	0.0614	0.733	0.53	1.015
	Incontinent	-0.3177	0.116	7.5023	0.0062	0.728	0.58	0.914
	Missing	-0.484	1.0602	0.2084	0.648	0.616	0.077	4.923
Regular bowel elimination pattern		-0.1393	0.063	4.886	0.0271	0.87	0.769	0.984
Diarrhea		0.2645	0.1271	4.3287	0.0375	1.303	1.015	1.671

UTI= Urinary tract infections

Table 4.7 continued

Parameter		Analysis of Maximum Likelihood Estimates				Odds Ratio Estimates		
		Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Point Estimate	95% Wald Confidence Limits	
Cognitive Performance Score	**Intact**	Reference						
	Borderline intact	0.0974	0.0864	1.2701	0.2597	1.102	0.931	1.306
	Mild impairment	-0.0566	0.1012	0.3127	0.576	0.945	0.775	1.152
	Moderate impairment	-0.3579	0.1004	12.713	0.0004	0.699	0.574	0.851
	Moderate severe impairment	-0.2763	0.2252	1.5057	0.2198	0.759	0.488	1.179
	Severe impairment	-0.3418	0.1487	5.2863	0.0215	0.71	0.531	0.951
	Very severe impairment	-0.1835	0.2081	0.7777	0.3779	0.832	0.554	1.252
	Missing	-0.1729	0.6044	0.0818	0.7749	0.841	0.257	2.751
Activities of Daily Living		-0.0177	0.00536	10.852	0.001	0.982	0.972	0.993
MDS Behavioral Score		-0.0475	0.0219	4.7003	0.0302	0.954	0.914	0.995
Hip Fracture in last 180 days		-0.5231	0.2149	5.9253	0.0149	0.593	0.389	0.903

MDS= Minimum Data Set

Aim 2

Aim 2: Determine whether initiation of BAM is associated with increased risk of fractures and impaired cognition.

Hypothesis 2a*: BAM will increase the risk of fractures in NH residents*

Hypothesis 2b*: BAM will negatively affect cognitive status as measured by MDS-CPS*

An important part of the analysis consisted in constructing the PS for new-users and non-users. The complete list of variables included in our PS model along with information on the maximum likelihood estimates and the corresponding odds ratio estimates can be found in Table 4.8 below. This PS model had a C-statistic of 0.713.

The distribution of PS for the two groups (see Figure 4.2 and Table 4.9) allowed for matching new-users with up to 5 non-users.

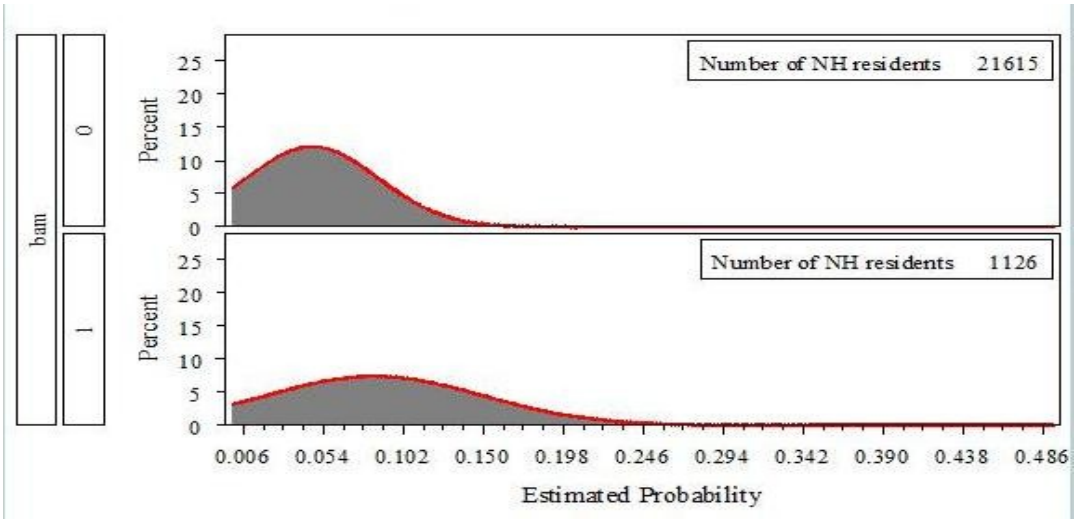


Figure 4.2: Distribution of propensity scores in new-users and non-users

Table 4.8: Propensity Score Model

Parameter		Odds Ratio Estimates		
		Point Estimate	95% Wald Confidence Limits	
Male		0.45	0.322	0.628
Age (reference=65 to 69)	70 to 74	1.269	0.993	1.622
	75 to 79	1.109	0.87	1.413
	80 to 84	1.355	1.07	1.715
	85+	1.161	0.9	1.497
Race (reference=white)	black	0.99	0.811	1.21
	other	0.943	0.737	1.208
VISN (reference=VISN 1)	2	0.859	0.535	1.379
	3	1.02	0.667	1.559
	4	1.59	1.104	2.291
	5	0.943	0.604	1.474
	6	1.32	0.882	1.974
	7	0.891	0.566	1.402
	8	1.064	0.723	1.568
	9	1.488	0.949	2.334
	10	0.928	0.6	1.434
	11	1.794	1.216	2.648
	12	1.138	0.732	1.769
	15	1.648	1.052	2.583
	16	1.586	1.062	2.369
	17	1.049	0.689	1.596
	18	2.164	1.443	3.247
	19	1.545	0.91	2.621
	20	1.052	0.636	1.74
	21	0.778	0.511	1.186
	22	0.658	0.376	1.152
	23	1.396	0.945	2.063
FY at admission (reference=2009)	2003	1.744	1.298	2.344
	2004	1.848	1.375	2.484
	2005	1.767	1.308	2.388
	2006	1.752	1.294	2.372
	2007	1.456	1.066	1.989
	2008	1.497	1.097	2.044

Table 4.8 continued

BMI (reference=normal)	Morbidly obese	1.975	1.089	3.581
	Obese	1.285	1.068	1.546
	Overweight	1.147	0.989	1.331
	Underweight	0.845	0.651	1.097
	Missing or extreme values	1.099	0.757	1.595
Bowel Continence (reference=continent)	Usually Continent	1.05	0.834	1.321
	Occasionally Incontinent	0.79	0.585	1.067
	Frequently Incontinent	0.748	0.535	1.045
	Incontinent	0.712	0.559	0.906
	Missing	0.728	0.091	5.846
Bladder Continence (reference=continent)	Usually Continent	1.39	1.096	1.763
	Occasionally Incontinent	1.469	1.107	1.949
	Frequently Incontinent	1.472	1.079	2.008
	Incontinent	1.462	1.145	1.866
	Missing	1.27	0.469	3.44
Scheduled toileting plan		0.96	0.807	1.141
Bladder retraining program		0.955	0.619	1.474
External catheter		1.113	0.867	1.428
Indwelling catheter		2.889	2.373	3.516
Intermittent catheter		0.826	0.543	1.256
Pads/Briefs Used		0.962	0.811	1.14
No appliance or program		0.861	0.707	1.048
UTI in last 30 days		1.249	1.041	1.499
Regular Bowel Elimination		0.87	0.76	0.995
Constipation		1.129	0.944	1.351
Diarrhea		1.299	1.002	1.684
Fecal Impaction		0.884	0.263	2.968
Cognitive Performance Score (reference=intact)	Borderline intact	1.109	0.929	1.323
	Mild impairment	0.926	0.751	1.143
	Moderate impairment	0.712	0.575	0.881
	Moderate severe impairment	0.799	0.509	1.254
	Severe impairment	0.694	0.508	0.948
	Very severe impairment	0.702	0.447	1.103
	Missing	0.862	0.259	2.867
Activities of Daily Living	(0=independent)	0.975	0.962	0.988
CHESS (reference=0)	CHESS=1	0.953	0.811	1.119
	CHESS=2	1.008	0.84	1.211
	CHESS=3	0.796	0.618	1.026
	CHESS=4	1.047	0.689	1.59
	CHESS=5	1.486	0.51	4.325
	Missing	0.861	0.643	1.153

Table 4.8 continued

MDS Behavioral Score	0=no problem behavior	0.965	0.923	1.008
Balance while standing (reference=0)	Unsteady, but able to rebalance w/o physical support	1.071	0.869	1.32
	Partial physical support during test or stands but does not follow directions for test	1.055	0.852	1.305
	Not able to attempt test w/o physical help	1.069	0.855	1.335
	Unknown (missing or out of range value)	1.389	0.936	2.062
Balance while sitting (reference=0)	Unsteady, but able to rebalance w/o physical support	0.873	0.69	1.106
	Partial physical support during test or stands but does not follow directions for test	0.998	0.769	1.294
	Not able to attempt test w/o physical help	1.326	1.03	1.708
	Unknown (missing or out of range value)	0.864	0.375	1.989
Number of comorbidities (inpatient and outpatient)		0.956	0.92	0.994
No hospitalizations and/or outpatient visits		0.785	0.623	0.99
Congestive Heart Failure		0.964	0.818	1.137
Cardiac Dysrhythmias		1.153	0.972	1.368
Hypertension		1.176	1	1.384
Hypertension complicated		0.937	0.732	1.2
Paralysis		1.562	1.123	2.173
COPD		1.029	0.878	1.206
Diabetes		1.022	0.879	1.187
Diabetes complicated		0.769	0.617	0.959
Tumor with metastasis		1.122	0.799	1.575
Hypotension		0.622	0.365	1.059
Osteoporosis		0.94	0.741	1.192
Cancer		1.307	1.117	1.528
Stroke		1.159	0.988	1.36
Depression		1.352	1.11	1.647
Psychosis		0.814	0.663	1
Unsteady Gait		0.979	0.857	1.118

Table 4.8 continued

Vision (reference=normal)	Impaired	1.128	0.965	1.317
	Moderately impaired	1.13	0.853	1.498
	Highly impaired	0.951	0.609	1.485
	Severely impaired	0.992	0.561	1.756
	Unknown (missing or out of range value)	1.211	0.475	3.088
Fell in past 30 days		0.972	0.825	1.145
Fell in past 31-180 days		1.135	0.975	1.322
Hip fracture in past 180 days		0.593	0.383	0.918
Other fracture in past 180 days		0.841	0.567	1.248
Number of meds in last 7 days		1.238	1.077	1.423
Alpha-blockers in last 30 days		1.462	1.281	1.669
ACE inhibitors in last 30 days		0.973	0.847	1.117
Antidepressants in last 30 days		1.088	0.954	1.241
Antipsychotics in last 30 days		0.934	0.792	1.102
Anticonvulsants in last 30 days		1.392	1.206	1.607
BZD in last 30 days		0.846	0.622	1.151
Antiparkinson meds in last 30 days		1.006	0.765	1.323
Antivertigo in last 30 days		1.131	0.686	1.865
CNS stimulants in last 30 days		0.909	0.751	1.101
Beta-blockers in last 30 days		0.954	0.834	1.09
Diuretics in last 30 days		0.863	0.746	0.997
Calcium channel blockers in last 30 days		0.925	0.798	1.072
ADS total in last 30 days		1.028	1.005	1.051

Table 4.9 Propensity Score Distribution

	BAM use		
PS Quintile	**Non-users**	**/New-users**	**Total**
1	4481 (20.73%)	67 (5.95%)	4548
2	4433 (20.51%)	115 (10.21%)	4548
3	4384 (20.28%)	165 (14.65%)	4549
4	4307 (19.93%)	241 (21.4%)	4548
5	4010 (18.55%)	538 (47.78%)	4548
Total	21615	1126	22741

Hip Fracture Analysis

Figure 4.3 depicts the flow diagram for the final groups included in the hip fracture analysis.

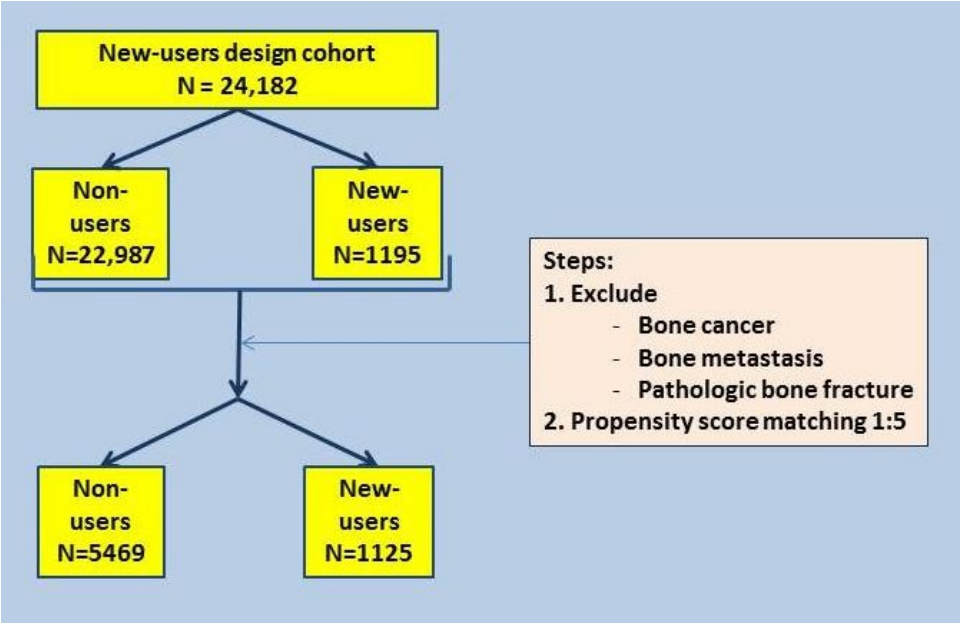


Figure 4.3: Flow diagram- Identification of study groups included in the hip fracture analysis

Table 4.10 summarizes the matching process and provides information on the comparability of new-users with their controls in terms of PS distribution for those included in the hip fracture analysis. After matching on PS, balance between the two groups was achieved for all of the variables included in the PS model (see table A 14 in the Appendix).

To summarize the PS matching process, out of the 1195 new-users identified in our cohort, after applying the exclusion criteria and defining the final event date, 1126 new-users entered the matching process. Of these, 1125 had at

Table 4.10: Propensity Score Matching- Summary

CONTROL	Users N	Label	N	Mean	Median	Minimum	10th Pctl	25th Pctl	75th Pctl	90th Pctl	Maximum	Sum
1	1125											
		PS/USER	1125	0.085	0.066	0.006	0.025	0.039	0.108	0.171	0.482	95.456
		PS/NON-USER	1125	0.085	0.066	0.006	0.025	0.039	0.108	0.171	0.487	95.478
2	1116											
		PS/USER	1116	0.083	0.066	0.006	0.025	0.039	0.107	0.168	0.369	92.409
		PS/NON-USER	1116	0.083	0.066	0.006	0.025	0.039	0.107	0.168	0.361	92.415
3	1100											
		PS/USER	1100	0.08	0.065	0.006	0.025	0.039	0.105	0.159	0.346	87.923
		PS/NON-USER	1100	0.08	0.065	0.006	0.025	0.039	0.105	0.159	0.349	87.886
4	1075											
		PS/USER	1075	0.076	0.063	0.006	0.025	0.038	0.102	0.146	0.346	81.661
		PS/NON-USER	1075	0.076	0.063	0.006	0.025	0.038	0.102	0.147	0.343	81.625
5	1053											
		PS/USER	1053	0.073	0.062	0.006	0.024	0.037	0.1	0.141	0.346	76.94
		PS/NON-USER	1053	0.073	0.062	0.006	0.024	0.037	0.1	0.14	0.35	76.899

*PS= propensity score

There were 1125 new-users that had at least one non-user matched by propensity score, 1116 had at least two matched non-users, 1100 had three, 1075 had four, and 1153 had five non-users matched by PS. In the matching process, each new-user was matched to one non-user first. The process continued and the second match was attempted for all the 1125 that had a first match; 1116 had a non-user with a similar PS identified. The process was reiterated until the fifth control was identified. For the first selected control, there was no difference in PS mean, median, minimum and 10^{th}, 25^{th}, 75^{th} and 90^{th} percentiles between new-users and non-users. The only difference was in the maximum PS score (0.482 vs 0.487). The distribution of PS in new-users and the second, third, fourth, and fifth matched non-users was similar.

least one non-user with a similar PS, with 1053 having five comparable controls. The final groups consisted in 1125 new-users and 5469 corresponding controls. The follow-up time was 1,280,201 person-days for all non-users and 181,669 person-days for new-users. The maximum follow-up time for matched non-users was 2505 days, with a mean of 234.08 days and a median of 95 days. The maximum follow-up time for new-users was 2045 days, with a mean of 161.48 days and a median of 49 days.

During the total follow-up time 13 hip fractures were identified in the new-users group and 100 hip fractures in the non-users group. Table 4.11 below presents the information on the source of data for identifying hip fractures. The distribution of ascertainment source did not differ between BAM users and non-users.

Table 4.11 Distribution of data sources to identify hip fractures

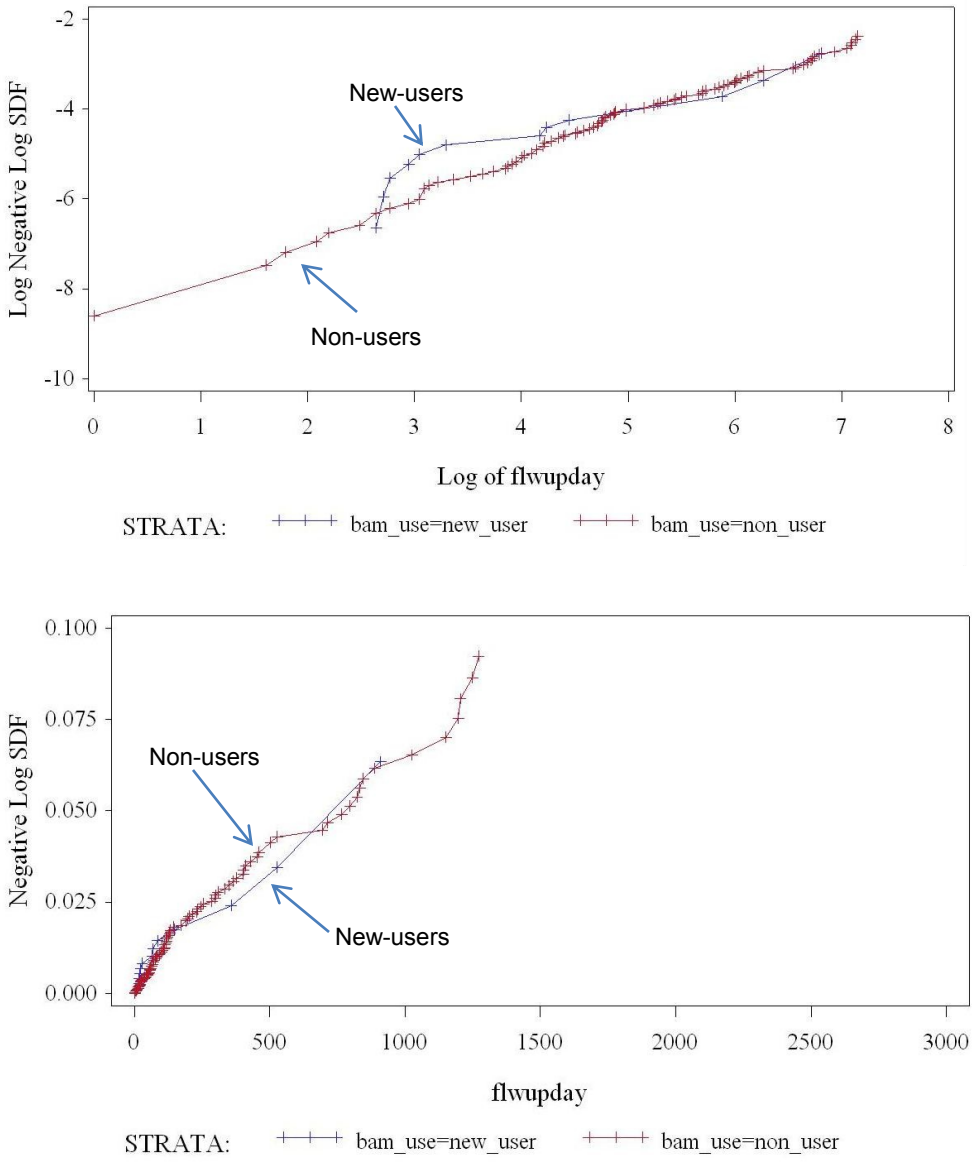
Data Source	BAM use		Total
	New-users	Non-users	
MDS only- N (Col Pct)	4 (30.77%)	24 (24.00%)	28
MDS and other source- N (Col Pct)	3 (23.08%)	31 (31.00%)	34
Other source only- N (Col Pct)	6 (46.15%)	45 (45.00%)	51
Total	13	100	113

*Note: other sources = hospital discharge and/or outpatient visits

Of the 113 hip fractures, 31 (1 in the new-users group and 30 in the non-users group) occurred less than 90 days before the date of death. Of these, the majority (N=22) had a hospital admission for the hip fracture; the remaining 9 (all in the non-users group) were identified from MDS exclusively.

As described in the ‘Statistical analyses’ section, our time to event analysis was conducted using a Cox proportional hazard model; the model

included an indicator of BAM use and a variable indicating the exposure time (defined as time during which the gap between two consecutive BAM prescriptions was less than 7 days) out of the total follow-up time. For our BAM exposure indicator, the proportionality assumption was evaluated by constructing survival curves stratified by exposure (see Figure 4.4 below). For the variable indicating the number of days with BAM exposure, the assumption was checked with the proportionality test on the interaction term with time (p-value=0.0185). Due to the fact that the proportionality assumption was violated, the final model also included interaction terms with time for both indicators of exposure mentioned above.



Note: flwupday=time to event; bam_use=indicator of BAM use; SDF= Survival Distribution Function

Figure 4.4: Cox Proportional Model Assumption for bladder antimuscarinics use indicator

The hazard ratio calculated with the Cox proportional hazard model mentioned earlier indicated an increased risk of hip fracture in new-users as compared with non-users (HR=3.688, 95% CI: 1.457 - 9.337, p=0.0059). Table 4.12 below summarizes the estimates for the Cox proportional hazard model.

Table 4.12 Hip fracture analysis- Cox proportional model parameter estimates

Parameter	Parameter estimate	Standard Error	Hazard ratio	p value
BAM use indicator (yes/no)	1.30504	0.47398	3.688	0.0059
Exposure duration	-0.00981	0.0037	0.990	0.008
BAM use*time	-0.0005107	0.00142	0.999	0.72
Exposure duration*time	7.81E-06	3.31E-06	1.00	0.0185

When restricting the analysis to only include new-users that had exposure to Oxybutynin IR, the hazard ratio suggested even a higher risk as compared to non-users (HR=4.899, 95%CI: 1.785 - 13.444, p=0.002).

We conducted two sensitivity analyses; in the first one we excluded fractures that were identified from MDS exclusively through the first assessment following the index date. With this approach, there is more certainty that all of the fractures included in the analysis occurred after the index date; four fractures (one in the BAM users group and three in the non-users group) were excluded. The hazard ratio suggested the increased risk associated with BAM exposure (HR=3.294, 95%CI: 1.294 – 8.687). Table 4.13 below shows the complete results for this sensitivity analysis.

Table 4.13 Sensitivity analysis- Excluding hip fractures with uncertain temporal relationship

Parameter	Parameter estimate	Standard Error	Hazard Ratio	p value
BAM use indicator (yes/no)	1.192	0.495	3.294	0.016
Exposure duration	-0.009	0.004	0.991	0.012
BAM use*time	-0.0004	0.0014	1.00	0.78
Exposure duration*time	7.15E-06	3.27E-06	1.00	0.03

The second sensitivity analysis aimed to eliminate the potential residual unmeasured confounding. We evaluated the hip fracture risk after trimming the PS distribution. This approach eliminated new-users with very low PS (thus suggesting that based on their baseline characteristics, their likelihood for getting treated was very low) and non-users with high PS (expected to be treated). The hazard ratio estimate slightly increased when 1% was trimmed at both ends of the distribution, and increased more substantially when 5% was trimmed (see Table 4.14 below). When trimming 5% of the distribution, 6 of the fractures that were not included in the analysis (1 in the new-users group and 5 in the non-users group) were part of the 31 described earlier as occurring less than 90 days from the date of death.

The two sensitivity analyses we conducted support the result from the main analysis and further supports that BAM initiation increases the risk of hip fractures.

Table 4.14 Sensitivity analysis- Propensity score distribution trimming

PS distribution	Number of fractures		Hazard ratio	95% CI	
	BAM users	Non-users			
No trimming	13	100	3.688	1.457	9.337
Trimming <1% and >99%	11	95	3.966	1.455	10.811
Trimming <5% and >95%	9	80	5.045	1.658	15.353

Any Fracture Analysis

The two groups included in the analysis for our 'any fracture' are depicted in Figure 3.5 below.

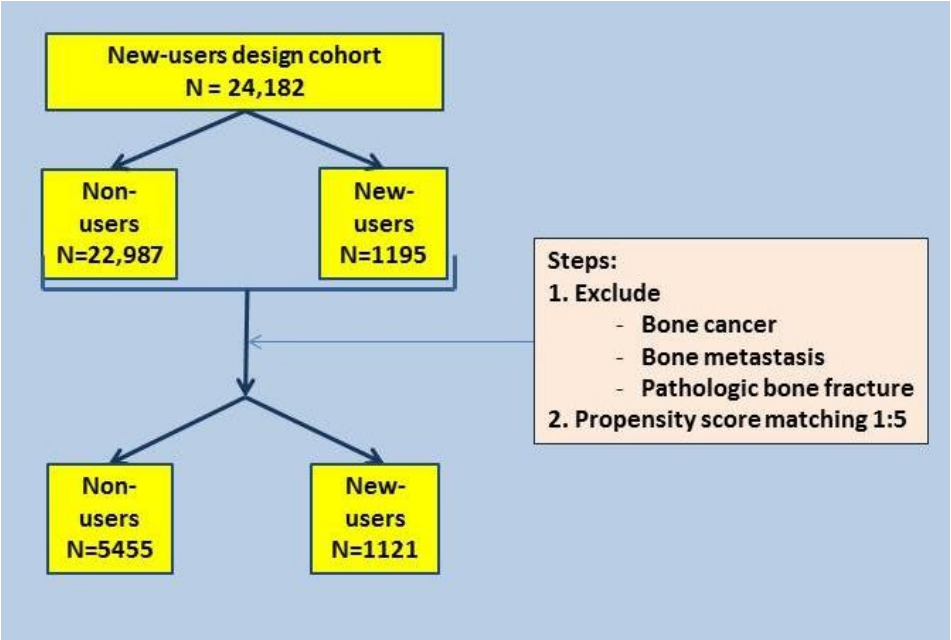


Figure 4.5: Flow diagram- Identification of study groups included in the 'any fracture' analysis

The difference in the number of new-users and non-users between this analysis and the hip fracture analysis resulted from the assignment of the event date for those fractures that were only identified from MDS. Specifically, since the index date was between two MDS assessments, if the fracture was identified based on the first MDS assessment following the index date, the only information available was of the event taking place sometime between the two consecutive assessments. Since our protocol assigned an event date as the mid-point

between the two assessments, for some of the fractures this date fell before the index date; therefore, they were excluded from the analysis.
There were 195 fractures identified, of which 23 occurred among new-users and 172 among non-users.

Similarly to the hip fracture analysis, after checking the proportionality assumption for the BAM use indicator and for the exposure duration indicator, the Cox proportional hazard model for the 'any fracture' analysis included interaction terms with time for the aforementioned variables.

When all of the BAM users were included in the analysis, there was a higher risk of fracture for new-users as compared to non-users (HR=2.64. 95% CI: 1.366 - 5.104, p=0.0039). The risk was even higher when only those using Oxybutynin IR were considered (HR=2.78, 95% CI: 1.311 - 5.892, p=0.0077).

Cognitive Performance Analysis

A flow diagram depicting the groups included in the repeated measures analyses (cognitive performance, improvement in urinary incontinence, and QOL) is shown below (Figure 4.6).

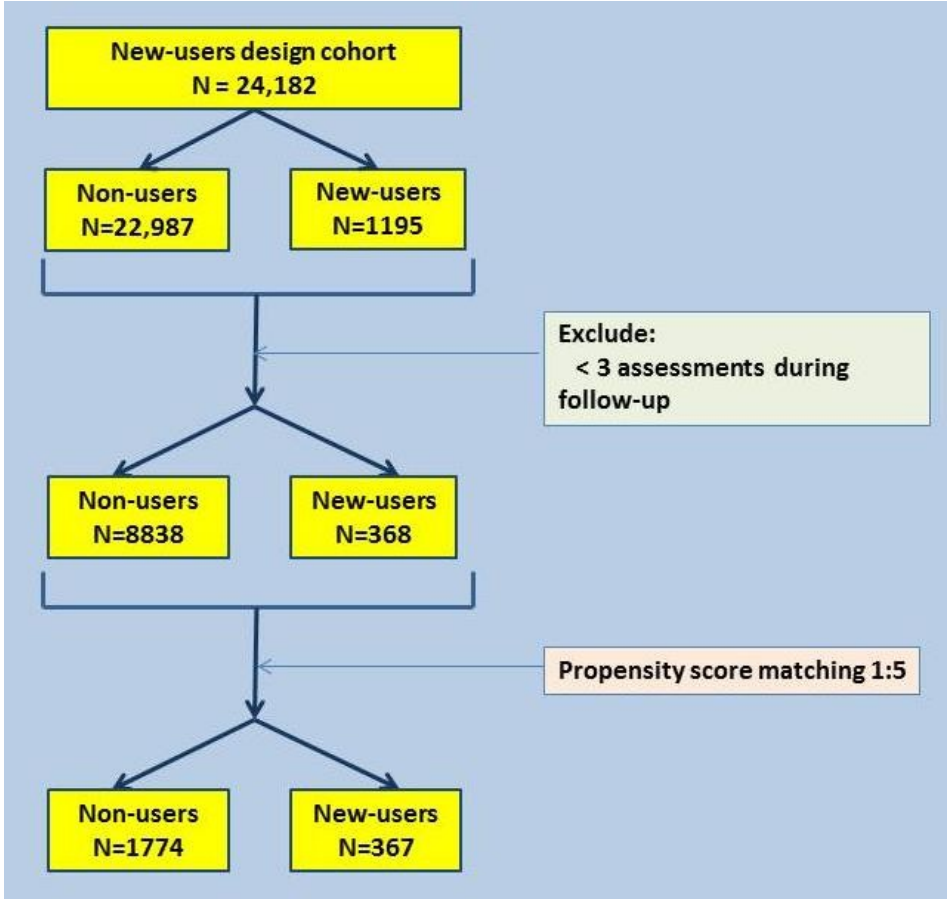


Figure 4.6: Flow diagram- Identification of study groups included in the repeated measures analysis

The two groups included in the longitudinal repeated measures analysis had similar distributions at baseline for cognitive performance measured by the MDS-CPS. There was no difference in the mean CPS between the two groups (p=0.1108); the mean CPS at baseline was 1.3842 (SD=1.6454) for new-users and 1.5372 (SD=1.6781) for non-users. The distribution by CPS categories was similar as well (p=0.4605) and is presented in Table 4.15 below.

Table 4.15 Distribution of Cognitive Performance Scale scores at baseline

CPS- N (Col %)	Non-users	New-users	Total
0	675 (38.05)	153 (41.69)	828
1	377 (21.25)	80 (21.8)	457
2	222 (12.51)	48 (13.08)	270
3	303 (17.08)	51 (13.9)	354
4	38 (2.14)	10 (2.72)	48
5	124 (6.99)	17 (4.63)	141
6	30 (1.69)	6 (1.63)	36
missing	5 (0.28)	2 (0.54)	7
Total	1774	367	2141

For the analysis evaluating the impact of BAM use on the cognitive performance, we assessed different models by including various time-varying covariates measured through the periodic MDS assessments. We also evaluated the potential effect modification by baseline CPS for the relationship between BAM use and cognitive performance at later times; this effect was assessed by including an interaction term between the BAM use indicator and baseline CPS, but was not included in the final model since it did not result in a significant estimate.

Table 4.16 presents the GEE estimates for BAM from the unadjusted and the final model.

The final model evaluated the longitudinal effect of BAM use while adjusting for CPS at baseline, age, stroke, and use of antianxiety medication at each MDS assessment. Although the unadjusted estimate suggested that BAM users had a lower mean CPS (better outcome) at each time-point during follow-up, after adjusting for baseline CPS and time-varying covariates it appears that there is no difference between the two groups with regard to the mean CPS.

Table 4.16 Cognitive performance analysis- Generalized estimating equations method parameter estimates

	BAM Estimate	Standard Error	95% Confidence Limits		p-value
Model 1	-0.2285	0.0883	-0.4015	-0.0554	0.0097
Model 2	0.0050	0.0511	-0.0951	0.1051	0.9214

Model 1: Unadjusted

Model 2:

- Adjusted for baseline CPS, age, stroke indicator, antianxiety medication use
- Other variables considered for inclusion: interaction BAM-baseline CPS , number of drugs used in the last 7 days, schizophrenia, depression/antidepressants use, anxiety disorder, bipolar disease, hypnotic medication use
- Model selection based on QIC

Table 4.17 below presents the GEE parameter estimates for all the variables included in the final model. BAM exposure did not significantly change the mean CPS. Baseline CPS was an important predictor for the mean CPS at each time point; in addition, age, stroke and use of antianxiety medication treated as time-varying indicators also resulted in a higher mean CPS value at each time point as compared with those without each of the indicators respectively.

Table 4.17 Cognitive performance analysis- Final model estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		p-value
Intercept	-0.4163	0.2282	-0.8635	0.0309	0.0681
BAM	0.0050	0.0511	-0.0951	0.1051	0.9214
BAM*Week	-0.0027	0.0004	-0.0035	-0.0019	<.0001
Baseline CPS	0.8833	0.0116	0.8606	0.9059	<.0001
Age	0.0077	0.0028	0.0022	0.0133	0.0065
Stroke	0.1295	0.0270	0.0766	0.1824	<.0001
Antianxiety medication	0.0807	0.0240	0.0336	0.1277	0.0008
Week	0.0043	0.0001	0.0040	0.0046	<.0001

BAM= Bladder Antimuscarinics; CPS= Cognitive Performance Scale

Aim 3

Aim 3: Determine whether BAM initiation is associated with improvement in incontinence and QOL.

Hypothesis 3a: BAM will improve incontinence as measured by MDS

Hypothesis 3b: BAM will improve social engagement as measured by MDS-ISE and overall QOL as measured by MDS-HSI

Improvement in Urinary Incontinence

The two groups included in the longitudinal repeated measures analysis had similar distributions at baseline for urinary continence status measured by the MDS. There was no difference in the mean urinary continence between the two groups (p=0.7835); the mean rating for continence at baseline was 1.1471 (SD=1.6263) for new-users and 1.1731 (SD=1.6481) for non-users. The distribution by continence categories was similar as well (p=0.3802) and is presented in Table 4.18 below.

Table 4.18 Distribution of continence rating at baseline

Continence- N (Col %)	Non-users	New-users	Total
Continent	1023 (57.67)	216 (58.86)	1239
1	196 (11.05)	32 (8.72)	228
2	128 (7.22)	32 (8.72)	160
3	124 (6.99)	33 (8.99)	157
4	294 (16.57)	52 (14.17)	346
missing	9 (0.51)	2 (0.54)	11
Total	1774	367	2141

BAM use significantly improved urinary incontinence in the unadjusted analysis. The results remained significant even after time-varying covariates were added to the GEE model (Table 4.19).

Table 4.19 Longitudinal analysis of bladder continence rating- Odds ratio estimates

	OR	Standard Error	95% Confidence Limits		p-value
Model 1	1.3432	0.1201	1.1273	1.6005	0.001
Model 2	1.2664	0.1098	1.0686	1.5009	0.0064

Model 1: Unadjusted
Model 2:

- Adjusted for baseline continence status, scheduled toileting plan, indwelling catheter, bowel continence
- Other variables considered for inclusion: bladder retraining program, external catheter, intermittent catheter, Pads/briefs used, no appliances or programs used for urinary incontinence management, regular bowel elimination pattern, constipation, ADL, MDS behavioral score, age, diabetes, CHF, PVD, antianxiety medication use, number of drugs use in the last 7 days, schizophrenia, depression/antidepressants use, anxiety disorder, bipolar disease, hypnotic medication use
- Model selection based on QIC

Final model OR estimates are shown in Table 4.20 below.

Table 4.20 Longitudinal analysis of bladder continence rating- Final generalized estimating equations method model

Parameter	OR Estimate	Standard Error	95% Confidence Limits		p-value
BAM	1.2664	0.1098	1.0686	1.5009	0.0064
Baseline continence	1.2542	0.0316	1.1938	1.3176	<.0001
Scheduled toileting plan	1.6995	0.1244	1.4724	1.9615	<.0001
Indwelling catheter	1.4595	0.1364	1.2151	1.7529	<.0001
Bowel continence	0.8261	0.0202	0.7874	0.8667	<.0001
Week	0.9962	0.0085	0.9797	1.0130	0.6569

BAM= Bladder antimuscarinics

Index of Social Engagement Analysis

The two groups included in the longitudinal repeated measures analysis had similar distributions at baseline for the social engagement measured by the MDS-ISE instrument. There was no difference in the ISE mean between the two groups (p=0.2038); the mean ISE at baseline was 1.8420 (SD=1.4957) for new-users and 1.7384 (SD=1.4039) for non-users. The distribution by ISE categories was similar as well (p=0.4423) and is presented in Table 4.21 below.

Table 4.21 Distribution of Index of Social Engagement score at baseline

ISE- N (Col %)	Non-users	New-users	Total
0	303 (17.08)	58 (15.80)	361
1	647 (36.47)	133 (36.24)	780
2	355 (20.01)	75 (20.44)	430
3	278 (15.67)	48 (13.08)	326
4	97 (5.47)	25 (6.81)	122
5	59 (3.33)	19 (5.18)	78
6	35 (1.97)	9 (2.45)	44
Total	1774	367	2141

In the unadjusted analysis, new-users had significantly higher scores as compared to non-users. The difference between the groups slightly changed, but remained statistically significant after MDS behavioral score (the higher the score, the more problematic behavior the patient exhibits) and vision (higher score means poorer vision) were included in the model as time-varying covariates (see Table 4.22). The GEE parameter estimates for all the variables included in the final model are shown in Table 4.23.

Table 4.22 Longitudinal evaluation of social engagement- generalized estimating equations method parameter estimates

	BAM Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Model 1	0.2075	0.0789	0.0529	0.3621	0.0085
Model 2	0.2074	0.0777	0.0550	0.3598	0.0076

Model 1: Unadjusted
Model 2:

- Adjusted for time-varying MDS behavioral score, time-varying vision
- Other variables considered for inclusion: diabetes, CHF, PVD, antianxiety medication use, number of drugs use in the last 7 days, depression/antidepressants use, anxiety disorder, bipolar disease, schizophrenia, hypnotic medication use
- Model selection based on QIC

Table 4.23 Longitudinal evaluation of social engagement- Final generalized estimating equations method model

Parameter	Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Intercept	1.8862	0.0337	1.8202	1.9523	<.0001
BAM	0.2074	0.0777	0.0550	0.3598	0.0076
Behavioral score	-0.0433	0.0070	-0.0569	-0.0297	<.0001
Vision	-0.1619	0.0183	-0.1977	-0.1260	<.0001
Week	0.0003	0.0002	0.0000	0.0006	0.0302

BAM= Bladder Antimuscarinics

Overall QOL Analysis

At baseline, the mean overall QOL as measured by MDS-HSI was 0.5648 (SD=0.2081) for BAM users and 0.5218 (SD=0.1921). The 0.0429 difference was statistically significant (p=0.0003).

In the unadjusted analysis, BAM users seemed to have a better mean MDS-HSI, at a difference that is considered clinically significant. However, this difference was similar to the one at baseline; after the inclusion of baseline (CPS, ADL, MDS behavioral score) and time-varying (age, number of medications used, antianxiety medication use) covariates, the two groups had similar mean MDS-HSI values (see Table 4.24 and Table 4.25).

Table 4.24 Longitudinal overall quality of life analysis- Final generalized estimating equations method parameter estimates

	BAM Estimate	Standard Error	95% Confidence Limits		Pr > |Z|
Model 1	0.0356	0.0104	0.0151	0.0560	0.0006
Model 2	-0.0005	0.0083	-0.0168	0.0158	0.9557

Model 1: Unadjusted
Model 2:

- Adjusted for baseline variables (CPS, ADL, MDS behavioral score), and time-varying covariates (age, number of medications used, antianxiety medication use)
- Other time-varying covariates considered for inclusion: stroke indicator, Parkinson's disease indicator, antidepressants use, hypnotics use
- Model selection based on QIC

Table 4.25 Longitudinal overall quality of life analysis- Final generalized estimating equations method model

Parameter	Estimate	Standard Error	95% Confidence Limits		p-value
Intercept	0.9783	0.0375	0.9048	1.0517	<.0001
BAM	-0.0005	0.0083	-0.0168	0.0158	0.9557
BAM*Week	0.0005	0.0001	0.0003	0.0006	<.0001
Baseline CPS	-0.0367	0.0020	-0.0407	-0.0327	<.0001
Baseline ADL	-0.0104	0.0004	-0.0111	-0.0096	<.0001
Baseline Behavioral Score	-0.0115	0.0020	-0.0155	-0.0075	<.0001
Age	-0.0027	0.0005	-0.0036	-0.0018	<.0001
Number of drugs used	-0.0101	0.0030	-0.0161	-0.0041	0.0009
Antianxiety medication	-0.0213	0.0043	-0.0297	-0.0129	<.0001
Week	-0.0004	0.0000	-0.0004	-0.0003	<.0001

BAM= Bladder Antimuscarinics; CPS= Cognitive Performance Scale; ADL= Activities of Daily Living;

Exploratory Analyses

Overall Mortality

Mortality was evaluated for the two groups matched by PS. Since this was exploratory, we conducted the analysis using two different censoring strategies. In the first one, BAM users were censored at outcome (death) or at treatment discontinuation. In the second strategy, maximum follow-up was extended 30 days after treatment discontinuation; therefore, deaths within 30 days after treatment discontinuation were included in the analysis. In both strategies, non-users were censored at outcome or at the end of follow-up.

When the first strategy was used, there was no difference between the two groups (HR=0.807; 95%CI: 0.572-1.140); however, when follow-up was extended to 30 days after treatment discontinuation, BAM users had a higher mortality risk as reflected by the higher hazard ratio (HR=1.82; 95%CI: 1.494-2.218).

Bowel Effects

At baseline, the frequency of constipation (p=0.7345) and fecal impaction (p=0.4565) was similar between the two study groups. We used the GEE method to determine the OR for the association between BAM initiation and bowel effects. There was no difference in risk for constipation or fecal impaction with BAM initiation; specifically, the OR was 1.0885 (95%CI: 0.7211-1.6431) for constipation and 1.4031 (95%CI: 0.4623-4.2587) for fecal impaction.

CHAPTER V- DISCUSSION

This study provides significant findings regarding the use of BAM in elderly institutionalized in the VA CLC. It suggests potential benefits associated with BAM initiation in terms of urinary incontinence improvement and increase in social engagement, but it also brings evidence that BAM increase the risk for fractures. It provides some limited reassurance that BAM use does not have a net adverse impact on overall QOL, however a net benefit was not seen either. Since the main BAM used in this population was Oxybutynin IR, the main question that remains is whether medication should not be considered in this population or whether other BAM with different receptor selectivity and physicochemical characteristics would provide the benefits without increasing the risks.

Summary of Findings

Predictors of BAM Initiation

Identifying what factors play an important role on BAM initiation is essential in understanding the role of medication in managing urinary incontinence in a specific population. During the study follow-up period, which ranged from October 1, 2002 to September 30, 2009, BAM were initiated for 1195 NH residents from the 24,182 included in the final cohort. There were several significant differences between new-users and non-users at baseline and these were considered in constructing the best model to predict medication initiation in this study population.

Age was an important independent predictor of BAM initiation and it seemed like older ages were more likely to initiate medication as compared to the youngest group in the study (65 to 69). Although this was a predominantly male population, women were more likely to receive a BAM (OR=2.106; 95% CI:

1.537-2.884) and this was suggested by previous research as well. The majority of the new-users were admitted in the earlier years following admission; this effect could be explained by either a change in care in the NH during the study period, or by the fact that earlier admissions had more the opportunity for a longer follow-up after admission.

Significant variability was identified among residents admitted in VA CLC in different VISN ($p<0.0001$). Although our data did not allow for further investigation, this could be explained by possible differences in care and local management.

In general, new-users had fewer of the comorbidities measured through the Elixhauser modified by Quan algorithm suggesting that patients were selected for treatment based on the absence of an important comorbidity load. Although diabetes increases the risk for urinary incontinence, those that had this condition were less likely to receive a BAM. What we see here might be the result of a thorough clinical decision making process since both diabetes and BAM increase the risk for urinary retention; in addition, urinary retention is a risk factor for urinary tract infections, which have are highly prevalent in diabetic patients regardless of the addition of other factors.

Other comorbidities increased the likelihood of BAM initiation. For instance, BAM users were more likely to be hypertensive, to have experienced a stroke or paralysis, to have had cancer, or to suffer from depression. They also had higher BMI as compared to non-users. In the case of hypertension, it might be that BAM initiation is triggered by occurrence or worsening of urinary incontinence caused by antihypertensive drugs. With regard to the other conditions listed, medication might be initiated to mitigate incontinence in those for which behavioral interventions (including scheduled toileting plan, prompted voiding) would be difficult to implement. For instance, patients that had a stroke

or paralysis, and those that are obese might have problems moving and these would negatively impact any of the aforementioned non-pharmacological strategies. In addition, in patients with stroke or paralysis, this might also reflect neurologic manifestations of these conditions which cause incontinence. With regard to depression, on one hand, those suffering from depression might not have a good adherence to behavioral interventions and/or their incontinence might worsen due to antidepressant medication use. On the other hand, urinary incontinence was shown to lead to depression, thus the association between this condition and BAM initiation might not be causal. However, the relationship might be more complex, with urinary incontinence leading to depression thus making behavioral interventions difficult to implement, which in the end would lead to BAM initiation.

Those who were started on a BAM were on multiple drug regimens and had a higher anticholinergic load. These patients might be the ones that are selected for treatment since they might tolerate medication well, including other drugs with anticholinergic properties. BAM might be initiated assuming that they would be at low risk for medication-related adverse events, without considering the additive effect of anticholinergics. The use of alpha-blockers and anticonvulsants increased the odds of treatment for urinary incontinence, whereas the use of diuretics was inversely related to BAM initiation. Alpha-blockers were shown to cause incontinence and this could explain their role in predicting BAM initiation. Diuretics cause polyuria, which leads to an increase in urinary frequency and urinary urgency; in those suffering from urinary incontinence, the addition of a diuretic would most likely worsen the condition. Assuming all these, the negative relationship between diuretics use and BAM initiation might be the result of a more complex relationship which was not captured in this study.

Not surprisingly, BAM new-users had more bladder problems at baseline (higher ratings of incontinence and previous urinary tract infections) and were more likely to be on an indwelling catheter before medication initiation. The effect of continence severity on treatment initiation is probably incompletely captured in our study given the definition of continence status to include those controlled by an indwelling catheter. Bowel incontinence was inversely related to the chance of a BAM initiation.

Those with cognitive impairment, less functional, with more problematic behaviors, or those that experienced a previous hip fracture were less likely to receive a BAM. These results suggest that the most fit and less-likely to experience adverse effects were the ones selected for treatment.

BAM users had better cognitive and physical function but were taking more medications and had greater prevalence of some comorbidities. Thus, the direction of treatment selection bias would be difficult to predict. The considerable number of differences between BAM users and nonusers at baseline (before propensity score matching) underscores the value of the rich MDS-administrative records linked data resource for studying treatment effectiveness in NH patients

Most of the previous research addressed factors associated with BAM adherence rather than factors associated with medication initiation. Two more recent studies evaluated BAM use in elderly residing in NH and looked of factors associated with medication use or with medication initiation. One of them used cross-sectional data from MDS assessments conducted in 378 skilled-nursing facilities (Jumadilova et al, 2005) and could only evaluate the concomitant use of BAM with different factors (demographic characteristics, functional status as measured by MDS ADL, cognitive performance measured by MDS CPS, and the MDS indicator for a hospitalization). Given the design, the temporal relationship

between residents' characteristics and the start of a BAM could not be evaluated in this study. Similarly to our results, Jumadilova et al showed that BAM user had more urinary tract infections, suffered from depression, and had fewer hospitalizations. However, contrary to our findings, their unadjusted analysis indicated that those being treated had more impairment on ADLs and CPS, differences that were no longer significant when adjusted by demographic and health characteristics. The differences in what the paper by Jumadilova et al found and our findings might be the result of their inclusion of prevalent BAM users as opposed to new-users.

The second study (Narayanan et al., 2007) was a two-year long (January 2002-December 2003) retrospective cohort study of residents in 373 skilled nursing facilities and assisted living centers operated by a single provider of long-term care. They looked at predictors of BAM initiation in NH residents identified as incontinent based on at least one MDS assessment during their NH stay and who had adequate mobility (measured by ADL items of < or =2) and/or cognitive ability to toilet (CPS score of < or =3). The study was not restricted to those 65 and older and included mostly women (65%). Similarly to our findings, Narayanan et al identified gender (female), age, bladder continence rating and bladder control management, bowel problems, better physical and cognitive functioning as important predictors for BAM initiation. Race (whites were more likely to receive treatment) was also an important predictor in their multivariate model, but was not significant in our study population. We also included medication and comorbidities measured from administrative data (pharmacy, inpatient and outpatient files) which were not considered by the other authors and we believe this addition provided a better understanding of the factors predicting medication initiation.

Our study identified several factors as predictors for BAM initiation in the VA NH population. Our results were similar to those from a previous cohort study on a population with different demographic characteristics; different relationships were observed in one cross-sectional study that included prevalent users.

Risks Associated with BAM Initiation

Fractures

Our study showed an increased risk of fractures associated with BAM initiation in institutionalized elderly. The hazard ratio was greater when the outcome was restricted to include only hip fractures (HR=3.688 for hip fractures and HR=2.64 for all fractures). This discrepancy can be explained by the difference in specificity of the outcome definition in relationship to the proposed mechanism of occurrence. Since falls were the hypothesized mechanism for fractures in this population, the intended outcome consisted in fall-related fractures exclusively. Unfortunately, given the need to combine multiple data sources and nature of these data sources (specifically MDS records of fractures) our 'any fracture' definition was less specific thus most likely resulting in a bias toward the null. For a more clinically meaningful interpretation of the HR, we estimated the number needed to harm (the number of patients that would be treated for a certain period of time and lead to one hip fracture) (Altman et al, 1999). In this NH population, the number needed to harm was 36 at 90 days.

We conducted two sensitivity analyses to evaluate the increase in fracture risk related to BAM initiation. Both analyses supported the main study result for the fracture risk and showed significant increase in HR for new-users. The first one aimed to include only those fractures for which the temporal relationship between exposure initiation and the study outcome was clearly established.

Therefore, fractures identified from first MDS assessment following the index date and with no inpatient or outpatient record were excluded from the analysis. In the second sensitivity analysis the risk of fracture was evaluated after trimming the PS distribution to exclude new-users and non-users with extreme PS for which unmeasured confounding could have been the deciding factor for treatment assignment.

Finally, the risk for fractures increased when analysis was restricted to Oxybutynin IR users (HR=4.899 for hip fractures, HR=2.78 for all fractures). This result was expected based on receptor selectivity and physicochemical characteristics.

Three recent studies evaluated the risk of falls and/or fractures in relationship to BAM use. None of the three included a non-user comparison group. There are also other significant differences in design between these studies and our investigation. One randomized placebo-controlled trial enrolled fifty women aged 65 and older with urge incontinence and cognitive impairment from twelve skilled nursing homes and followed them for four weeks to evaluate safety of Oxybutynin extended-release (ER) (Lackner et al, 2008). The incidence of falls was not different between the study groups. However, given the small sample size and the short follow-up, it is hard to conclude that Oxybutynin ER does not differ from placebo. In addition, this study included Oxybutynin extended-release as opposed to Oxybutynin IR that represented the most frequently used BAM in our population.

A retrospective cohort study of 33,067 patients with overactive bladder compared the risk of fractures associated with different BAM use (Tolterodine ER, Oxybutynin ER and Oxybutynin IR) (Jumadilova et al, 2006). Each of the Oxybutynin groups was compared against Tolterodine ER using PS matching. The study showed no difference in hazard between any of the Oxybutynin groups

and Tolterodine users. As compared to our investigation, this was a younger and predominantly female population selected from patients participating in 82 health plans across the United States. Fractures were identified using the ICD-9 codes from medical claims; however, the fracture definition was not restricted to only include fall-related fractures.

Finally, a recent Canadian population-based retrospective cohort study compared the risk for fall-related hospitalizations within 90 days of Oxybutynin or Tolterodine initiation in community-dwelling patients 66 years or older (Gomes et al, 2011). The study had several secondary outcomes, including all fractures. The authors concluded that Oxybutynin was not related to an increase risk for hospitalizations for falls or fractures as compared to Tolterodine users. The study had a large sample size and used high-dimensional PS to balance the two groups. However, there are reasons to question these results or their interpretation. (1) Fractures were evaluated as a secondary outcome and were not restricted to those most likely to occur through a fall mechanism. (2) Oxybutynin and Tolterodine have different abilities to cross the BBB and to bind to the muscarinic receptors in the brain, therefore it is expected to identify a clinical difference between the two (Kay et al, 2005; Scheife et al, 2005). (3) Oxybutynin IR might pose an increased risk for side effects as compared to Oxybutynin ER (Birns et al, 2000). It is not clear if this study included both Oxybutynin, thus diluting the effect when comparing it to Tolterodine. All these make it difficult to conclude that no difference exists between Oxybutynin and Tolterodine or the null result is determined by a bias toward the null. Even if the results are valid, given the potential for anticholinergic effects that could increase the risk for falls in elderly and the null result of the study, the remaining question is whether these drugs elevate the baseline risk for falls and fall-related fractures in those treated as compared to non-treated.

Our study used a similar approach in balancing differences at baseline but was additionally able to evaluate and balance on measures not available in claims data, notably bladder control management, cognition, ability to move, BMI, and showed an increase in the risk for fractures with BAM initiation as compared to non-users. Although non-users comparison groups have their own potential limitations (see below), restriction to a more homogeneous exposed group and the results from our sensitivity analyses all supported the finding in the main comparison.

Decline in Cognitive Performance

We found no effect on cognitive performance as measured by CPS, a validated instrument constructed with MDS items on memory impairment, level of consciousness, and executive function. We modeled the mean CPS score at each time point during follow-up using the GEE method and evaluated the difference between BAM users and non-users.

The null finding for this analysis could be explained by two factors: (1) the small number of BAM users that were followed for a long time to allow for repeated measures, and (2) the inability of the CPS to provide a good measure for the cognitive changes determined by BAM.

(1) Only about 30% of the residents that initiated a BAM continued to take the drug for a longer time (i.e. had 3 or more MDS assessments during follow-up). It is not possible to evaluate the reason for treatment discontinuation; however, early discontinuation caused by an increased rate of side effects is a well-known issue for BAM. For some of the early stoppers the reason could have been the detection by the NH staff of a possible medication impact on cognition; if this is true, the loss to follow-up would introduce a bias toward the null.

(2) We chose CPS based on its mapping to MMSE, a standardized tool to assess cognition in elderly. MMSE was one of the instruments used to measure cognition in a single-blind crossover design study on nine patients with Alzheimer disease (Jewart et al., 2005). Although conducted with a small sample, this study showed significant impact on cognitive function when BAM were administered. There are two main differences between this crossover design study and our investigation. In the previous study, patients were evaluated by trained investigators and they used different instruments to evaluate cognitive function. The one that is most similar to the measurement we used, MMSE, allows for detection of smaller differences since the score ranges from 0 to 30. In our study, cognitive function was measured with secondary data and CPS has values from 0 to 6 thus making it more difficult to capture small differences between measurements.

Based on all these, in the context of a small sample and a measurement that might not capture small changes, it is hard to rule out a possible BAM effect on cognition.

Benefits Associated with BAM Initiation

Improvement in Urinary Continence

Our study measured improvement in urinary incontinence by combining the information from two MDS items- ‘Bladder continence rating’ and “Change in urinary continence’. Using the GEE method and modeling improvement as a binary outcome, we were able to show that BAM users had better odds for improvement after controlling for scheduled toileting, indwelling catheter, and bowel continence treated as time-varying covariates. Our results are similar to

clinical trials and other prospective studies that evaluated the efficacy of adding a BAM to a behavioral management plan for urinary incontinence. However, when looking at the effect by comparing the absolute number of individuals with a beneficial effect, the results are less promising. Specifically, 90 days after BAM initiation, only 60 new-users (16.35%) showed improvement (as compared to 13.02% for non-users). After 180 days, 93 new-users (25.34%) had a positive outcome in terms of urinary incontinence improvement as compared to 20.34% in the non-users group. Similarly to the hip fracture analysis, for a more clinically meaningful interpretation, the number needed to treat to benefit was calculated based on the OR from the analysis and the rate at 90 days (McAlister et al, 2000); this analysis showed that 32 patients should be treated to obtain improvement in urinary incontinence in one patient after 90 days of treatment. Given the data available, we were not able to measure improvement based on patient diaries as most of the prospective studies or randomized clinical trials do; however, considering the study population, our study provides the evaluation of change based on the caregiver assessment and brings evidence for the real-world effectiveness of BAM in improving urinary incontinence in a population where incontinence is prevalent. Moreover, our result might be biased toward the null since we could not distinguish between the different types of urinary incontinence. BAM are only indicated in urge and mixed urinary incontinence; the inclusion of stress incontinence could diminish the beneficial effect.

Improvement in QOL Indicators

Quality of life indicators are among the outcomes most frequently incorporated in clinical research evaluating medication efficacy and effectiveness. In this study, two instruments were used to measure different aspects of what the World Health Organization defines as QOL domains;

specifically, the Index of Social Engagement and the Health Status Index were measured at any point in time an MDS assessment was conducted.

The two study groups had similar social engagement at baseline as measured by the mean ISE for each group and the distribution of the ISE score categories. After BAM initiation, the mean ISE was higher for the users group, suggesting a positive impact of the medication on social interaction. The difference was statistically significant even with the addition of time-varying covariates to the GEE model; however, the difference between the two groups cannot be considered clinically significant (i.e. a difference of at least 1 point is considered a clinically significant difference). Given the negative impact that urinary incontinence has on social and emotional well-being (Fultz et al, 2001), it would be desired to obtain improvement through treatment. In order to fully characterize our result, an important limitation of using ISE in our study (as a measure of psycho-social well-being) comes from the fact that information is not self-reported. However, ISE is a reliable and valid scale that measures key components of social engagement: desire, ability, opportunity, and action (Mor et al, 1995); it was also validated in a nursing home population by comparing scores with actual time spent in activity programs. Although potential residual confounders should always be considered, given the good balance between the two study groups for characteristics that would impact social interaction (ADL, CPS, problematic behaviors) and the balance in baseline ISE score, we do not have reasons to believe that an unmeasured factor would be unbalanced between new-users and non-users.

The Health Status Index, an MDS derived index mapped to the generic HUI2 instrument, was used to provide a multidimensional evaluation of the impact of BAM initiation on QOL. The two groups were unbalanced at baseline and the same difference in the mean HSI values for the two groups was identified

throughout the longitudinal follow-up suggesting no benefit with treatment initiation. This negative finding could be the result of using a generic measurement for QOL when a disease-specific one would be more sensitive to change. Another factor that could have influenced the result is the small sample for this repeated measures analysis. Although an improvement in overall QOL was hypothesized, it is perhaps somewhat reassuring that there was not a net decrease in overall QOL associated with BAM use.

Strengths and Evaluation of Potential Limitations

Our study combined multiple data sources from the VA system and thus allowed for measurement of exposure, outcomes, and covariates. Most phamacoepidemiologic studies rely on pharmacy and inpatient and/or outpatient automated data. We added the MDS that provides information collected through mandatory assessments conducted by licensed health care professionals, usually registered nurses. Given the work overload for those involved in conducting the assessments and the fact that these data are not collected for research purposes, the potential for error cannot be ignored. However, despite its limitations in terms of data completeness and the potential for coding errors, the addition of the MDS permitted us to incorporate information otherwise unavailable in pharmacoepidemiologic studies using claims exclusively.
With this setting, we had the opportunity to examine clinical outcomes and to investigate outcomes that are usually measured through patient-reported measurements. Moreover, the combination of data sources provided the opportunity not only to assess risks but also potential benefits of adding BAM to the urinary continence management plan.

Some of the challenges encountered while conducting the study, along with their potential influence on the results are described in the following sections.

Cohort Identification

This research aimed to include all of the NH residents admitted for long term care in a VA CLC between FY 2003 and FY 2009. We intended to exclude those admitted for rehabilitation care in order to assure homogeneity within our study population in terms of level of care. The approach was based on previous research and it ensured that the sample included only long-term care. However, this algorithm potentially introduced sample selection bias that precludes generalization to those admitted with the intention for long-term care but who died or those that were transferred before residing in the facilities for the required minimum time. However, the MDS data does not provide a better method to identify intent for long-term versus rehabilitation care and we do not have reasons to believe that this bias was different between the study groups.

Selection of the comparison group and Index date assignment for non-users

The study was conducted using a new-users design and the index date for BAM users was considered the first prescription date during the NH stay included in the analysis. Ideally, the comparison group would have had a similar 'natural' starting point for follow-up and would have included individuals with a similar indication for treatment. Different active comparisons groups were considered (different BAM groups, initiation of a non-pharmacological management plan), but not chosen based on data availability. The final comparison group for the study included those that never used a BAM during their NH stay and in the one-

year look back period before NH admission. There are important issues that could arise from choosing non-users as comparison.

(1) Non-users are different than users. In general non-users might not have any indication for treatment and might not use care at the same level as users do, thus leading to outcome detection bias. The availability of baseline incontinence measures in the MDS was an advantage in this regard, as incontinence itself may be a risk factor for fracture. Moreover, given the nature of the study population, we do not feel that major differences exist for the two groups; specifically, since all of the patients in our study reside in the NH they are all seen regularly by trained personnel and benefit from the same level of care regardless of study group assignment. In addition, we addressed the well-known issues of out-of-system care for the VA population by evaluating medical services use before NH admission (hospital discharges, outpatient visits, and/or pharmacy prescriptions for any medication).

(2) Treatment selection bias. There is an important risk for treatment selection bias since medication is not initiated at random. In the absence of precise treatment guidelines for urinary incontinence, one approach we considered was to restrict the cohort to only include patients diagnosed with urge urinary incontinence and control for severity of the condition. This option would have made the groups more comparable in terms of treatment indication; in addition, given the fact that urge urinary incontinence is a known risk factor for falls and fractures, would have allowed for better measurement for the baseline risk. Unfortunately, this approach was not possible since there are no validated algorithms to identify urge urinary incontinence using ICD-9 codes and MDS does not distinguish between urge, stress, and mixed urinary incontinence. In

addition, the MDS continence rating scale for bladder includes complete bladder control achieved through use of indwelling catheter in the 'continent' group, thus making it more difficult to identify those that are truly in perfect bladder control. To account for this, both the continence rating and the use of appliances and programs for urinary incontinence management (i.e. scheduled toileting plan, bladder retraining, catheter use, pads/briefs used) were measured and accounted for in our study population. Finally, we addressed the issue of confounding by indication by matching new-users and non-users on PS calculated with patient characteristics at baseline; continence control rating and management approaches were included in the PS model and balance was achieved.

Follow-up

In longitudinal studies it is vital to have a precise identification of the beginning and final time points for participants' follow-up. For our fracture analysis, given the imprecise determination for the event date, the end of follow-up was also imprecisely determined for those who experienced a fracture that was identified from MDS exclusively. This misclassification is most likely non-differential and leading to a bias toward the null, given the similar distribution for the source of fractures identification between the groups.

As mentioned earlier in the Summary section 'Decline in cognitive performance', the fact that only 30% of the new-users had a long follow-up could have underestimated the effect of BAM initiation, both on the adverse and the beneficial effects. If treatment discontinuation was caused by tolerability, those lost to follow-up might be patients with a higher chance of experiencing a fall, or have a negative impact on cognitive performance. Looking from the other angle,

positive impact on continence management would be missed for those that discontinued early.

Future Research Directions

Additional studies are needed to further elucidate the proper role of medication, especially BAM with other receptor and physicochemical properties, in treating elderly with urinary incontinence.

One avenue would be to bring additional data sources that would allow for a better outcome ascertainment in our population. Given the possibility of out-of-system care for the VA population, one approach to improve our study would be to combine the VA data used for the present investigation with VA fee-for-service data and Medicare and/or Medicaid claims for the veterans that qualify for these services.

Evaluating the long-term effects of BAM in a different setting, like Medicare NH would bring not only a more diverse population into the study, but would also allow for additional information on the level of care (e.g. staff-patient ratio, size of the NH, type of care) to be considered in the analysis.

Comparative effectiveness research to evaluate difference in effects for different BAM would provide the opportunity to influence treatment guidelines for urinary incontinence in elderly. Given the differences in receptor selectivity and physicochemical characteristics, it is likely that risks would vary for different BAM, potentially shifting the apparent neutral risk-benefit balance in favor of a positive effect on overall QOL. In our study, the majority of users were exposed to Oxybutynin IR, thus making these types of comparison impossible.

Conclusion

This study evaluated BAM initiation in a population that is different than the typical RCT population, thus allowing for a better understanding of the role of medication in a real-life setting. RCT evaluating different BAM predominantly enroll younger (<65) individuals, mostly women, in good health; the trials aimed at elderly populations exclude those with comorbidities or with a poor functional status (cognitive performance, mobility). Although these characteristics proved to be important predictors of BAM initiation in our study, the observational nature of this research allowed for follow-up and evaluation to include the 'non-typical' RCT population. Similar to RCT, our study indicated that NH residents are also selected for treatment based on a better health status (fewer comorbidities, better cognitive performance and ability to perform activities of daily living). Surprisingly, although BAM new-users seem healthier, they were using more drugs and had a higher anticholinergic burden. This suggests treatment selection either based on patient tolerability (fewer adverse effects with previous medication could increase the chance of getting a new drug) or based on patient's preference for urinary incontinence management.

We used different methodological approaches to investigate risks and benefits associated with initiation of a BAM. The purpose of the study was to clarify the proper role of medication use in the management of urinary incontinence in elderly in the VA CLC. Based on the results of this study, the question is whether the balance is too weighted towards the potential risks and the extent to which this should be driving future treatment decisions. Considering that Oxybutynin IR was the main BAM used in this population the results raise questions about the continued use of this drug. If we compare the number needed to harm based on the hip fracture analysis (NNH=36) and the number

needed to treat to obtain improvement in urinary incontinence (NNT=32), we could conclude that risks and benefits are balanced and the fair comparison should incorporate patients' values and preferences. However, if we add the increased risk of death and the costs associated with a hip fracture (Braithwaite et al, 2003), given the risk for fractures in the context of limited improvement in urinary continence with no clinically significant improvement in social engagement, a wiser step might be to investigate the safety profile for newer BAM for situations when an addition to non-pharmacologic management for urinary incontinence is desired for elderly in long-term care. . Although there are no long follow-up head-to-head comparisons in elderly NH populations, the better choice might be of a BAM with high M_3 receptor selectivity, low CNS penetration and/or extended-release formulation.

Despite its limitations, the added value of this study can be viewed from two perspectives: (1) it provides additional knowledge regarding the pattern of use and the impact of BAM initiation in NH, and (2) it establishes a useful framework for future research evaluating the role of medication in this elderly and frail NH population by incorporating various secondary data sources.

APPENDIX

Table A1: List of urinary antispasmodics

IEN	Generic	VA category
04911	ATROPINE/BENZOIC/HYOSCYAMINE/ METHENAMINE/METHYLENE/PHENYL	ANTISPASMODICS,URINARY, OTHER
04068	ATROPINE/HYOSCYAMINE/ PHENOBARBITAL/SCOPOLAMINE	ANTIMUSCARINIC/ANTIPASMODIC COMBINATIONS
17131	DARIFENACIN	ANTISPASMODICS,URINARY
17132	DARIFENACIN	ANTISPASMODICS,URINARY
01997	DICYCLOMINE	PARASYMPATHOLYTICS
01998	DICYCLOMINE	PARASYMPATHOLYTICS
01999	DICYCLOMINE	PARASYMPATHOLYTICS
02000	DICYCLOMINE	PARASYMPATHOLYTICS
02570	FLAVOXATE	ANTISPASMODICS,URINARY
06193	HYOSCYAMINE	PARASYMPATHOLYTICS
06194	HYOSCYAMINE	PARASYMPATHOLYTICS
06195	HYOSCYAMINE	PARASYMPATHOLYTICS
06196	HYOSCYAMINE	PARASYMPATHOLYTICS
06198	HYOSCYAMINE	PARASYMPATHOLYTICS
06199	HYOSCYAMINE	PARASYMPATHOLYTICS
06200	HYOSCYAMINE	PARASYMPATHOLYTICS
18028	HYOSCYAMINE	PARASYMPATHOLYTICS
06140	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
06141	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
13040	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
13041	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
13042	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
13799	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
16372	OXYBUTYNIN CHLORIDE	ANTISPASMODICS,URINARY
17038	SOLIFENACIN	ANTISPASMODICS,URINARY
17040	SOLIFENACIN	ANTISPASMODICS,URINARY
12842	TOLTERODINE	PARASYMPATHOLYTICS
12843	TOLTERODINE	PARASYMPATHOLYTICS
12844	TOLTERODINE	PARASYMPATHOLYTICS
12845	TOLTERODINE	PARASYMPATHOLYTICS
14927	TOLTERODINE	PARASYMPATHOLYTICS
14928	TOLTERODINE	PARASYMPATHOLYTICS
16844	TROSPIUM	ANTISPASMODICS,URINARY
19361	TROSPIUM	ANTISPASMODICS,URINARY

Table A2: List of Alpha-blockers

IEN	Generic	VA category
16660	ALFUZOSIN	ALPHA BLOCKERS/RELATED
08837	DOXAZOSIN	ALPHA BLOCKERS/RELATED
08838	DOXAZOSIN	ALPHA BLOCKERS/RELATED
08839	DOXAZOSIN	ALPHA BLOCKERS/RELATED
08840	DOXAZOSIN	ALPHA BLOCKERS/RELATED
15721	DOXAZOSIN	ALPHA BLOCKERS/RELATED
06341	PRAZOSIN	ALPHA BLOCKERS/RELATED
06342	PRAZOSIN	ALPHA BLOCKERS/RELATED
06343	PRAZOSIN	ALPHA BLOCKERS/RELATED
13602	PRAZOSIN	ALPHA BLOCKERS/RELATED
14449	PRAZOSIN	ALPHA BLOCKERS/RELATED
12741	TAMSULOSIN	ALPHA BLOCKERS/RELATED
08290	TERAZOSIN	ALPHA BLOCKERS/RELATED
08291	TERAZOSIN	ALPHA BLOCKERS/RELATED
08292	TERAZOSIN	ALPHA BLOCKERS/RELATED
08293	TERAZOSIN	ALPHA BLOCKERS/RELATED
08294	TERAZOSIN	ALPHA BLOCKERS/RELATED
08295	TERAZOSIN	ALPHA BLOCKERS/RELATED
08296	TERAZOSIN	ALPHA BLOCKERS/RELATED
08297	TERAZOSIN	ALPHA BLOCKERS/RELATED
13610	TERAZOSIN	ALPHA BLOCKERS/RELATED
13611	TERAZOSIN	ALPHA BLOCKERS/RELATED
13685	TERAZOSIN	ALPHA BLOCKERS/RELATED
15938	TERAZOSIN	ALPHA BLOCKERS/RELATED

Table A3: List of Beta-blockers

IEN	Generic	VA category
01030	NADOLOL	BETA BLOCKERS/RELATED
01032	NADOLOL	BETA BLOCKERS/RELATED
01034	NADOLOL	BETA BLOCKERS/RELATED
01788	PROPRANOLOL	BETA BLOCKERS/RELATED
01789	PROPRANOLOL	BETA BLOCKERS/RELATED
01790	PROPRANOLOL	BETA BLOCKERS/RELATED
01791	PROPRANOLOL	BETA BLOCKERS/RELATED
01792	PROPRANOLOL	BETA BLOCKERS/RELATED
01794	PROPRANOLOL	BETA BLOCKERS/RELATED
01795	PROPRANOLOL	BETA BLOCKERS/RELATED
01796	PROPRANOLOL	BETA BLOCKERS/RELATED
01799	PROPRANOLOL	BETA BLOCKERS/RELATED
01800	PROPRANOLOL	BETA BLOCKERS/RELATED
01801	PROPRANOLOL	BETA BLOCKERS/RELATED
01802	PROPRANOLOL	BETA BLOCKERS/RELATED
02822	ACEBUTOLOL	BETA BLOCKERS/RELATED
04055	METOPROLOL	BETA BLOCKERS/RELATED
04056	METOPROLOL	BETA BLOCKERS/RELATED
04057	METOPROLOL	BETA BLOCKERS/RELATED
04058	METOPROLOL	BETA BLOCKERS/RELATED
04059	METOPROLOL	BETA BLOCKERS/RELATED
04060	METOPROLOL	BETA BLOCKERS/RELATED
04328	ATENOLOL	BETA BLOCKERS/RELATED
04329	ATENOLOL	BETA BLOCKERS/RELATED
04331	ATENOLOL	BETA BLOCKERS/RELATED
04332	ATENOLOL	BETA BLOCKERS/RELATED
04966	BETAXOLOL	BETA BLOCKERS/RELATED
04967	BETAXOLOL	BETA BLOCKERS/RELATED
05907	PINDOLOL	BETA BLOCKERS/RELATED
05908	PINDOLOL	BETA BLOCKERS/RELATED
06076	LABETALOL	BETA BLOCKERS/RELATED
06077	LABETALOL	BETA BLOCKERS/RELATED
06078	LABETALOL	BETA BLOCKERS/RELATED
06079	LABETALOL	BETA BLOCKERS/RELATED
07975	ESMOLOL	BETA BLOCKERS/RELATED
07976	ESMOLOL	BETA BLOCKERS/RELATED
08475	PENBUTOLOL	BETA BLOCKERS/RELATED
09890	SOTALOL	BETA BLOCKERS/RELATED
09891	SOTALOL	BETA BLOCKERS/RELATED
09892	SOTALOL	BETA BLOCKERS/RELATED
09893	SOTALOL	BETA BLOCKERS/RELATED

Table A3 continued

11986	BISOPROLOL	BETA BLOCKERS/RELATED
11987	BISOPROLOL	BETA BLOCKERS/RELATED
12719	CARVEDILOL	BETA BLOCKERS/RELATED
12720	CARVEDILOL	BETA BLOCKERS/RELATED
12721	CARVEDILOL	BETA BLOCKERS/RELATED
12722	CARVEDILOL	BETA BLOCKERS/RELATED
13686	ATENOLOL	BETA BLOCKERS/RELATED
13912	METOPROLOL	BETA BLOCKERS/RELATED
13976	PROPRANOLOL	BETA BLOCKERS/RELATED
14752	ATENOLOL	BETA BLOCKERS/RELATED
14755	METOPROLOL	BETA BLOCKERS/RELATED
14762	LABETALOL	BETA BLOCKERS/RELATED
15070	METOPROLOL	BETA BLOCKERS/RELATED
15770	SOTALOL	BETA BLOCKERS/RELATED
16581	METOPROLOL	BETA BLOCKERS/RELATED
17138	ESMOLOL	BETA BLOCKERS/RELATED
18060	METOPROLOL	BETA BLOCKERS/RELATED

Table A4: List of Calcium Channel Blockers

IEN	Generic	VA category
03057	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03058	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03059	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03060	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03061	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03062	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03064	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
03067	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
04030	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04031	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04032	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04033	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04034	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04035	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04036	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
04037	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
06144	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06145	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06146	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06147	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06148	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06149	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06150	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06151	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06154	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06155	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06156	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06157	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06158	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06159	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06160	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06161	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06162	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06163	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06164	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06165	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06166	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
06170	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
07978	NICARDIPINE	CALCIUM CHANNEL BLOCKERS
07979	NICARDIPINE	CALCIUM CHANNEL BLOCKERS
07980	NICARDIPINE	CALCIUM CHANNEL BLOCKERS

Table A4 continued

07982	NICARDIPINE	CALCIUM CHANNEL BLOCKERS
07983	NICARDIPINE	CALCIUM CHANNEL BLOCKERS
08822	ISRADIPINE	CALCIUM CHANNEL BLOCKERS
08823	ISRADIPINE	CALCIUM CHANNEL BLOCKERS
09685	FELODIPINE	CALCIUM CHANNEL BLOCKERS
09686	FELODIPINE	CALCIUM CHANNEL BLOCKERS
09687	FELODIPINE	CALCIUM CHANNEL BLOCKERS
09874	AMLODIPINE	CALCIUM CHANNEL BLOCKERS
09875	AMLODIPINE	CALCIUM CHANNEL BLOCKERS
09876	AMLODIPINE	CALCIUM CHANNEL BLOCKERS
13002	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
13057	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
13058	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
13059	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
13060	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
13061	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
13357	FELODIPINE	CALCIUM CHANNEL BLOCKERS
13358	FELODIPINE	CALCIUM CHANNEL BLOCKERS
13359	FELODIPINE	CALCIUM CHANNEL BLOCKERS
13621	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
13622	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
13623	VERAPAMIL	CALCIUM CHANNEL BLOCKERS
13680	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
13681	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
13682	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
14322	AMLODIPINE	CALCIUM CHANNEL BLOCKERS
15254	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
15363	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
15584	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
15728	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
16476	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
16477	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
16478	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
16479	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
16480	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
17050	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17356	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17357	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17358	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17359	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17360	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17361	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS

Table A4 continued

17362	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17368	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17369	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
17370	NIFEDIPINE	CALCIUM CHANNEL BLOCKERS
18212	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
19516	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
19517	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
19518	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
19520	DILTIAZEM	CALCIUM CHANNEL BLOCKERS
19521	DILTIAZEM	CALCIUM CHANNEL BLOCKERS

Table A5: List of ACE Inhibitors

IEN	Generic	VA category
01132	CAPTOPRIL	ACE INHIBITORS
01133	CAPTOPRIL	ACE INHIBITORS
01134	CAPTOPRIL	ACE INHIBITORS
01135	CAPTOPRIL	ACE INHIBITORS
02384	ENALAPRIL	ACE INHIBITORS
02385	ENALAPRIL	ACE INHIBITORS
02386	ENALAPRIL	ACE INHIBITORS
02387	ENALAPRIL	ACE INHIBITORS
08116	LISINOPRIL	ACE INHIBITORS
08117	LISINOPRIL	ACE INHIBITORS
08118	LISINOPRIL	ACE INHIBITORS
08119	LISINOPRIL	ACE INHIBITORS
08120	LISINOPRIL	ACE INHIBITORS
08604	ENALAPRILAT	ACE INHIBITORS
08827	RAMIPRIL	ACE INHIBITORS
08828	RAMIPRIL	ACE INHIBITORS
08829	RAMIPRIL	ACE INHIBITORS
08830	RAMIPRIL	ACE INHIBITORS
09691	QUINAPRIL	ACE INHIBITORS
09704	BENAZEPRIL	ACE INHIBITORS
09705	BENAZEPRIL	ACE INHIBITORS
09706	BENAZEPRIL	ACE INHIBITORS
09707	BENAZEPRIL	ACE INHIBITORS
09708	FOSINOPRIL	ACE INHIBITORS
09709	FOSINOPRIL	ACE INHIBITORS
09710	FOSINOPRIL	ACE INHIBITORS
12545	TRANDOLAPRIL	ACE INHIBITORS
13363	LISINOPRIL	ACE INHIBITORS
13370	BENAZEPRIL	ACE INHIBITORS
13371	BENAZEPRIL	ACE INHIBITORS
13372	BENAZEPRIL	ACE INHIBITORS
13373	BENAZEPRIL	ACE INHIBITORS
13551	CAPTOPRIL	ACE INHIBITORS
13552	CAPTOPRIL	ACE INHIBITORS
13575	FOSINOPRIL	ACE INHIBITORS
13586	LISINOPRIL	ACE INHIBITORS
13630	ENALAPRIL	ACE INHIBITORS
13631	ENALAPRIL	ACE INHIBITORS
13632	ENALAPRIL	ACE INHIBITORS
13633	ENALAPRIL	ACE INHIBITORS
13645	LISINOPRIL	ACE INHIBITORS

Table A5 continued

13646	LISINOPRIL	ACE INHIBITORS
13647	LISINOPRIL	ACE INHIBITORS
13759	CAPTOPRIL	ACE INHIBITORS
14576	FOSINOPRIL	ACE INHIBITORS
16756	LISINOPRIL	ACE INHIBITORS

Table A6: List of Diuretics

IEN	Generic	VA category
01349	CHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
01350	CHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
02068	HYDROCHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
02069	HYDROCHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
02072	HYDROCHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
02073	HYDROCHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
02074	CHLORTHALIDONE	THIAZIDES/RELATED DIURETICS
02075	CHLORTHALIDONE	THIAZIDES/RELATED DIURETICS
03333	METOLAZONE	THIAZIDES/RELATED DIURETICS
03334	METOLAZONE	THIAZIDES/RELATED DIURETICS
03335	METOLAZONE	THIAZIDES/RELATED DIURETICS
03336	METOLAZONE	THIAZIDES/RELATED DIURETICS
05810	INDAPAMIDE	THIAZIDES/RELATED DIURETICS
05811	INDAPAMIDE	THIAZIDES/RELATED DIURETICS
13584	HYDROCHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
13595	METOLAZONE	THIAZIDES/RELATED DIURETICS
19630	HYDROCHLOROTHIAZIDE	THIAZIDES/RELATED DIURETICS
01611	BUMETANIDE	LOOP DIURETICS
01612	BUMETANIDE	LOOP DIURETICS
01613	BUMETANIDE	LOOP DIURETICS
01614	BUMETANIDE	LOOP DIURETICS
01783	FUROSEMIDE	LOOP DIURETICS
01784	FUROSEMIDE	LOOP DIURETICS
01785	FUROSEMIDE	LOOP DIURETICS
01786	FUROSEMIDE	LOOP DIURETICS
01787	FUROSEMIDE	LOOP DIURETICS
02276	ETHACRYNIC ACID	LOOP DIURETICS
02277	ETHACRYNIC ACID	LOOP DIURETICS
02278	ETHACRYNIC ACID	LOOP DIURETICS
11930	TORSEMIDE	LOOP DIURETICS
11931	TORSEMIDE	LOOP DIURETICS
11932	TORSEMIDE	LOOP DIURETICS
11933	TORSEMIDE	LOOP DIURETICS
11934	TORSEMIDE	LOOP DIURETICS
12994	FUROSEMIDE	LOOP DIURETICS
12995	FUROSEMIDE	LOOP DIURETICS
13576	FUROSEMIDE	LOOP DIURETICS
13577	FUROSEMIDE	LOOP DIURETICS
02135	ACETAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
02136	ACETAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
02137	ACETAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
02138	ACETAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR

Table A6 continued

02176	METHAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
02177	METHAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
02057	HYDROCHLOROTHIAZIDE/ SPIRONOLACTONE	POTASSIUM SPARING/COMBINATIONS
02110	SPIRONOLACTONE	POTASSIUM SPARING/COMBINATIONS
02111	SPIRONOLACTONE	POTASSIUM SPARING/COMBINATIONS
02112	SPIRONOLACTONE	POTASSIUM SPARING/COMBINATIONS
02145	HYDROCHLOROTHIAZIDE/TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
02146	HYDROCHLOROTHIAZIDE/TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
02148	HYDROCHLOROTHIAZIDE/TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
02151	HYDROCHLOROTHIAZIDE/TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
02280	AMILORIDE	POTASSIUM SPARING/COMBINATIONS
07059	TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
07060	TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
13617	HYDROCHLOROTHIAZIDE/TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
13618	HYDROCHLOROTHIAZIDE/TRIAMTERENE	POTASSIUM SPARING/COMBINATIONS
14227	SPIRONOLACTONE	POTASSIUM SPARING/COMBINATIONS
15987	EPLERENONE	POTASSIUM SPARING/COMBINATIONS
15988	EPLERENONE	POTASSIUM SPARING/COMBINATIONS
15989	EPLERENONE	POTASSIUM SPARING/COMBINATIONS
05477	MANNITOL	DIURETICS,OTHER
05478	MANNITOL	DIURETICS,OTHER
05480	MANNITOL	DIURETICS,OTHER
05481	MANNITOL	DIURETICS,OTHER

Table A7: List of Cognitive Enhancers

IEN	Generic	VA category
12607	DONEPEZIL	CNS MEDICATIONS,OTHER
12608	DONEPEZIL	CNS MEDICATIONS,OTHER
13569	DONEPEZIL	CNS MEDICATIONS,OTHER
13629	DONEPEZIL	CNS MEDICATIONS,OTHER
17442	DONEPEZIL	CNS MEDICATIONS,OTHER
17443	DONEPEZIL	CNS MEDICATIONS,OTHER
14936	GALANTAMINE	CNS MEDICATIONS,OTHER
14937	GALANTAMINE	CNS MEDICATIONS,OTHER
14938	GALANTAMINE	CNS MEDICATIONS,OTHER
16270	GALANTAMINE	CNS MEDICATIONS,OTHER
17214	GALANTAMINE	CNS MEDICATIONS,OTHER
17215	GALANTAMINE	CNS MEDICATIONS,OTHER
17216	GALANTAMINE	CNS MEDICATIONS,OTHER
16456	MEMANTINE	CNS MEDICATIONS,OTHER
16457	MEMANTINE	CNS MEDICATIONS,OTHER
16512	MEMANTINE	CNS MEDICATIONS,OTHER
16579	MEMANTINE	CNS MEDICATIONS,OTHER
16580	MEMANTINE	CNS MEDICATIONS,OTHER
18026	MEMANTINE	CNS MEDICATIONS,OTHER
14395	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14396	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14397	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14398	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14399	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14400	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14401	RIVASTIGMINE	CNS MEDICATIONS,OTHER
14402	RIVASTIGMINE	CNS MEDICATIONS,OTHER
15022	RIVASTIGMINE	CNS MEDICATIONS,OTHER
18757	RIVASTIGMINE	CNS MEDICATIONS,OTHER
18758	RIVASTIGMINE	CNS MEDICATIONS,OTHER
11772	TACRINE	CNS MEDICATIONS,OTHER
11773	TACRINE	CNS MEDICATIONS,OTHER
11774	TACRINE	CNS MEDICATIONS,OTHER
11775	TACRINE	CNS MEDICATIONS,OTHER

Table A8: List of Benzodiazepines

IEN	Generic	VA Category
00092	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00093	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00094	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00095	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00096	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00097	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00098	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00099	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00109	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
00560	AMOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
14514	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
14515	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
14769	PHENOBARBITAL	BARBITURIC ACID DERIVATIVE SEDATIVES/HYPNOTICS
01622	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01623	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01624	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01625	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01680	CHLORDIAZEPOXIDE	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01681	CHLORDIAZEPOXIDE	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01682	CHLORDIAZEPOXIDE	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01693	MIDAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01694	MIDAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01763	FLURAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01764	FLURAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01871	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01872	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01873	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01874	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01875	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01876	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01878	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01879	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01880	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01881	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
01882	LORAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02115	TEMAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02116	TEMAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02117	TEMAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02572	OXAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02573	OXAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02574	OXAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS

Table A8 continued

02836	TRIAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02837	TRIAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02863	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02864	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02865	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02866	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
02869	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
05564	CLORAZEPATE	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
05565	CLORAZEPATE	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
14132	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
14739	OXAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
14911	ALPRAZOLAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
15264	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
15704	CHLORDIAZEPOXIDE	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
15726	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS
15727	DIAZEPAM	BENZODIAZEPINE DERIVATIVE SEDATIVES/HYPNOTICS

Table A9: List of antipsychotics

IEN	Generic	VA category
01290	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01291	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01292	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01293	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01295	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01296	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01297	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01298	FLUPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01925	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01926	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01927	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01928	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01929	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01930	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01931	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01937	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
01940	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02090	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02091	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02092	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02093	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02094	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02095	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02096	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02097	THIORIDAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
04522	THIOTHIXENE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
04523	THIOTHIXENE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
04524	THIOTHIXENE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
04525	THIOTHIXENE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
04529	THIOTHIXENE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06026	PERPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06028	PERPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06029	PERPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06030	PERPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06031	PERPHENAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06279	TRIFLUOPERAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06280	TRIFLUOPERAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06281	TRIFLUOPERAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
06282	TRIFLUOPERAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
07147	MESORIDAZINE BESYLATE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS

Table A9 continued

07148	MESORIDAZINE BESYLATE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
16054	CHLORPROMAZINE	PHENOTHIAZINE/RELATED ANTIPSYCHOTICS
02204	LOXAPINE	ANTIPSYCHOTICS,OTHER
02205	LOXAPINE	ANTIPSYCHOTICS,OTHER
02206	LOXAPINE	ANTIPSYCHOTICS,OTHER
02207	LOXAPINE	ANTIPSYCHOTICS,OTHER
03042	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03043	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03044	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03045	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03046	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03047	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03048	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03049	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03050	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03051	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03052	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03053	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
03054	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
04638	MOLINDONE	ANTIPSYCHOTICS,OTHER
04639	MOLINDONE	ANTIPSYCHOTICS,OTHER
04640	MOLINDONE	ANTIPSYCHOTICS,OTHER
04641	MOLINDONE	ANTIPSYCHOTICS,OTHER
08564	CLOZAPINE	ANTIPSYCHOTICS,OTHER
08565	CLOZAPINE	ANTIPSYCHOTICS,OTHER
11804	RISPERIDONE	ANTIPSYCHOTICS,OTHER
11805	RISPERIDONE	ANTIPSYCHOTICS,OTHER
11806	RISPERIDONE	ANTIPSYCHOTICS,OTHER
11807	RISPERIDONE	ANTIPSYCHOTICS,OTHER
11808	RISPERIDONE	ANTIPSYCHOTICS,OTHER
12588	OLANZAPINE	ANTIPSYCHOTICS,OTHER
12589	OLANZAPINE	ANTIPSYCHOTICS,OTHER
12590	OLANZAPINE	ANTIPSYCHOTICS,OTHER
12591	OLANZAPINE	ANTIPSYCHOTICS,OTHER
12750	QUETIAPINE	ANTIPSYCHOTICS,OTHER
12751	QUETIAPINE	ANTIPSYCHOTICS,OTHER
12752	QUETIAPINE	ANTIPSYCHOTICS,OTHER
12971	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
13582	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
13583	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
13608	RISPERIDONE	ANTIPSYCHOTICS,OTHER

Table A9 continued

13636	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
13641	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
13656	RISPERIDONE	ANTIPSYCHOTICS,OTHER
13657	RISPERIDONE	ANTIPSYCHOTICS,OTHER
13665	RISPERIDONE	ANTIPSYCHOTICS,OTHER
13666	RISPERIDONE	ANTIPSYCHOTICS,OTHER
14091	OLANZAPINE	ANTIPSYCHOTICS,OTHER
14129	QUETIAPINE	ANTIPSYCHOTICS,OTHER
14130	QUETIAPINE	ANTIPSYCHOTICS,OTHER
14131	QUETIAPINE	ANTIPSYCHOTICS,OTHER
14450	OLANZAPINE	ANTIPSYCHOTICS,OTHER
14535	OLANZAPINE	ANTIPSYCHOTICS,OTHER
14536	OLANZAPINE	ANTIPSYCHOTICS,OTHER
14912	QUETIAPINE	ANTIPSYCHOTICS,OTHER
14932	ZIPRASIDONE	ANTIPSYCHOTICS,OTHER
14933	ZIPRASIDONE	ANTIPSYCHOTICS,OTHER
14934	ZIPRASIDONE	ANTIPSYCHOTICS,OTHER
14935	ZIPRASIDONE	ANTIPSYCHOTICS,OTHER
15030	OLANZAPINE	ANTIPSYCHOTICS,OTHER
15156	OLANZAPINE	ANTIPSYCHOTICS,OTHER
15157	OLANZAPINE	ANTIPSYCHOTICS,OTHER
15193	OLANZAPINE	ANTIPSYCHOTICS,OTHER
15194	OLANZAPINE	ANTIPSYCHOTICS,OTHER
15308	OLANZAPINE	ANTIPSYCHOTICS,OTHER
15368	CLOZAPINE (MYLAN)	ANTIPSYCHOTICS,OTHER
15369	CLOZAPINE (MYLAN)	ANTIPSYCHOTICS,OTHER
15370	CLOZAPINE (UDL)	ANTIPSYCHOTICS,OTHER
15372	CLOZAPINE (CLOZARIL)	ANTIPSYCHOTICS,OTHER
15373	CLOZAPINE (CLOZARIL)	ANTIPSYCHOTICS,OTHER
15374	CLOZAPINE (CLOZARIL)	ANTIPSYCHOTICS,OTHER
15375	CLOZAPINE (CLOZARIL)	ANTIPSYCHOTICS,OTHER
15484	OLANZAPINE	ANTIPSYCHOTICS,OTHER
16005	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16006	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16007	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16008	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16009	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16010	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16011	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER

Table A9 continued

16012	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16268	ZIPRASIDONE	ANTIPSYCHOTICS,OTHER
16364	RISPERIDONE	ANTIPSYCHOTICS,OTHER
16365	RISPERIDONE	ANTIPSYCHOTICS,OTHER
16366	RISPERIDONE	ANTIPSYCHOTICS,OTHER
16474	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
16515	RISPERIDONE	ANTIPSYCHOTICS,OTHER
16516	RISPERIDONE	ANTIPSYCHOTICS,OTHER
16517	RISPERIDONE	ANTIPSYCHOTICS,OTHER
16701	OLANZAPINE	ANTIPSYCHOTICS,OTHER
16813	HALOPERIDOL	ANTIPSYCHOTICS,OTHER
17129	OLANZAPINE	ANTIPSYCHOTICS,OTHER
17311	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
17573	QUETIAPINE	ANTIPSYCHOTICS,OTHER
17574	QUETIAPINE	ANTIPSYCHOTICS,OTHER
17575	QUETIAPINE	ANTIPSYCHOTICS,OTHER
17576	QUETIAPINE	ANTIPSYCHOTICS,OTHER
17585	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
17658	RISPERIDONE	ANTIPSYCHOTICS,OTHER
18169	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
18232	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER
18341	RISPERIDONE	ANTIPSYCHOTICS,OTHER
19487	ARIPIPRAZOLE	ANTIPSYCHOTICS,OTHER

Table A10: List of antidepressants

IEN	Generic	VA category
00603	NORTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
00604	NORTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
00605	NORTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
00606	NORTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
00607	NORTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01367	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01368	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01369	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01370	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01371	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01375	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
01892	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01893	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01894	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01895	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01896	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01897	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01898	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
01946	IMIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
01947	IMIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
01948	IMIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
02215	AMOXAPINE	TRICYCLIC ANTIDEPRESSANTS
02216	AMOXAPINE	TRICYCLIC ANTIDEPRESSANTS
02257	PROTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
02258	PROTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
05082	DESIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
05083	DESIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
05084	DESIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
08586	CLOMIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
08587	CLOMIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
08588	CLOMIPRAMINE	TRICYCLIC ANTIDEPRESSANTS
13543	AMITRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
13570	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
14905	DOXEPIN	TRICYCLIC ANTIDEPRESSANTS
15720	NORTRIPTYLINE	TRICYCLIC ANTIDEPRESSANTS
05178	PHENELZINE SULFATE	MONAMINE OXIDASE INHIBITOR ANTIDEPRESSANTS
17700	SELEGILINE	MONAMINE OXIDASE INHIBITOR ANTIDEPRESSANTS
17701	SELEGILINE	MONAMINE OXIDASE INHIBITOR ANTIDEPRESSANTS
17702	SELEGILINE	MONAMINE OXIDASE INHIBITOR ANTIDEPRESSANTS
06009	MAPROTILINE	ANTIDEPRESSANTS,OTHER
06010	MAPROTILINE	ANTIDEPRESSANTS,OTHER

Table A10 continued

06132	TRAZODONE	ANTIDEPRESSANTS,OTHER
06133	TRAZODONE	ANTIDEPRESSANTS,OTHER
06134	TRAZODONE	ANTIDEPRESSANTS,OTHER
08147	FLUOXETINE	ANTIDEPRESSANTS,OTHER
08148	FLUOXETINE	ANTIDEPRESSANTS,OTHER
08149	FLUOXETINE	ANTIDEPRESSANTS,OTHER
08525	BUPROPION	ANTIDEPRESSANTS,OTHER
08526	BUPROPION	ANTIDEPRESSANTS,OTHER
09714	SERTRALINE	ANTIDEPRESSANTS,OTHER
09715	SERTRALINE	ANTIDEPRESSANTS,OTHER
09716	SERTRALINE	ANTIDEPRESSANTS,OTHER
09880	PAROXETINE	ANTIDEPRESSANTS,OTHER
09881	PAROXETINE	ANTIDEPRESSANTS,OTHER
09882	PAROXETINE	ANTIDEPRESSANTS,OTHER
09883	PAROXETINE	ANTIDEPRESSANTS,OTHER
09884	PAROXETINE	ANTIDEPRESSANTS,OTHER
11810	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11811	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11812	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11813	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11814	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11815	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11816	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11817	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11818	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11819	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
11820	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
12351	NEFAZODONE	ANTIDEPRESSANTS,OTHER
12352	NEFAZODONE	ANTIDEPRESSANTS,OTHER
12353	NEFAZODONE	ANTIDEPRESSANTS,OTHER
12354	NEFAZODONE	ANTIDEPRESSANTS,OTHER
12355	FLUVOXAMINE	ANTIDEPRESSANTS,OTHER
12356	FLUVOXAMINE	ANTIDEPRESSANTS,OTHER
12357	FLUVOXAMINE	ANTIDEPRESSANTS,OTHER
12552	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
12553	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
12880	BUPROPION	ANTIDEPRESSANTS,OTHER
12881	BUPROPION	ANTIDEPRESSANTS,OTHER
12882	BUPROPION	ANTIDEPRESSANTS,OTHER
12926	CITALOPRAM	ANTIDEPRESSANTS,OTHER
12927	CITALOPRAM	ANTIDEPRESSANTS,OTHER
12928	CITALOPRAM	ANTIDEPRESSANTS,OTHER

Table A10 continued

12929	CITALOPRAM	ANTIDEPRESSANTS,OTHER
13076	BUPROPION	ANTIDEPRESSANTS,OTHER
13406	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
13526	NEFAZODONE	ANTIDEPRESSANTS,OTHER
13574	FLUOXETINE	ANTIDEPRESSANTS,OTHER
13616	TRAZODONE	ANTIDEPRESSANTS,OTHER
13626	PAROXETINE	ANTIDEPRESSANTS,OTHER
13667	SERTRALINE	ANTIDEPRESSANTS,OTHER
13668	SERTRALINE	ANTIDEPRESSANTS,OTHER
13742	FLUOXETINE	ANTIDEPRESSANTS,OTHER
13744	FLUOXETINE	ANTIDEPRESSANTS,OTHER
13745	FLUOXETINE	ANTIDEPRESSANTS,OTHER
14142	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
14143	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
14299	CITALOPRAM	ANTIDEPRESSANTS,OTHER
14369	SERTRALINE	ANTIDEPRESSANTS,OTHER
14956	VENLAFAXINE	ANTIDEPRESSANTS,OTHER
15069	FLUOXETINE	ANTIDEPRESSANTS,OTHER
15286	CITALOPRAM	ANTIDEPRESSANTS,OTHER
15335	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
15336	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
15337	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
15873	PAROXETINE	ANTIDEPRESSANTS,OTHER
15874	PAROXETINE	ANTIDEPRESSANTS,OTHER
15944	ESCITALOPRAM	ANTIDEPRESSANTS,OTHER
15945	ESCITALOPRAM	ANTIDEPRESSANTS,OTHER
15946	ESCITALOPRAM	ANTIDEPRESSANTS,OTHER
16458	BUPROPION	ANTIDEPRESSANTS,OTHER
16459	BUPROPION	ANTIDEPRESSANTS,OTHER
16577	BUPROPION	ANTIDEPRESSANTS,OTHER
16710	BUPROPION	ANTIDEPRESSANTS,OTHER
16851	DULOXETINE	ANTIDEPRESSANTS,OTHER
16853	DULOXETINE	ANTIDEPRESSANTS,OTHER
16854	DULOXETINE	ANTIDEPRESSANTS,OTHER
16855	DULOXETINE	ANTIDEPRESSANTS,OTHER
16856	DULOXETINE	ANTIDEPRESSANTS,OTHER
17317	BUPROPION	ANTIDEPRESSANTS,OTHER
17342	MIRTAZAPINE	ANTIDEPRESSANTS,OTHER
18750	BUPROPION	ANTIDEPRESSANTS,OTHER

Table A11: List of antivertigo agents

IEN	Generic	VA category
01852	MECLIZINE	ANTIVERTIGO AGENTS
01853	MECLIZINE	ANTIVERTIGO AGENTS
01854	MECLIZINE	ANTIVERTIGO AGENTS
12889	SCOPOLAMINE	ANTIVERTIGO AGENTS
13648	MECLIZINE	ANTIVERTIGO AGENTS
13649	MECLIZINE	ANTIVERTIGO AGENTS

Table A12: List of anti-parkinson agents

IEN	Generic	VA category
02368	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02369	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02370	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02371	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02372	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02373	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02374	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
02375	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
08535	SELEGILINE	ANTIPARKINSON AGENTS
08536	SELEGILINE	ANTIPARKINSON AGENTS
08714	PERGOLIDE MESYLATE	ANTIPARKINSON AGENTS
08715	PERGOLIDE MESYLATE	ANTIPARKINSON AGENTS
08716	PERGOLIDE MESYLATE	ANTIPARKINSON AGENTS
12431	CARBIDOPA	ANTIPARKINSON AGENTS
12725	PRAMIPEXOLE	ANTIPARKINSON AGENTS
12726	PRAMIPEXOLE	ANTIPARKINSON AGENTS
12727	PRAMIPEXOLE	ANTIPARKINSON AGENTS
12728	PRAMIPEXOLE	ANTIPARKINSON AGENTS
12729	PRAMIPEXOLE	ANTIPARKINSON AGENTS
12753	ROPINIROLE	ANTIPARKINSON AGENTS
12754	ROPINIROLE	ANTIPARKINSON AGENTS
12755	ROPINIROLE	ANTIPARKINSON AGENTS
12756	ROPINIROLE	ANTIPARKINSON AGENTS
12757	ROPINIROLE	ANTIPARKINSON AGENTS
12828	TOLCAPONE	ANTIPARKINSON AGENTS
13364	PRAMIPEXOLE	ANTIPARKINSON AGENTS
13365	PRAMIPEXOLE	ANTIPARKINSON AGENTS
13857	ENTACAPONE	ANTIPARKINSON AGENTS
13963	ROPINIROLE	ANTIPARKINSON AGENTS
14763	SELEGILINE	ANTIPARKINSON AGENTS
15309	ROPINIROLE	ANTIPARKINSON AGENTS
15592	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
16461	CARBIDOPA/ENTACAPONE/LEVODOPA	ANTIPARKINSON AGENTS
16462	CARBIDOPA/ENTACAPONE/LEVODOPA	ANTIPARKINSON AGENTS
16463	CARBIDOPA/ENTACAPONE/LEVODOPA	ANTIPARKINSON AGENTS
17106	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
17107	CARBIDOPA/LEVODOPA	ANTIPARKINSON AGENTS
17705	RASAGILINE	ANTIPARKINSON AGENTS
17706	RASAGILINE	ANTIPARKINSON AGENTS
17827	SELEGILINE	ANTIPARKINSON AGENTS
18347	ROTIGOTINE	ANTIPARKINSON AGENTS
19448	PRAMIPEXOLE	ANTIPARKINSON AGENTS

Table A13: List of anticonvulsants

IEN	Generic	VA category
01602	CLONAZEPAM	ANTICONVULSANTS
01603	CLONAZEPAM	ANTICONVULSANTS
01604	CLONAZEPAM	ANTICONVULSANTS
01630	DIAZEPAM	ANTICONVULSANTS
01631	DIAZEPAM	ANTICONVULSANTS
01633	DIAZEPAM	ANTICONVULSANTS
01914	PHENYTOIN	ANTICONVULSANTS
01915	PHENYTOIN	ANTICONVULSANTS
01916	PHENYTOIN	ANTICONVULSANTS
01917	PHENYTOIN	ANTICONVULSANTS
01918	PHENYTOIN	ANTICONVULSANTS
01920	PHENYTOIN	ANTICONVULSANTS
01921	PHENYTOIN	ANTICONVULSANTS
01923	PHENYTOIN	ANTICONVULSANTS
01924	PHENYTOIN	ANTICONVULSANTS
02007	CARBAMAZEPINE	ANTICONVULSANTS
02008	CARBAMAZEPINE	ANTICONVULSANTS
02009	CARBAMAZEPINE	ANTICONVULSANTS
02010	CARBAMAZEPINE	ANTICONVULSANTS
02011	CARBAMAZEPINE	ANTICONVULSANTS
02012	CARBAMAZEPINE	ANTICONVULSANTS
03723	MEPHOBARBITAL	ANTICONVULSANTS
04442	PRIMIDONE	ANTICONVULSANTS
04443	PRIMIDONE	ANTICONVULSANTS
05670	VALPROIC ACID	ANTICONVULSANTS
05671	VALPROIC ACID	ANTICONVULSANTS
05673	VALPROATE SODIUM	ANTICONVULSANTS
05724	DIVALPROEX	ANTICONVULSANTS
05725	DIVALPROEX	ANTICONVULSANTS
05726	DIVALPROEX	ANTICONVULSANTS
05727	DIVALPROEX	ANTICONVULSANTS
11777	FELBAMATE	ANTICONVULSANTS
11800	GABAPENTIN	ANTICONVULSANTS
11801	GABAPENTIN	ANTICONVULSANTS
11802	GABAPENTIN	ANTICONVULSANTS
12365	LAMOTRIGINE	ANTICONVULSANTS
12366	LAMOTRIGINE	ANTICONVULSANTS
12367	LAMOTRIGINE	ANTICONVULSANTS
12368	LAMOTRIGINE	ANTICONVULSANTS

Table A13 continued

12665	TOPIRAMATE	ANTICONVULSANTS
12666	TOPIRAMATE	ANTICONVULSANTS
12667	TOPIRAMATE	ANTICONVULSANTS
12783	TIAGABINE	ANTICONVULSANTS
12978	TOPIRAMATE	ANTICONVULSANTS
12997	CARBAMAZEPINE	ANTICONVULSANTS
12998	CARBAMAZEPINE	ANTICONVULSANTS
13382	LAMOTRIGINE	ANTICONVULSANTS
13553	CARBAMAZEPINE	ANTICONVULSANTS
13637	GABAPENTIN	ANTICONVULSANTS
13638	GABAPENTIN	ANTICONVULSANTS
13639	GABAPENTIN	ANTICONVULSANTS
13672	CARBAMAZEPINE	ANTICONVULSANTS
13683	PHENYTOIN	ANTICONVULSANTS
13684	PHENYTOIN	ANTICONVULSANTS
13840	GABAPENTIN	ANTICONVULSANTS
13841	GABAPENTIN	ANTICONVULSANTS
14097	OXCARBAZEPINE	ANTICONVULSANTS
14099	OXCARBAZEPINE	ANTICONVULSANTS
14101	OXCARBAZEPINE	ANTICONVULSANTS
14102	OXCARBAZEPINE	ANTICONVULSANTS
14217	LEVETIRACETAM	ANTICONVULSANTS
14218	LEVETIRACETAM	ANTICONVULSANTS
14219	LEVETIRACETAM	ANTICONVULSANTS
14485	ZONISAMIDE	ANTICONVULSANTS
14486	ZONISAMIDE	ANTICONVULSANTS
14528	DIVALPROEX	ANTICONVULSANTS
14725	DIVALPROEX	ANTICONVULSANTS
14756	DIVALPROEX	ANTICONVULSANTS
15091	CARBAMAZEPINE	ANTICONVULSANTS
15092	CARBAMAZEPINE	ANTICONVULSANTS
15093	CARBAMAZEPINE	ANTICONVULSANTS
15094	CARBAMAZEPINE	ANTICONVULSANTS
15095	CARBAMAZEPINE	ANTICONVULSANTS
15096	CARBAMAZEPINE	ANTICONVULSANTS
15119	PHENYTOIN	ANTICONVULSANTS
15175	GABAPENTIN	ANTICONVULSANTS
15723	CLONAZEPAM	ANTICONVULSANTS
15724	CLONAZEPAM	ANTICONVULSANTS
15725	CLONAZEPAM	ANTICONVULSANTS
15740	FOSPHENYTOIN	ANTICONVULSANTS

Table A13 continued

16140	DIVALPROEX	ANTICONVULSANTS
16634	LEVETIRACETAM	ANTICONVULSANTS
16759	ZONISAMIDE	ANTICONVULSANTS
16763	CLONAZEPAM	ANTICONVULSANTS
16765	CLONAZEPAM	ANTICONVULSANTS
16988	GABAPENTIN	ANTICONVULSANTS
16989	GABAPENTIN	ANTICONVULSANTS
16990	GABAPENTIN	ANTICONVULSANTS
17096	TOPIRAMATE	ANTICONVULSANTS
17455	CARBAMAZEPINE	ANTICONVULSANTS
18058	LEVETIRACETAM	ANTICONVULSANTS
18729	LEVETIRACETAM	ANTICONVULSANTS

Table A14: Balance between BAM new-users and non-users groups after propensity score matching

Variable		New users (N=1125)	Non-users (N=5469)	p-value
Gender- female: N(%)		45 (4.00%)	216 (3.95%)	0.937
Age categories- no (%)				0.9231
	65 to 69	107 (9.51%)	513 (9.38%)	
	70 to 74	207 (18.40%)	989 (18.08%)	
	75 to 79	238 (21.16%)	1112 (20.33%)	
	80 to 84	342 (30.40%)	1672 (30.57%)	
	85+	231 (20.53%)	1183 (21.63%)	
Race				0.8638
	White	913 (81.16%)	4421 (80.84%)	
	Black	131 (11.64%)	666 (12.18%)	
	Other	81 (7.20%)	382 (6.98%)	
Veteran Integrated Service Network				1.0000
	VISN 1: VA New England Healthcare System	45 (4.00%)	229 (4.19%)	
	VISN 2: VA Health Care Upstate New York	33 (2.93%)	164 (3.00%)	
	VISN 3: VA NY/NJ Veterans Healthcare Network	51 (4.53%)	255 (4.66%)	
	VISN 4: VA Healthcare	116 (10.31%)	551 (10.07%)	
	VISN 5: VA Capitol Health Care Network	42 (3.73%)	214 (3.91%)	
	VISN 6: VA Mid-Atlantic Health Care Network	65 (5.78%)	311 (5.69%)	
	VISN7: VA Southeast Network	38 (3.38%)	190 (3.47%)	
	VISN 8: VA Sunshine Healthcare Network	84 (7.47%)	428 (7.83%)	
	VISN 9: VA Mid South Healthcare Network	41 (3.64%)	203 (3.71%)	
	VISN 10: VA Healthcare System of Ohio	46 (4.09%)	213 (3.89%)	
	VISN 11: Veterans In Partnership	87 (7.73%)	409 (7.48%)	
	VISN 12: VA Great Lakes Health Care System	43 (3.82%)	201 (3.68%)	
	VISN 15: VA Heartland Network	42 (3.73%)	193 (3.53%)	
	VISN 16: South Central VA Health Care Network	70 (6.22%)	365 (6.67%)	
	VISN 17: VA Heart of Texas Health Care Network	53 (4.71%)	259 (4.74%)	
	VISN 18: VA Southwest Health Care Network	66 (5.87%)	287 (5.25%)	
	VISN 19: Rocky Mountain Network	24 (2.13%)	125 (2.29%)	
	VISN 20: Northwest Network	27 (2.40%)	125 (2.29%)	
	VISN 21: Sierra Pacific Network	51 (4.53%)	274 (5.01%)	
	VISN 22: Desert Pacific Healthcare Network	19 (1.69%)	93 (1.70%)	
	VISN 23: VA Midwest Health Care Network	82 (7.29%)	380 (6.95%)	

Table A14 continued

Fiscal year at admission			0.9999
2003	232 (20.62%)	1123 (20.53%)	
2004	217 (19.29%)	1044 (19.09%)	
2005	179 (15.91%)	881 (16.11%)	
2006	167 (14.84%)	796 (14.55%)	
2007	133 (11.82%)	644 (11.78%)	
2008	134 (11.91%)	667 (12.20%)	
2009	63 (5.60%)	314 (5.74%)	
Body Mass Index: BMI categories- no (%)			0.9744
Normal weight	473 (42.04%)	2309 (42.22%)	
Underweight	71 (6.31%)	351 (6.42%)	
Overweight	341 (30.31%)	1641 (30.01%)	
Obese	194(17.24%)	925 (16.91%)	
Morbidly obese	13 (1.16%)	57 (1.04%)	
Missing or extreme value (1% trimming at both ends)	33 (2.93%)	186 (3.40%)	
Bowel Continence			0.8712
Continent	665 (59.11%)	3238 (59.21%)	
Usually Continent	124 (11.02%)	551 (10.07%)	
Occasionally Incontinent	63 (5.60%)	302 (5.52%)	
Frequently Incontinent	52 (4.62%)	240 (4.39%)	
Incontinent	220 (19.56%)	1129 (20.64%)	
Unknown (missing or out of range value)	1 (0.09%)	9 (0.16%)	
Bladder Continence			0.9632
Continent	685 (60.89%)	3282 (60.01%)	
Usually Continent	112 (9.96%)	545 (9.97%)	
Occasionally Incontinent	78 (6.93%)	384 (7.02%)	
Frequently Incontinent	70 (6.22%)	329 (6.02%)	
Incontinent	175 (15.56%)	909 (16.62%)	
Unknown (missing or out of range value)	5 (0.44%)	20 (0.37%)	

Table A14 continued

Bladder Continence Management			
Scheduled toileting plan	256 (22.76%)	1249 (22.84%)	0.9523
Bladder retraining program	24 (2.13%)	116 (2.12%)	0.9792
External catheter	88 (7.82%)	466 (8.52%)	0.4418
Indwelling catheter	329 (29.24%)	1505 (27.52%)	0.2394
Intermittent catheter	26 (2.31%)	135 (2.47%)	0.7555
Pads/Briefs Used	393 (34.93%)	1925 (35.20%)	0.8653
No appliance or program	380 (33.78%)	1904 (34.81%)	0.5057
UTI in last 30 days- no (%)	172 (15.29%)	794 (14.52%)	0.5056
Bowel Elimination Pattern- no (%)			
Regular	452 (40.18%)	2287 (41.82%)	0.3094
Constipation	190 (16.89%)	877 (16.04%)	0.4792
Diarrhea	76 (6.76%)	348 (6.36%)	0.6251
Fecal Impaction	3 (0.27%)	15 (0.27%)	0.9645
Cognitive Performance Score			0.9215
Intact: CPS=0	481 (42.76%)	2296 (41.98%)	
Borderline intact: CPS=1	217 (19.29%)	1079 (19.73%)	
Mild impairment: CPS=2	137 (12.18%)	686 (12.54%)	
Moderate impairment: CPS=3	167 (14.84%)	824 (15.07%)	
Moderate severe impairment: CPS=4	24 (2.13%)	118 (2.16%)	
Severe impairment: CPS=5	68 (6.04%)	284 (5.19%)	
Very severe impairment: CPS=6	28 (2.49%)	164 (3.00%)	
Missing	3 (0.27%)	18 (0.33%)	
Activities of Daily Living (ADL score)- Mean ±SD	11.2 ± 8.2257	11.3313 ± 8.2916	0.6716
CHESS- no (%)			0.9816
CHESS=0	364 (32.36%)	1744 (31.89%)	
CHESS=1	327 (29.07%)	1607 (29.38%)	
CHESS=2	246 (21.87%)	1164 (21.28%)	
CHESS=3	95 (8.44%)	476 (8.70%)	
CHESS=4	29 (2.58%)	134 (2.45%)	
CHESS=5	4 (0.36%)	17 (0.31%)	
Missing	60 (5.33%)	327 (5.98%)	
MDS Behavioral Score - Mean ±SD	0.5387 ± 1.4978	0.5076 ± 1.4708	0.4569

Table A14 continued

Balance while standing			0.9904
Maintained position as required in test	212 (18.84%)	1011 (18.49%)	
Unsteady, but able to rebalance w/o physical support	208 (18.49%)	995 (18.19%)	
Partial physical support during test or stands but does not follow directions for test	236 (20.98%)	1136 (20.77%)	
Not able to attempt test w/o physical help	424 (37.69%)	2103 (38.45%)	
Unknown (missing or out of range value)	45 (4.00%)	224 (4.10%)	
Balance while sitting			0.9714
Maintained position as required in test	829 (73.69%)	4007 (73.27%)	
Unsteady, but able to rebalance w/o physical support	92 (8.18%)	474 (8.67%)	
Partial physical support during test or stands but does not follow directions for test	84 (7.47%)	389 (7.11%)	
Not able to attempt test w/o physical help	113 (10.04%)	563 (10.29%)	
Unknown (missing or out of range value)	7 (0.62%)	36 (0.66%)	
Comorbidities			
Number of Elixhauser Comorbidities (hospitalization or outpatient visits)-Mean (SD)	3.9413 (2.8316)	3.9406 (2.8069)	0.8836
No hospitalization or outpatient visits (Elixhauser)	125 (11.11%)	606 (11.08%)	0.9763
Congestive Heart Failure	284 (25.24%)	1373 (25.11%)	0.9219
Cardiac dysrhythmias	198 (17.60%)	939 (17.17%)	0.7278
Hypertension	874 (77.69%)	4214 (77.05%)	0.6433
Hypertension complicated	98 (8.71%)	478 (8.74%)	0.9749
Paralysis	47 (4.18%)	224 (4.10%)	0.8996
COPD	348 (30.93%)	1685 (30.81%)	0.935
Diabetes	452 (40.18%)	2238 (40.92%)	0.6439
Diabetes complicated	149 (13.24%)	756 (13.82%)	0.6073
Tumor with metastasis	46 (4.09%)	230 (4.21%)	0.8588
Hypotension	15 (1.33%)	85 (1.55%)	0.5809
Cancer	273 (24.27%)	1318 (24.10%)	0.905
Osteoporosis	87 (7.73%)	400 (7.31%)	0.6243
Cerebrovascular accident (stroke)	232 (20.62%)	1104 (20.19%)	0.7405

Table A14 continued

Depression	151 (13.42%)	731 (13.37)	0.9599
Psychosis	138 (12.27%)	681 (12.45%)	0.8637
Unsteady Gait	498 (44.27%)	2362 (43.19%)	0.5065
Vision			0.9608
Adequate	783 (69.60%)	3821 (69.87%)	
Impaired	243 (21.60%)	1146 (20.95%)	
Moderately impaired	59 (5.24%)	280 (5.12%)	
Highly impaired	22 (1.96%)	128 (2.34%)	
Severely impaired	13 (1.16%)	64 (1.17%)	
Unknown (missing or out of range value)	5 (0.44%)	30 (0.55%)	
Fell in past 30 days	210 (18.67%)	1032 (18.87%)	0.8738
Fell in past 31-180 days	262 (23.29%)	1299 (23.75%)	0.7393
Hip fracture in last 180 days	23 (2.04%)	99 (1.81%)	0.5954
Other fracture in past 180 days	29 (2.58%)	142 (2.60%)	0.9714
Medication use- number of medications (last 7 days)			0.2153
≤ 3	21 (1.87%)	70 (1.28%)	
3 -10	339 (30.13%)	1728 (31.60%)	
>10	765 (68.00%)	3671 (67.12%)	
Medication use 30 days before index date			
Alpha-blockers	451 (40.09%)	2233 (40.83%)	0.6449
ACE inhibitors	398 (35.38%)	1946 (35.58%)	0.8961
Antidepressants	601 (53.42%)	2872 (52.51%)	0.5785
Antipsychotics	265 (23.56%)	1262 (23.08%)	0.7281
Anticonvulsants	304 (27.02%)	1446 (26.44%)	0.6871
BZD	49 (4.36%)	251 (4.59%)	0.7317
Antiparkinson medication	62 (5.51%)	317 (5.80%)	0.7082
Antivertigo medication	18 (1.60%)	92 (1.68%)	0.8446
CNS stimulants	160 (14.22%)	794 (14.52%)	0.7972
Beta-blockers	527 (46.84%)	2519 (46.06%)	0.6306
Diuretics	444 (39.47%)	2134 (39.02%)	0.7797
Calcium channel blockers	235 (20.89%)	1161 (21.23%)	0.7994
Anticholinergic burden (ADS score)- Mean (SD)	3.44 (3.2339)	3.3337 (3.1975)	0.1996

REFERENCES

Abrams, P., Andersson, K. E., & Buccafusco, J. J. (2006). Muscarinic receptors: Their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol., 148*, 565-578.

Aizenberg, D., Sigler, M., Weizman, A., & Barak, Y. (2002). Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: A 4-year case-control study. *International Psychogeriatrics, 14*(3), 307-310. doi:10.1017/S1041610202008505

Albert, S. M., Jacobs, D. M., Sano, M., Marder, K., Bell, K., Devanand, D., . . . Stern, Y. (2001). Longitudinal study of quality of life in people with advanced Alzheimer's disease. *The American Journal of Geriatric Psychiatry, 9*(2), 160.

Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 1999;319:1492-5.

Anderson, R. U., Mobley, D., Blank, B., Saltzstein, D., Susset, J., & Brown, J. S. (1999). Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. OROS oxybutynin study group. *The Journal of Urology, 161*(6), 1809.

Andersson, K. (2004). Antimuscarinics for treatment of overactive bladder. *Lancet Neurology, 3*(1), 46.

Andersson, K., Sarawate, C., Kahler, K., Stanley, E., & Kulkarni, A. (2010). Cardiovascular morbidity, heart rates and use of antimuscarinics in patients with overactive bladder. *BJU International, 106*(2), 268.

Arnold, N., Hynes, D. M., & Stroupe, K. T. (2006). VIReC technical report 1: Comparison of VA outpatient prescriptions in the DSS datasets and the PBM database. *VA Information Resource Center Edward Hines, Jr. VA Hospital: Hines, IL.,* Retrieved from http://www.virec.research.va.gov/References/TechnicalReports/VIReCTechnicalReport1.pdf

Arnold, N., & Joseph, G. (2003). VIReC research user guide: VHA pharmacy prescription data. *Veterans Affairs Information Resource Center, Hines, IL.,* Retrieved from http://www.virec.research.va.gov/References/RUG/RUG-Pharmacy-2nd-Ed-er.pdf

Austin, P., Grootendorst, P., & Anderson, G. (2007). A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: A monte carlo study. *Statistics in Medicine, 26*(4), 734.

Austin, P., & Mamdani, M. (2006). A comparison of propensity score methods: A case-study estimating the effectiveness of post-AMI statin use. *Statistics in Medicine, 25*(12), 2084.

Beers, M. H. (1997). Explicit criteria for determining potentially inappropriate medication use by the elderly. an update. *Archives of Internal Medicine, 157*(14), 1531.

Bell, A. J., Talbot-Stern, J. K., & Hennessy, A. (2000). Characteristics and outcomes of older patients presenting to the emergency department after a fall: A retrospective analysis. *Medical Journal of Australia, 173*(4), 179.

Bergstrm, U., Bjrnstig, U., Stenlund, H., Jonsson, H., & Svensson, O. (2008). Fracture mechanisms and fracture pattern in men and women aged 50 years and older: A study of a 12-year population-based injury register, umeÃƒÂ¥, sweden. *Osteoporosis International, 19*(9), 1267.

Bharucha, A., Vasilescu, M., Dew, M., Begley, A., Stevens, S., Degenholtz, H., & Wactlar, H. (2008). Prevalence of behavioral symptoms: Comparison of the minimum data set assessments with research instruments. *Journal of the American Medical Directors Association, 9*(4), 244.

Birns, J., Lukkari, E., & Malone Lee, J. G. (2000). A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU International, 85*(7), 793-798. doi:10.1046/j.1464-410x.2000.00623.x

Blennow, K., Wallin, A., Fredman, P., Karlsson, I., Gottfries, C. G., & Svennerholm, L. (1990). Blood-brain barrier disturbance in patients with alzheimer's disease is related to vascular factors. *Acta Neurologica Scandinavica, 81*(4), 323-326. doi:10.1111/j.1600-0404.1990.tb01563.x

Bowers, B. J., Esmond, S., & Jacobson, N. (2000). The relationship between staffing and quality in long-term care facilities: Exploring the views of nurse aides. *Journal of Nursing Care Quality, 14*(4), 55-64. doi:10.1097/00001786-200007000-00009

Braithwaite, R. S., Col, N., & Wong, J. (2003). Estimating hip fracture morbidity, mortality and costs. Journal of the American Geriatrics Society, 51(3), 364-370. doi:10.1046/j.1532-5415.2003.51110.x

Brookhart, M. A., Schneeweiss, S., Rothman, K., Glynn, R., Avorn, J., & Strmer, T. (2006). Variable selection for propensity score models. *American Journal of Epidemiology, 163*(12), 1149.

Brown, J. S., Vittinghoff, E., Wyman, J. F., Stone, K. L., Nevitt, M. C., Ensrud, K. E., & Grady, D. (2000). Urinary incontinence: Does it increase risk for falls and fractures? study of osteoporotic fractures research group. *Journal of the American Geriatrics Society, 48*(7), 721.

Burgio, K., Goode, P., Johnson, T., Hammontree, L., Ouslander, J., Markland, A., . . . Redden, D. (2011). Behavioral versus drug treatment for overactive bladder in men: The male overactive bladder treatment in veterans (MOTIVE) trial. *Journal of the American Geriatrics Society, 59*(12), 2209-2216. doi:10.1111/j.1532-5415.2011.03724.x

Callegari, E., Malhotra, B., Bungay, P., Webster, R., Fenner, K., Kempshall, S., . . . Kay, G. (2011). A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. *British Journal of Clinical Pharmacology, 72*(2), 235-246. doi:10.1111/j.1365-2125.2011.03961.x

Campbell, A. J., Robertson, M. C., Gardner, M. M., Norton, R. N., & Buchner, D. M. (1999). Psychotropic medication withdrawal and a home-based exercise program to prevent falls: A randomized, controlled trial. *Journal of the American Geriatrics Society, 47*(7), 850.

Cancelli, I., Beltrame, M., Gigli, G., & Valente, M. (2009). Drugs with anticholinergic properties: Cognitive and neuropsychiatric side-effects in elderly patients. *Neurological Sciences, 30*(2), 87-92. doi:10.1007/s10072-009-0033-y

Carnahan, R., Lund, B., Perry, P., Pollock, B., & Culp, K. (2006). The anticholinergic drug scale as a measure of drug-related anticholinergic burden: Associations with serum anticholinergic activity. *The Journal of Clinical Pharmacology, 46*(12), 1481-1486. doi:10.1177/0091270006292126

Carrire, I., Fourrier Reglat, A., Dartigues, J., Rouaud, O., Pasquier, F., Ritchie, K., & Ancelin, M. (2009). Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: The 3-city study. *Archives of Internal Medicine, 169*(14), 1317-1324. doi:10.1001/archinternmed.2009.229

Centers for Disease Control and Prevention. (2011). *Falls in nursing homes.* Retrieved 02/21, 2012, from http://www.cdc.gov/HomeandRecreationalSafety/Falls/nursing.html

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. (2011). *Web–based injury statistics query and reporting system (WISQARS)* Retrieved 02/21, 2012, from www.cdc.gov/ncipc/wisqars

Chapple, C. R., Martinez Garcia, R., Selvaggi, L., Toozs Hobson, P., Warnack, W., Drogendijk, T., . . . Bolodeoku, J. (2005). A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: Results of the STAR trial. *European Urology, 48*(3), 464-470. doi:10.1016/j.eururo.2005.05.015

Charalambous, S., Trantafylidis, A. (2009). [Impact of urinary incontinence on quality of life] *Pelviperineology,* (28), 51-55.

Chess-Williams, R., Chapple, C. R., Yamanishi, T., Yasuda, K., & Sellers, D. J. (2001). The minor population of M3-receptors mediate contraction of human detrusor muscle in vitro. *Journal of Autonomic Pharmacology, 21*(5-6), 243.

Chrischilles, E., Rubenstein, L., Chao, J., Kreder, K. J., Gilden, D., & Shah, H. (2001). Initiation of nonselective alpha1-antagonist therapy and occurrence

of hypotension-related adverse events among men with benign prostatic hyperplasia: A retrospective cohort study. *Clinical Therapeutics, 23*(5), 727.

Cornford, E. M., & Hyman, S. (1999). Blood-brain barrier permeability to small and large molecules. *Advanced Drug Delivery Reviews, 36*(2-3), 145.

Currie, C., McEwan, P., Poole, C., Odeyemi, I. A. O., Datta, S., & Morgan, C. (2006). The impact of the overactive bladder on health-related utility and quality of life. *BJU International, 97*(6), 1267.

De Ridder, D. (2006). Antimuscarinics and cognitive function. *European Urology, 50*(2), 211.

Dingwall, L., & McLafferty, E. (2006). Do nurses promote urinary continence in hospitalized older people?: An exploratory study. *Journal of Clinical Nursing, 15*(10), 1276.

Diokno, A., Appell, R., Sand, P., Dmochowski, R., Gburek, B., Klimberg, I., & Kell, S. (2003). Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: Results of the OPERA trial. *Mayo Clinic Proceedings, 78*(6), 687-695. doi:10.4065/78.6.687

Diokno, A., Sand, P., Labasky, R., Sieber, P., Antoci, J., Leach, G., . . . Albrecht, D. (2002). Long-term safety of extended-release oxybutynin chloride in a community-dwelling population of participants with overactive bladder: A one-year study. *International Urology and Nephrology, 34*(1), 43.

Divani, A., Vazquez, G., Barrett, A., Asadollahi, M., & Luft, A. (2009). Risk factors associated with injury attributable to falling among elderly population with history of stroke. *Stroke, 40*(10), 3286.

Drummond, M. (2001). Introducing economic and quality of life measurements into clinical studies. *Annals of Medicine (Helsinki), 33*(5), 344.

Drutz, H. P., Appell, R. A., Gleason, D., Klimberg, I., & Radomski, S. (1999). Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. *International Urogynecology Journal and Pelvic Floor Dysfunction, 10*(5), 283-289. doi:10.1007/s001929970003

Dubeau, C. (2005). Improving urinary incontinence in nursing home residents: Are we FIT to be tied? *Journal of the American Geriatrics Society, 53*(7), 1254-1256. doi:10.1111/j.1532-5415.2005.53366.x

Dubeau, C., Simon, S., & Morris, J. (2006). The effect of urinary incontinence on quality of life in older nursing home residents. *Journal of the American Geriatrics Society, 54*(9), 1325.

Eglen, R. M. (2006). Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. *Autonomic Autacoid Pharmacology, 26*(3), 219.

Elixhauser, A., Steiner, C., Harris, D. R., & Coffey, R. M. (1998). Comorbidity measures for use with administrative data. *Medical Care, 36*(1), 8.

EuroQol--a new facility for the measurement of health-related quality of life. the EuroQol group. (1990). *Health Policy, 16*(3), 199.

Fatalities and injuries from falls among older adults--united states, 1993-2003 and 2001-2005. (2006). *Morbidity and Mortality Weekly Report, 55*(45), 1221.

Feder, G., Cryer, C., Donovan, S., & Carter, Y. (2000). Guidelines for the prevention of falls in people over 65. the guidelines' development group. *BMJ.British Medical Journal, 321*(7267), 1007.

Ferrucci, L., Guralnik, J., Studenski, S., Fried, L., Cutler, G., & Walston, J. (2004). Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: A consensus report. *Journal of the American Geriatrics Society, 52*(4), 625.

Fetscher, C., Fleichman, M., Schmidt, M., Krege, S., & Michel, M. (2002). M(3) muscarinic receptors mediate contraction of human urinary bladder. *British Journal of Pharmacology, 136*(5), 641.

Fick, D., Cooper, J., Wade, W., Waller, J., Maclean, J. R., & Beers, M. (2003). Updating the beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. *Archives of Internal Medicine, 163*(22), 2716.

Fink, H., Taylor, B., Tacklind, J., Rutks, I., & Wilt, T. (2008). Treatment interventions in nursing home residents with urinary incontinence: A systematic review of randomized trials. *Mayo Clinic Proceedings, 83*(12), 1332-1343.

Fitzmaurice G.M., Laird N.M., Ware J.H. (2004). Section 15.2. In *Applied longitudinal analysis.* (). Hoboken, NJ.: John Wiley & Sons.

Formiga, F., Navarro, M., Duaso, E., Chivite, D., Ruiz, D., Perez Castejon, J., . . . Pujol, R. (2008). Factors associated with hip fracture-related falls among patients with a history of recurrent falling. *Bone, 43*(5), 941-944. doi:10.1016/j.bone.2008.06.014

Fox, C., Richardson, K., Maidment, I., Savva, G., Matthews, F., Smithard, D., . . . Brayne, C. (2011). Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study. *Journal of the American Geriatrics Society, 59*(8), 1477-1483. doi:10.1111/j.1532-5415.2011.03491.x

Frederiksen, K., Tariot, P., & De Jonghe, E. (1996). Minimum data set plus (MDS) scores compared with scores from five rating scales. *Journal of the American Geriatrics Society, 44*(3), 305.

French, D., Campbell, R., & Rubenstein, L. (2008). Long-stay nursing home residents' hospitalizations in the VHA: The potential impact of aligning financial incentives on hospitalizations. *Journal of the American Medical Directors Association, 9*(7), 499.

French, D., Campbell, R., Rubenstein, L., & Spehar, A. (2008). Acquisition costs and use of medicare part D-excluded drugs in veterans health administration long-stay nursing home residents: A national, descriptive, secondary data analysis. *Drugs Aging, 25*(10), 855.

French, D., Campbell, R., Spehar, A., Rubenstein, L., & Cunningham, F. (2007). Drug costs and use in VHA nursing homes: A national overview of long-stay residents. *Journal of the American Medical Directors Association, 8*(8), 515.

French, D., Werner, D., Campbell, R., Powell-Cope, G., Nelson, A., Rubenstein, L., . . . Spehar, A. (2007). A multivariate fall risk assessment model for VHA nursing homes using the minimum data set. *Journal of the American Medical Directors Association, 8*(2), 115.

Friedman, S., Munoz, B., West, S., Rubin, G., & Fried, L. (2002). Falls and fear of falling: Which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. *Journal of the American Geriatrics Society, 50*(8), 1329.

Fultz, N. H., & Herzog, A. R. (2001). Self-reported social and emotional impact of urinary incontinence. *Journal of the American Geriatrics Society, 49*(7), 892-899. doi:10.1046/j.1532-5415.2001.49179.x

Furlong, W. J., Feeny, D. H., Torrance, G. W., & Barr, R. D. (2001). The health utilities index (HUI) system for assessing health-related quality of life in clinical studies. *Annals of Medicine (Helsinki), 33*(5), 375.

Gerritsen, D. L., Steverink, N., Ooms, M. E., & Ribbe, M. W. (2004). Finding a useful conceptual basis for enhancing the quality of life of nursing home residents. *Quality of Life Research, 13*(3), 611-624. doi:10.1023/B:QURE.0000021314.17605.40

Gill, S., Mamdani, M., Naglie, G., Streiner, D., Bronskill, S., Kopp, A., . . . Rochon, P. (2005). A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Archives of Internal Medicine, 165*(7), 808-813.

Glavind, K., & Chancellor, M. (2011). Antimuscarinics for the treatment of overactive bladder: Understanding the role of muscarinic subtype selectivity. *International Urogynecology Journal and Pelvic Floor Dysfunction, 22*(8), 907-917. doi:10.1007/s00192-011-1411-6

Gomes, T., Juurlink, D., Ho, J. M., Schneeweiss, S., & Mamdani, M. (2011). Risk of serious falls associated with oxybutynin and tolterodine: A population based study. *The Journal of Urology, 186*(4), 1340-1344. doi:10.1016/j.juro.2011.05.077

Groeneveld, P., Yang, L., Greenhut, A., & Yang, F. (2009). Comparative effectiveness of carotid arterial stenting versus endarterectomy. *Journal of Vascular Surgery, 50*(5), 1040-1048. doi:10.1016/j.jvs.2009.05.054

Gruber-Baldini, A. L., Zimmerman, S. I., Mortimore, E., & Magaziner, J. (2000). The validity of the minimum data set in measuring the cognitive impairment of persons admitted to nursing homes. *Journal of the American Geriatrics Society, 48*(12), 1601.

Halaska, M., Ralph, G., Wiedemann, A., Primus, G., Ballering-Brhl, B., Hfner, K., & Jonas, U. (2003). Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World Journal of Urology, 20*(6), 392-399. doi:10.1007/s00345-003-0321-8

Hannestad, Y. S., Rortveit, G., Sandvik, H., & Hunskaar, S. (2000). A community-based epidemiological survey of female urinary incontinence: The norwegian EPINCONT study. epidemiology of incontinence in the county of nord-TrÃƒÂ¸ndelag. *Journal of Clinical Epidemiology, 53*(11), 1150.

Hartmaier, S. L., Sloane, P. D., Guess, H. A., & Koch, G. G. (1994). The MDS cognition scale: A valid instrument for identifying and staging nursing home residents with dementia using the minimum data set. *Journal of the American Geriatrics Society, 42*(11), 1173.

Hartmaier, S. L., Sloane, P. D., Guess, H. A., Koch, G. G., Mitchell, C. M., & Phillips, C. D. (1995). Validation of the minimum data set cognitive performance scale: Agreement with the mini-mental state examination. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 50*(2), M128.

Hausdorff, J. M., Rios, D. A., & Edelberg, H. K. (2001). Gait variability and fall risk in community-living older adults: A 1-year prospective study. *Archives of Physical Medicine and Rehabilitation, 82*(8), 1050.

Hawes, C., Morris, J. N., Phillips, C. D., Fries, B. E., Murphy, K., & Mor, V. (1997). Development of the nursing home resident assessment instrument in the USA. *Age and Ageing, 26 Suppl 2*, 19.

Hawes, C., Morris, J. N., Phillips, C. D., Mor, V., Fries, B. E., & Nonemaker, S. (1995). Reliability estimates for the minimum data set for nursing home resident assessment and care screening (MDS). *Gerontologist, the, 35*(2), 172.

Hegde, S. S., & Eglen, R. M. (1999). Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. *Life Sciences, 64*(6-7), 419.

Hegde, S. S., & Eglen, R. M. (1999). Muscarinic receptor subtypes modulating smooth muscle contractility in the urinary bladder. *Life Sciences, 64*(6-7), 419-428.

Hill, J. (2008). Discussion of research using propensity-score matching: Comments on 'A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003' by peter austin, statistics in medicine. Statistics in Medicine, 27(12), 2055-61. doi:10.1002/sim.3245

Hirdes, J., Frijters, D., & Teare, G. (2003). The MDS-CHESS scale: A new measure to predict mortality in institutionalized older people. *Journal of the American Geriatrics Society, 51*(1), 96.

Hornbrook, M. C., Stevens, V. J., Wingfield, D. J., Hollis, J. F., Greenlick, M. R., & Ory, M. G. (1994). Preventing falls among community-dwelling older persons: Results from a randomized trial. *Gerontologist, the, 34*(1), 16.

Hu, T., Wagner, T., Bentkover, J., Leblanc, K., Zhou, S., & Hunt, T. (2004). Costs of urinary incontinence and overactive bladder in the united states: A comparative study. *Urology, 63*(3), 461-465.

Jewart, R., Green, J., Lu, C., Cellar, J., & Tune, L. (2005). Cognitive, behavioral, and physiological changes in alzheimer disease patients as a function of incontinence medications. *The American Journal of Geriatric Psychiatry, 13*(4), 324.

Johnson, T. M., Ouslander, J. G., Uman, G. C., & Schnelle, J. F. (2001). Urinary incontinence treatment preferences in long-term care. *Journal of the American Geriatrics Society, 49*(6), 710.

Jumadilova, Z., Varadharajan, S., Girase, P., & Ollendorf, D. (2006). Retrospective evaluation of outcomes in patients with overactive bladder receiving tolterodine versus oxybutynin. *American Journal of Health-System Pharmacy, 63*(23), 2357-2364. doi:10.2146/ajhp060038

Jumadilova, Z., Zyczynski, T., Paul, B., & Narayanan, S. (2005). Urinary incontinence in the nursing home: Resident characteristics and prevalence of drug treatment. *The American Journal of Managed Care, 11*(4 Suppl), S112-S120.

Kallin, K. (2002). Precipitating factors for falls among older people in residential care. *Public Health, 116*, 263-71.

Kay, G., Abou-Donia, M., Messer, W., Murphy, D., Tsao, J., & Ouslander, J. (2005). Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. *Journal of the American Geriatrics Society, 53*(12), 2195.

Kay, G., Crook, T., Rekeda, L., Lima, R., Ebinger, U., Arguinzoniz, M., & Steel, M. (2006). Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *European Urology, 50*(2), 317.

Kelleher, C. J., Cardozo, L. D., Khullar, V., & Salvatore, S. (1997). A new questionnaire to assess the quality of life of urinary incontinent women. *British Journal of Obstetrics and Gynaecology, 104*(12), 1374.

Kelleher, C., Kreder, K., Pleil, A., Burgess, S., & Reese, P. (2002). Long-term health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. *The American Journal of Managed Care, 8*(19 Suppl), S616.

Kelleher, C., Reese, P., Pleil, A., & Okano, G. (2002). Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. *The American Journal of Managed Care, 8*(19 Suppl), S608.

Kiely, D., & Flacker, J. (2003). The protective effect of social engagement on 1-year mortality in a long-stay nursing home population. *Journal of Clinical Epidemiology, 56*(5), 472-478. doi:10.1016/S0895-4356(03)00030-1

King-Kallimanis, B., Schonfeld, L., Molinari, V., Algase, D., Brown, L., Kearns, W., . . . Nelson, A. (2010). Longitudinal investigation of wandering behavior in department of veterans affairs nursing home care units. *International Journal of Geriatric Psychiatry, 25*(2), 166.

Koski, K., Luukinen, H., Laippala, P., & Kivel, S. L. (1998). Risk factors for major injurious falls among the home-dwelling elderly by functional abilities. A prospective population-based study. *Gerontology, 44*(4), 232.

Koski, K., Luukinen, H., Laippala, P., & Kivela, S. L. (1996). Physiological factors and medications as predictors of injurious falls by elderly people: A prospective population-based study. *Age and Ageing, 25*(1), 29.

Lackner, T., Wyman, J., McCarthy, T., Monigold, M., & Davey, C. (2008). Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence. *Journal of the American Geriatrics Society, 56*(5), 862-870. doi:10.1111/j.1532-5415.2008.01680.x

Lawlor, D., Patel, R., & Ebrahim, S. (2003). Association between falls in elderly women and chronic diseases and drug use: Cross sectional study. *BMJ.British Medical Journal, 327*(7417), 712.

Lee, Y., Choo, M., Lee, J. Y., & Oh, S. (2011). Symptom change after discontinuation of successful antimuscarinic treatment in patients with overactive bladder symptoms: A randomised, multicentre trial. *International Journal of Clinical Practice, 65*(9), 997-1004. doi:10.1111/j.1742-1241.2011.02728.x

Leipzig, R. M., Cumming, R. G., & Tinetti, M. E. (1999). Drugs and falls in older people: A systematic review and meta-analysis: I. psychotropic drugs. *Journal of the American Geriatrics Society, 47*(1), 30.

Leipzig, R. M., Cumming, R. G., & Tinetti, M. E. (1999). Drugs and falls in older people: A systematic review and meta-analysis: II. cardiac and analgesic drugs. *Journal of the American Geriatrics Society, 47*(1), 40.

Lekan Rutledge, D., Palmer, M. H., & Belyea, M. (1998). In their own words: Nursing assistants' perceptions of barriers to implementation of prompted voiding in long-term care. *Gerontologist, the, 38*(3), 370-378. doi:10.1093/geront/38.3.370

Li, P., Kim, M., & Doshi, J. (2010). Comparison of the performance of the CMS hierarchical condition category (CMS-HCC) risk adjuster with the charlson and elixhauser comorbidity measures in predicting mortality. *BMC Health Services Research, 10*, 245-245. doi:10.1186/1472-6963-10-245

Malone Lee, J., Shaffu, B., Anand, C., & Powell, C. (2001). Tolterodine: Superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: A randomized controlled trial. *The Journal of Urology, 165*(5), 1452-1456. doi:10.1016/S0022-5347(05)66326-4

Malone, D. C., & Okano, G. J. (1999). Treatment of urge incontinence in veterans affairs medical centers. *Clinical Therapeutics, 21*(5), 867.

Maser, R., Stabley, J., Lenhard, M. J., & Provost Craig, M. (2009). Autonomic nerve fiber function and bone mineral density in individuals with type 1 diabetes: A cross-sectional study. Diabetes Research and Clinical Practice, 84(3), 252-258. doi:10.1016/j.diabres.2009.02.012

McAlister, F. A., Straus, S. E., Guyatt, G. H., & Haynes, R. B. (2000). Users' guides to the medical literature: XX. integrating research evidence with the care of the individual patient. evidence-based medicine working group. JAMA (Chicago, Ill.), 283(21), 2829-2836. doi:10.1001/jama.283.21.2829

Messinger Rapport, B., & Dumas, L. (2009). Falls in the nursing home: A collaborative approach. *The Nursing Clinics of North America, 44*(2), 187-195. doi:10.1016/j.cnur.2009.03.001

Milsom, I., Abrams, P., Cardozo, L., Roberts, R. G., Throff, J., & Wein, A. J. (2001). How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU International, 87*(9), 760.

Mo, F., Choi, B. C. K., Li, F. C. K., & Merrick, J. (2004). Using health utility index (HUI) for measuring the impact on health-related quality of life (HRQL) among individuals with chronic diseases. *TheScientificWorldjournal, 4*, 746.

Mor, V., Branco, K., Fleishman, J., Hawes, C., Phillips, C., Morris, J., & Fries, B. (1995). The structure of social engagement among nursing home residents. *The Journals of Gerontology.Series B, Psychological Sciences and Social Sciences, 50*(1), P1.

Morris, J. N., Fries, B. E., Mehr, D. R., Hawes, C., Phillips, C., Mor, V., & Lipsitz, L. A. (1994). MDS cognitive performance scale. *Journal of Gerontology, 49*(4), M174.

Morris, J. N., Fries, B. E., & Morris, S. A. (1999). Scaling ADLs within the MDS. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 54*(11), M546.

Morris, J. N., Nonemaker, S., Murphy, K., Hawes, C., Fries, B. E., Mor, V., & Phillips, C. (1997). A commitment to change: Revision of HCFA's RAI. *Journal of the American Geriatrics Society, 45*(8), 1011.

Mustard, C. A., & Mayer, T. (1997). Case-control study of exposure to medication and the risk of injurious falls requiring hospitalization among nursing home residents. *American Journal of Epidemiology, 145*(8), 738.

Nanda, S., Dey, T., Gulstrand, R., Cudnik, D., & Haller, H. (2011). Fall risk assessment in geriatric-psychiatric inpatients to lower events (FRAGILE). *Journal of Gerontological Nursing, 37*(2), 22-30. doi:10.3928/00989134-20100730-01

Narayanan, S., Cerulli, A., Kahler, K., & Ouslander, J. (2007). Is drug therapy for urinary incontinence used optimally in long-term care facilities? *Journal of the American Medical Directors Association, 8*(2), 98.

National Center for Health Statistics. (2005). In National Center for Health Statistics (Ed.), *Chartbook on trends in the health of americans*. Hyattsville (MD):

Naughton, M. J., & Wyman, J. F. (1997). Quality of life in geriatric patients with lower urinary tract dysfunction. *The American Journal of the Medical Sciences, 314*(4), 219.

Newman, D.*Managing and treating urinary incontinence / by diane kaschak newman.*

Newman, D. (2006). Urinary incontinence, catheters, and urinary tract infections: An overview of CMS tag F 315. *Ostomy/wound Management, 52*(12), 34-6, 38, 40.

Newman, D.K., Wein, A.J.: Managing and Treating Urinary Incontinence. 2nd ed. Baltimore, MD. Health Professions Press, 2009

Nurmi, I., & Lthje, P. (2002). Incidence and costs of falls and fall injuries among elderly in institutional care. *Scandinavian Journal of Primary Health Care, 20*(2), 118-122.

Ooms, M. E., Vlasman, P., Lips, P., Nauta, J., Bouter, L. M., & Valkenburg, H. A. (1994). The incidence of hip fractures in independent and institutionalized elderly people. *Osteoporosis International, 4*(1), 6.

Ouslander, J. G., Ai Samarrai, N., & Schnelle, J. F. (2001). Prompted voiding for nighttime incontinence in nursing homes: Is it effective? *Journal of the American Geriatrics Society, 49*(6), 706-709.

Ouslander, J. G., Maloney, C., Grasela, T. H., Rogers, L., & Walawander, C. A. (2001). Implementation of a nursing home urinary incontinence management program with and without tolterodine. *Journal of the American Medical Directors Association, 2*(5), 207.

Ouslander, J. G., Maloney, C., Grasela, T. H., Rogers, L., & Walawander, C. A. (2001). Implementation of a nursing home urinary incontinence management program with and without tolterodine. *Journal of the American Medical Directors Association, 2*(5), 207-214. doi:10.1016/S1525-8610(04)70206-6

Ouslander, J. G., & Schnelle, J. F. (1995). Incontinence in the nursing home. *Annals of Internal Medicine, 122*(6), 438-449.

Ouslander, J. G., Schnelle, J. F., Uman, G., Fingold, S., Nigam, J. G., Tuico, E., & Bates-Jensen, B. (1995). Predictors of successful prompted voiding among incontinent nursing home residents. *JAMA (Chicago, Ill.), 273*(17), 1366.

Ouslander, J. G., Schnelle, J. F., Uman, G., Fingold, S., Nigam, J. G., Tuico, E., & Jensen, B. B. (1995). Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among nursing home residents? A placebo-controlled trial. *Journal of the American Geriatrics Society, 43*(6), 610-617.

Pagoria, D., O'Connor, R. C., & Guralnick, M. (2011). Antimuscarinic drugs: Review of the cognitive impact when used to treat overactive bladder in elderly patients. *Current Urology Reports, 12*(5), 351-357. doi:10.1007/s11934-011-0198-9

Pak, R., Petrou, S., & Staskin, D. (2003). Trospium chloride: A quaternary amine with unique pharmacologic properties. *Current Urology Reports, 4*(6), 436.

Pan, W. (2001). Akaike's information criterion in generalized estimating equations. *Biometrics, 57*(1), 120-125. doi:10.1111/j.0006-341X.2001.00120.x

Phillips, C. D., & Morris, J. N. (1997). The potential for using administrative and clinical data to analyze outcomes for the cognitively impaired: An assessment of the minimum data set for nursing homes. *Alzheimer Disease and Associated Disorders, 11 Suppl 6*, 162.

Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J., . . . Ghali, W. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care, 43*(11), 1130.

Ray, W. A., Griffin, M. R., Schaffner, W., Baugh, D. K., & Melton, L. J. (1987). Psychotropic drug use and the risk of hip fracture. *The New England Journal of Medicine, 316*(7), 363-369.

Ray, W. A., Thapa, P. B., & Gideon, P. (2000). Benzodiazepines and the risk of falls in nursing home residents. *Journal of the American Geriatrics Society, 48*(6), 682.

Ray, W. (2003). Evaluating medication effects outside of clinical trials: New-user designs. *American Journal of Epidemiology, 158*(9), 915.

Resnick, B., Keilman, L., Calabrese, B., Parmelee, P., Lawhorne, L., Pailet, J., & Ouslander, J. (2006). Nursing staff beliefs and expectations about continence care in nursing homes. *Journal of Wound, Ostomy, and Continence Nursing, 33*(6), 610-618. doi:10.1097/00152192-200611000-00004

Resnick, N. M., Brandeis, G. H., Baumann, M. M., & Morris, J. N. (1996). Evaluating a national assessment strategy for urinary incontinence in nursing home residents: Reliability of the minimum data set and validity of the resident assessment protocol. *Neurourology and Urodynamics, 15*(6), 583.

Robinson, D., Cardozo, L., Terpstra, G., & Bolodeoku, J. (2007). A randomized double-blind placebo-controlled multicentre study to explore the efficacy and safety of tamsulosin and tolterodine in women with overactive bladder syndrome. *BJU International, 100*(4), 840.

Rubenstein, L. Z., Josephson, K. R., & Robbins, A. S. (1994). Falls in the nursing home. *Annals of Internal Medicine, 121*(6), 442-451.

Rubin, D. B. (1987). Multiple imputation for nonresponse In *Surveys* (). New York: John Wiley & Sons, Inc.

Rubin DB, Thomas N. Combining propensity score matching with additional adjustments for prognostic covariates. Journal of the American Statistical Association 2000; 95:573–585.

Rudolph, J., Salow, M., Angelini, M., & McGlinchey, R. (2008). The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Archives of Internal Medicine, 168*(5), 508-513. doi:10.1001/archinternmed.2007.106

Sahyoun N. R., Pratt L. A., Lentzner H., Dey A., Robinson K. N. (2001). *The changing profile of nursing home residents: 1985–1997. aging trends* . Hyattsville (MD): National Center for Health Statistics.

SAS Institute Inc., SAS/STAT ® User's Guide, Version 8, Cary, NC: SAS Institute Inc., 1999

Scheife, R., & Takeda, M. (2005). Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clinical Therapeutics, 27*(2), 144.

Schliebs, R., & Arendt, T. (2006). The significance of the cholinergic system in the brain during aging and in alzheimer's disease. *Journal of Neural Transmission, 113*(11), 1625-1644. doi:10.1007/s00702-006-0579-2

Schliebs, R., & Arendt, T. (2011). The cholinergic system in aging and neuronal degeneration. *Behavioural Brain Research, 221*(2), 555-563. doi:10.1016/j.bbr.2010.11.058

Schnelle, J. F., MacRae, P. G., Ouslander, J. G., Simmons, S. F., & Nitta, M. (1995). Functional incidental training, mobility performance, and incontinence care with nursing home residents. *Journal of the American Geriatrics Society, 43*(12), 1356.

Schnelle, J., Alessi, C., Simmons, S., Al-Samarrai, N., Beck, J., & Ouslander, J. (2002). Translating clinical research into practice: A randomized controlled trial of exercise and incontinence care with nursing home residents. *Journal of the American Geriatrics Society, 50*(9), 1476.

Scott, J. C. (1990). Osteoporosis and hip fractures. *Rheumatic Diseases Clinics of North America, 16*(3), 717-740.

Shih, Y., Hartzema, A., & Tolleson-Rinehart, S. (2003). Labor costs associated with incontinence in long-term care facilities. *Urology, 62*(3), 442.

Sink, K., Thomas, J., Xu, H., Craig, B., Kritchevsky, S., & Sands, L. (2008). Dual use of bladder anticholinergics and cholinesterase inhibitors: Long-term functional and cognitive outcomes. *Journal of the American Geriatrics Society, 56*(5), 847.

Smith, M., & Joseph, G. (2003). Pharmacy data in the VA health care system. *Medical Care Research and Review, 60*(3 Suppl), 92.

Snowden, M., McCormick, W., Russo, J., Srebnik, D., Comtois, K., Bowen, J., . . . Larson, E. B. (1999). Validity and responsiveness of the minimum data set. *Journal of the American Geriatrics Society, 47*(8), 1000.

Song, C., Park, J., Heo, K., Lee, K., & Choo, M. (2006). Effects of bladder training and/or tolterodine in female patients with overactive bladder syndrome: A prospective, randomized study. *Journal of Korean Medical Science, 21*(6), 1060-1063. doi:10.3346/jkms.2006.21.6.1060

Starr, J. M., Wardlaw, J., Ferguson, K., MacLullich, A., Deary, I. J., & Marshall, I. (2003). Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. *Journal of Neurology, Neurosurgery and Psychiatry, 74*(1), 70-76. doi:10.1136/jnnp.74.1.70

Stevens J. A. (2005). *Falls among older adults–risk factors and prevention strategies.* (No. NCOA Falls Free: Promoting a National Falls Prevention Action Plan. Research Review Papers). Washington DC: The National Council on the Aging.

Sugarman, J., Connell, F., Hansen, A., Helgerson, S., Jessup, M., & Lee, H. (2002). Hip fracture incidence in nursing home residents and community-dwelling older people, washington state, 1993-1995. *Journal of the American Geriatrics Society, 50*(10), 1638.

Torrance, G. W., Feeny, D. H., Furlong, W. J., Barr, R. D., Zhang, Y., & Wang, Q. (1996). Multiattribute utility function for a comprehensive health status classification system. health utilities index mark 2. *Medical Care, 34*(7), 702.

Uebersax, J. S., Wyman, J. F., Shumaker, S. A., McClish, D. K., & Fantl, J. A. (1995). Short forms to assess life quality and symptom distress for urinary incontinence in women: The incontinence impact questionnaire and the urogenital distress inventory. continence program for women research group. *Neurourology and Urodynamics, 14*(2), 131.

VA Long Term Care. (2004). *GAO. VA long-term care: Oversight of nursing home program impeded by data gaps. GAO-05-65.* Retrieved August/2, 2010, from http://www.gao.gov/new.items/d0565.pdf.

VA Long Term Care. (2006). *Trends and planning challenges to providing nursing home care to veterans. GAO-06-333T* Retrieved August/2, 2010, from http://www.gao.gov/new.items/d06333t.pdf

van der Steen, J., Volicer, L., Gerritsen, D., Kruse, R., Ribbe, M., & Mehr, D. (2006). Defining severe dementia with the minimum data set. *International Journal of Geriatric Psychiatry, 21*(11), 1099.

van Dijk, P. T. M., Mehr, D., Ooms, M., Madsen, R., Petroski, G., Frijters, D., . . . Ribbe, M. (2005). Comorbidity and 1-year mortality risks in nursing home residents. *Journal of the American Geriatrics Society, 53*(4), 660.

van Lenthe, F., Avendano, M., van Beeck, E. F., & Mackenbach, J. (2011). Childhood and adulthood socioeconomic position and the hospital-based incidence of hip fractures after 13 years of follow-up: The role of health behaviours. *Journal of Epidemiology and Community Health, 65*(11), 980-985. doi:10.1136/jech.2010.115782

Wagg, A., Verdejo, C., & Molander, U. (2010). Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. *International Journal of Clinical Practice, 64*(9), 1279.

Wagg, A., Wyndaele, J., & Sieber, P. (2006). Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: A pooled analysis. *The American Journal of Geriatric Pharmacotherapy, 4*(1), 14-24. doi:10.1016/j.amjopharm.2006.03.004

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. *Medical Care, 30*(6), 473.

Weinhandl, E. D., Snyder, J. J., Israni, A. K., & Kasiske, B. L. (2009). Effect of comorbidity adjustment on CMS criteria for kidney transplant center performance. *American Journal of Transplantation, 9*(3), 506-516. doi:10.1111/j.1600-6143.2008.02527.x

Westreich, D., Cole, S., Funk, M., Brookhart, M. A., & Strmer, T. (2011). The role of the c-statistic in variable selection for propensity score models. *Pharmacoepidemiology and Drug Safety, 20*(3), 317-320. doi:10.1002/pds.2074

Wodchis, W., Hirdes, J., & Feeny, D. (2003). Health-related quality of life measure based on the minimum data set. *International Journal of Technology Assessment in Health Care, 19*(3), 490.

Wodchis, W., Maxwell, C., Venturini, A., Walker, J., Zhang, J., Hogan, D., & Feeny, D. (2007). Study of observed and self-reported HRQL in older frail adults found group-level congruence and individual-level differences. *Journal of Clinical Epidemiology, 60*(5), 502.

World Health Organization.*Health promotion glossary.* Retrieved August 28, 2010, from http://whqlibdoc.who.int/hq/1998/WHO_HPR_HEP_98.1.pdf

Yamada, M., Miyakawa, T., Duttaroy, A., Yamanaka, A., Moriguchi, T., Makita, R., . . . Wess, J. (2001). Mice lacking the M3 muscarinic acetylcholine receptor are hypophagic and lean. *Nature, 410*(6825), 207.

Yamanishi, T., Chapple, C., Yasuda, K., & Chess-Williams, R. (2002). The role of M2 muscarinic receptor subtypes in mediating contraction of the pig bladder base after cyclic adenosine monophosphate elevation and/or selective M3 inactivation. *The Journal of Urology, 167*(1), 397.

Zarowitz, B., & Ouslander, J. (2007). The application of evidence-based principles of care in older persons (issue 6): Urinary incontinence. *Journal of the American Medical Directors Association, 8*(1), 35-45. doi:10.1016/j.jamda.2006.09.011

Zinner, N., Mattiasson, A., & Stanton, S. (2002). Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *Journal of the American Geriatrics Society, 50*(5), 799-807. doi:10.1046/j.1532-5415.2002.50203.x

Zinner, N., Noe, L., Rasouliyan, L., Marshall, T., Runken, M. C., & Seifeldin, R. (2009). Impact of solifenacin on quality of life, medical care use, work productivity, and health utility in the elderly: An exploratory subgroup analysis. *The American Journal of Geriatric Pharmacotherapy, 7*(6), 373.