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Dated: 09/09/2013

**INAPPROPRIATE ANTICHOLINERGIC MEDICATION USE IN ELDERLY PATIENTS**

by

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*For*

*My Grandfather and Parents*

*&*

*To the loving memory of my Grandmother*

# ABSTRACT

## INAPPROPRIATE ANTICHOLINERGIC MEDICATION USE IN ELDERLY PATIENTS

**Objectives:** The purpose of this study was (i) to determine the prevalence of inappropriate anticholinergic medication use in the elderly in general and elderly with dementia patients in specific (ii) to determine the predictors of inappropriate anticholinergic medication use in the elderly (iii) to determine the predictors of inappropriate anticholinergic medication use in elderly dementia patients

**Methods:** Retrospective cross-sectional study design was conducted using the 2009-2010 Medical Expenditure Panel Survey (MEPS) data, a nationally representative data on the community dwelling, non-institutionalized US population to determine the prevalence and predictors of inappropriate anticholinergic medication use in elderly and elderly dementia patients. The study sample for the first and second objective included patients aged ≥65 years whereas the study sample for the third objective included patients aged ≥65 years with a diagnosis of dementia. The inappropriate anticholinergic drugs were identified using revised 2012 American Geriatrics Society (AGS) Beers criteria. Weighted descriptive statistics were used to estimate the prevalence of inappropriate anticholinergic medication use in the elderly and elderly dementia patients. Multiple logistic regression within the conceptual framework of Anderson Behavioral Model was used to identify predictors associated with the use of inappropriate anticholinergic medications in the elderly and elderly dementia patients. Use of inappropriate anticholinergic medication as defined by the Beers' criteria was the dependent variable. The independent variables were various predisposing, enabling, and need characteristics.

**Results:** Analysis of 2009 - 2010 MEPS data revealed that an estimated 78.60 million (95% CI: 73.71 to 83.49) were elderly participants (12.78% of US population); of which, 7.51 million (95% CI: 6.64 to 8.38) reported using inappropriate anticholinergic medications for an overall prevalence of 9.56%. The most frequently prescribed drugs among the elderly were found to be cyclobenzaprine (2.08%), promethazine (1.75%), amitriptyline (1.47%), hydroxyzine (0.95%), and dicyclomine (0.84%). Of the predisposing factors, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly lower for patients between 75 to 84 years of age (OR: 0.64; 95% CI: 0.49 – 0.85) compared to the reference group, 65 to 74 years of age. Further, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly much lower for patients >=85 years of age (OR: 0.52; 95% CI: 0.33 – 0.81) compared to the reference group, 65 to 74 years of age. The odds of receiving inappropriate anticholinergic drugs in the elderly were significantly higher for female patients (OR: 1.37; 95% CI: 1.06 – 1.77) compared to the male reference group. Also, the odds of receiving inappropriate anticholinergic drugs in the elderly were significantly lower for patients having >15 years of education (OR: 0.54; 95% CI: 0.35 – 0.84) compared to the reference group, <12 years of education. Of the enabling factors, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly higher for patients who resided in the South region (OR: 1.88; 95% CI: 1.25 – 2.84) compared to the reference group, Northeast. Among the need factors, elderly patients suffering from anxiety (OR: 2.15; 95% CI: 1.57 - 2.94) were more likely to use inappropriate anticholinergic drugs.

A total of 3.78 million (95% CI: 3.17 to 4.38) elderly patients were found to have been diagnosed with dementia for an overall prevalence of 4.81%. Of those, 1.02 million dementia patients (95% CI: 704,993 to 1,330,606) were reported to use inappropriate anticholinergic medications for a prevalence of 26.95%. Among the elderly dementia patients, the most frequently

prescribed drugs were found to be oxybutynin (4.54%), solifenacin (4.48%), paroxetine (2.81%), tolterodine (2.47%) and promethazine (2.41%). Of the predisposing factors, the odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly lower for patients between 75 - 84 years of age (OR: 0.35; 95% CI: 0.15 - 0.81) compared to the reference group, 65 - 74 years of age. Of the need factors, the odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly higher for patients having fair/poor general health status (OR: 5.09; 95% CI: 1.36 - 19.08) compared to the reference group, patients having excellent general health status The odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly higher for patients suffering from anxiety (OR: 3.02; 95% CI: 1.21 - 7.54) and patients suffering from mood disorder (OR: 4.15; 95% CI: 1.87 - 9.22). None of the enabling factors were significantly associated with the use of inappropriate anticholinergic drugs in elderly dementia patients.

**Conclusions:** The study found that approximately one in ten elderly patients used inappropriate anticholinergic medications. Female gender, south region and anxiety increased the likelihood of receiving inappropriate anticholinergic medications whereas age between 75 to 84 years, age >=85 years and >15 years of education decreased the likelihood of receiving inappropriate anticholinergic medications. However, the study found that approximately one in four elderly dementia patients used inappropriate anticholinergic medications. While, fair/poor general health status, anxiety and mood disorder increased the likelihood of receiving inappropriate anticholinergic medications, age between 75 to 84 years decreased the likelihood of receiving inappropriate anticholinergic medications. Drugs with anticholinergic properties are associated with central and peripheral adverse effects in vulnerable elderly populations. Hence, there is urgent need to optimize anticholinergic use in elderly patients. Both educational and

regulatory approaches are needed to improve inappropriate prescribing practices to optimize appropriate anticholinergic medication use in elderly as well as elderly dementia patients.

**Key words:** Inappropriate anticholinergic medications, Anticholinergic drugs, elderly, dementia, Beers Criteria

# Table of Contents

CHAPTER IV



CHAPTER V



CHAPTER VI

# List of tables

# List of figures

# CHAPTER 1
# INTRODUCTION AND STATEMENT OF PROBLEM

## HEALTHY PEOPLE

Healthy People is a national program that provides science-based, goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts to improve the health of all people in the United States. These are set by the United States Department of Health and Human Services (DHHS). These goals were first set in 1979 and were then, subsequently updated for Healthy People 1990, Healthy People 2000, Healthy People 2010, and Healthy People 2020. (www.healthypeople.gov/2020/about/history.aspx)

### *Healthy People 2020*

In December 2010, DHHS launched Healthy People 2020, the successor health promotion initiative for the second decade of the 21st century that frames itself from the strengths of Healthy People 2010 while laying new ground in the scope, outreach, and scientific underpinning of the initiative. Developed under the leadership of the Federal Interagency Workgroup (FIW), the Healthy People 2020 framework is the product of an exhaustive collaborative process among the U.S. Department of Health and Human Services (DHHS) and other federal agencies, public stakeholders, and the advisory committee. In contrast with the two goals of Healthy People 2010, Healthy People 2020 has four overarching goals to:

1. Attain high quality, longer lives free of preventable disease, disability, injury, and premature death.
2. Achieve health equity and eliminate disparities.
3. Create social and physical environments that promote good health for all.

4. Promote quality of life, healthy develop

The framework of Healthy People 2020 is organized into 42 Topic Areas (formerly Focus Areas), with 13 new areas added. One of these 13 new focus areas is "Older Adults." Older adults are among the fastest growing age groups. The first “baby boomers” (adults born between 1946 and 1964) turned 65 in 2011. More than 37 million people in this group (60 percent) will manage more than 1 chronic condition by 2030. With the goal of improving the health, function and quality of life in older adults, this focus area was introduced in the Healthy People 2020. (www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=31)

**QUALITY OF HEALTH CARE**

Medical errors and the quality of health care in the United States have drawn attention from the media in recent years (Gordon et al., 2002). Particularly troubling was the report by the Institute of Medicine indicating that medical errors in inpatient care alone are responsible for between 44,000 and 98,000 deaths each year, far more than the number of people dying from many other causes, including vehicle accidents (43,458), breast cancer (42,297), and acquired immune deficiency syndrome (16,516) (Kohn et al., 2000) Deaths and death rates for the 10 leading causes of death in specified age groups, by race and sex, 1997). Inappropriate prescribing constitutes the major portion of these medical errors. In a controlled study involving 706 elderly patients, Bero et al. found 20% of all hospital readmissions to be drug-related and noted that three-fourths of these admissions could have been prevented if medications had been used properly (Bero et al., 1991).

Avoidable adverse drug reactions (ADRs) are the most serious consequence of inappropriate prescribing (Gurwitz et al., 1990). Less serious ADRs that remain frequently

unrecognized may lead to prescriptions for additional agents and hence, a diminished quality of life (Beers et al., 1992; Willcox et al., 1994). However, more serious ADRs may result in unnecessary hospitalizations along with increased morbidity and mortality (Anonymous, 1995) leading to poorer health and health care outcomes (Gordon et al., 2002). Among the general population, for example, a meta-analysis estimated that 1.5 million, or 4.7%, of all hospital admissions were attributable to ADRs (Lazarou et al., 1998). The percentage is likely much higher for the elderly. Studies limited to elderly persons found frequency rates as high as 17% (Col et al., 1990; Beard, 1992)

## DRUG THERAPY PROBLEMS IN THE ELDERLY

The elderly (65 years or older) constitute only 14% of the United States population, yet they are prescribed over one-third of all prescription medications (Hall, 1997; Stewart, 1995). They are at a higher risk for drug-related problems for many reasons, polypharmacy being the primary one. Polypharmacy is defined simply as the use of multiple medications by a patient. Although the minimum number of medications used to define "polypharmacy" is variable, it generally ranges from 5 to 10 (Ferner et al., 2006). The issue of polypharmacy is of particular concern in elderly people because they tend to suffer from multiple chronic conditions for which therapies are prescribed. The use of greater numbers of drug therapies has been independently associated with an increased risk for an adverse drug event (Tinetti et al., 2004). In addition to polypharmacy, more emphasis is placed on appropriate use of medications due to burden of drug-related morbidity in the elderly.

Age-related changes in the pharmacokinetics and pharmacodynamics of drugs alter the drug disposition and response to medications in elderly patients. Pharmacokinetic changes can

result in increased serum drug concentrations and enhanced drug effects. Elderly patients may also require lower doses of drugs, such as narcotics and anticoagulants, due to increased pharmacodynamic sensitivity (Shelton et al., 2000). Hence, suboptimal prescribing for elderly patients is important and challenging (Gurwitz, 1994).

## INAPPROPRIATE MEDICATIONS: BEERS CRITERIA

Inappropriate medications are defined as medications in which the risk outweighs the benefit (Beers et al., 1991; Stuck et al., 1994). Inappropriate prescribing has become a major concern from both humanistic and economic viewpoints. Up to 40% of nursing home residents and 25% of board and care facility residents in the US are prescribed an inappropriate medication (Beers et al., 1992; Spore et al., 1997). The risk/benefit ratios of some medications are unfavorably affected by age-related changes in the medications' pharmacokinetic and pharmacodynamic parameters in older persons (Beers, 1989; Everitt, 1986; Mahoney, 1991). Aparasu et al. evaluated prescriptions by office-based physicians in elderly ambulatory patients within the continental US and found that at least one inappropriate medication was prescribed in over 8 million clinic visits (Aparasu et al., 1997). Tamblyn et al. found high-risk prescribing, i.e. the use of rational or questionable drug combinations, excessive treatment duration or the use of drugs relatively contraindicated for use in elderly people, in 52.6% of 63,268 elderly Medicare registrants in Quebec (Tamblyn et al., 1994). Because of this growing evidence of drug-related problems in the elderly during the past decade, many geriatric clinicians and researchers have developed variety of methods and tools to identify inappropriate and high-risk prescribing patterns.

An explicit criterion for determining potentially inappropriate medications to be avoided in the elderly was developed using the Delphi consensus by Beers and colleagues in 1991.

Medications believed to have risks that outweighed benefits for their primary indication in frail nursing home residents were the target (Shelton et al., 2000). These criteria included lists of 12 medications or classes of medications that could be avoided generally and 12 medications or classes of medications that should be avoided based on frequency, dose and duration (Beers et al., 1991).

In 1997, using the same Delphi technique with a panel of 6 nationally recognized experts in gerontological therapeutics, Beers revised the criteria, naming 28 medications or classes of medications that should be generally avoided and 35 medications or classes of medications that should be avoided due to 15 common medical conditions (Beers et al., 1997). This was further revised by Fick et al. in 2003 to comprise of 48 individual medications or classes of medications to avoid in elderly and 20 diseases/conditions and medications to be avoided in adults with these conditions. Of these potentially inappropriate drugs, 66 were considered by the panel to have adverse outcomes of high severity (Fick et al., 2003).

More recently, this criteria was updated by the American Geriatrics Society (AGS) and an inter-disciplinary panel of 11 experts in geriatric care and pharmacotherapy who applied a modified Delphi method to the systematic review and grading in order to reach a consensus on the updated 2012 AGS Beers Criteria. Fifty-three medications or medication classes were included in the final list, which were divided into three categories: (1) potentially inappropriate medications and classes to avoid in older adults, (2) potentially inappropriate medications and classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate, and (3) medications to be used with caution in older adults. This update is stronger than previous approaches due to the use of an evidence-based approach based on the Institute of Medicine standards and the development of a partnership to regularly update the Criteria. Proper

application of the AGS 2012 Beers Criteria will allow for (a) closer monitoring of drug use, (b) application of real-time e-prescribing and interventions to decrease ADEs in older adults, and (c) better patient outcomes (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012).

The updated Beers list includes several agents with anticholinergic properties as the risks for these agents outweigh the benefits. One of the quality of care indicators in the Accessing Care of Vulnerable Elders (ACOVE) for elderly patients also recommends to avoid drugs with strong anticholinergic properties. Adverse effects of anticholinergic agents are of significant concern in the elderly because of polypharmacy, co-morbidities and age-related changes in pharmacokinetics and pharmacodynamics parameters.

## ANTICHOLINERGIC DRUGS

Anticholinergics comprise drugs from a multitude of therapeutic classes. They are broadly classified under two categories. (1) Drugs that are specifically used for their anticholinergic properties - Antiparkinsons, Antispasmodics, Antimuscarinics such as atropine or oxybutynin. (2) Drugs that have anticholinergic properties that are not fundamental to the primary indication and are therefore generally considered undesirable because they can produce adverse effects - Antihistamines, Antipsychotics, Antidepressants such as brompheniramine or amitriptyline (Carnahan et al., 2004). Anticholinergic medications block the action of neurotransmitter acetylcholine on the parasympathetic nervous system and are commonly prescribed to the 36 million older Americans for treating conditions such as allergies, depression, hypertension, Parkinson's disease, vertigo, asthma, cardiovascular disease, urinary incontinence, psychotic symptoms and behavioral problems. However, they are associated with multiple

adverse effects to which older individuals are particularly more susceptible, causing a range of peripheral and central side-effects. Central anticholinergic effects include memory deficits, confusion and disorientation, agitation, hallucinations and delirium. In the extreme, anticholinergic toxicity depresses brain function, with coma and circulatory collapse. Peripheral side-effects include dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating and anxiety, and tachycardia (Mintzer, 2000)

Elderly people are particularly vulnerable to anticholinergic-related cognitive effects for two main reasons. First, elderly have a high probability of being exposed to anticholinergics owing to their high medical comorbidity and their use of multiple prescribed and over-the-counter medications (Flacker et al., 1998; Blazer., 1983; Mulsant et al., 2003). Second, older adults are more sensitive to develop serious anticholinergic-related cognitive adverse effects owing to their age (Tune, 2001) .Tune et al. studied the anticholinergic effects of 25 drugs most frequently prescribed in the elderly and found that 10 of these had levels that had been associated with impairments in the memory and attention in normal elderly subjects. Hence, drugs with anticholinergic effects are considered potentially inappropriate for prescribing in the elderly population (Tune et al., 1992)

## ANTICHOLINERGIC MEDICATIONS AND SCALE

Anticholinergics, based on the degree of their action can be classified in different ways. Evidence in previous literature suggests that there were six scales available for rating anticholinergic drugs; Drug Risk Number, Clinician Rated Anticholinergic Score, Drug Burden Index, Anticholinergic Risk Scale, Anticholinergic Cognitive Burden Scale, and Anticholinergic Drug Scale. The first anticholinergic scale was developed by William K. Summers in 1978 as

Drug Risk Number (DRN). This scale calculates exposure to psychoactive drugs as the drug risk number (DRN) where: DRN = (class of agent) x (daily effective dosage). The drugs were classified as Class I, Class 2 and Class 3. Class I included known synergistic effect with anticholinergic agents, but not known as a direct cause of acute organic mental syndrome. Class II comprised of agents known to cause delirium, but currently not documented to have CNS anticholinergic properties. Class III included agents known to cause delirium reversed by CNS active anticholinesterases or known to have central nervous system anticholinergic effect and to cause delirium . Similar parameters were set for Daily effective dosage: Dosage level 1 - that dose range which would not give therapeutic effect for a twenty-four hour period; Dosage level 2 - that dose range which would give therapeutic effect for a twenty-four hour period if administered in equal appropriately divided doses; Dosage level 3 - that dose range which exceeds the usual therapeutic range for a twenty-four hour period. This scale was developed for 62 medications. Medications that were not included in this list were given a score of 0 (Summers, 1978; Han et al., 2001).

However, Summers' DRN classification did not include newer medications, Han and Colleagues developed an alternative scale for anticholinergic medication exposure, a Clinician Rated Anticholinergic Score (CR-ACh) - an ordinal scale originally developed to assess potential effects of anticholinergic medication use on severity of delirium symptoms in elderly patients with scores ranging from 0 (no effect) to 3 (strong effect). A clinician-rated anticholinergic score was used to quantify potential anticholinergic effects of each study medication. This scale established a list of 340 medications and then assessed the inter-rater reliability of 3 expert geriatricians who rated them between 0 (no activity) to 3 (high activity). However, strong association was found between the mean of clinician ratings for the 340

medications with median ratings for Summers Class of drug and laboratory data (Han et al., 2008; Han et al., 2001).

Further in 2007, Hilmer and his colleagues developed the Drug Burden Index – an evidence based tool for measuring an individual's total exposure to anticholinergic and sedative drugs, using the principles of dose-response and maximal effect. With the use of data from existing studies on the effects of medications on physical and mental function in older people, a formula for drug burden was derived. Medications were characterized with respect to risk into 3 groups: (1) drugs with anticholinergic effects, (2) drugs with sedative effects, and (3) total number of medications (Gnjidic et al., 2012; Wilson et al., 2011; Hilmer et al., 2007).

Recently, the Anticholinergic Risk Scale (ARS) was developed by Rudolph et al in 2008. This scale was a tool for estimating the extent to which an individual patient may be at risk of anticholinergic adverse effects that can lead to cognitive dysfunction and delirium. The ARS ranked medications for anticholinergic potential on a 3-point scale (0, no or low risk; 3, high anticholinergic potential). The ARS score for a patient was calculated as the sum of points for his or her number of medications. The experts reviewed the medical literature, the National Institute of Mental Health Psychoactive Drug Screening Program and the Micromedex databases to determine medications with known potential to cause anticholinergic adverse effects of the 500 most prescribed medications within the Veterans Affairs Boston Healthcare System with the help of 1 geriatrician and 2 geropharmacists (Rudolph et al., 2008).

Further, Boustani et al. established the anticholinergic Cognitive Burden (ACB) scale which was a practical tool used to identify the severity of anticholinergic effects on cognition of prescribed and over-the-counter medications. Drugs with possible anticholinergic effects (affinity for muscarinic receptors but no clinically relevant negative cognitive effects) are given a

score of 1. Drugs with established and clinically relevant cognitive anticholinergic effects are given a score of 2 or 3, based on blood-brain barrier permeability and association with development of delirium. All other drugs with no anticholinergic effects can be considered as having a score of 0. The total added score of different drugs taken by the patient determines the accumulative anticholinergic cognitive burden (The Anticholinergic Cognitive Burden, 2012; Campbell et al., 2009; Boustani et al., 2008).

However, the most efficient rating scale of anticholinergic medications was established by Carnahan and colleagues as the Anticholinergic Drug Scale which determined their anticholinergic property based on their effects on the Serum Anticholinergic Activity (SAA). Serum anticholinergic activity (SAA), despite a number of limitations, is still considered the current gold standard in quantifying anticholinergic burden (Carnahan et al., 2002). In this scale, drugs are rated in an ordinal fashion from 0 to 3, with 0 signifying no known anticholinergic activity and 3 signifying marked anticholinergic activity. Scores of all the medications a subject receives are then summed to determine a total score (Carnahan et al., 2006). This scale was previously referred to as the Clinician-Rated Anticholinergic Scale–modified version due to the origin of the rating concepts and original ratings (Han et al., 2001). However, the name had been changed to the Anticholinergic Drug Scale (ADS) for brevity. Many of the high level ADS medications are included in the 2012 AGS criteria.

## USE OF ANTICHOLINERGIC IN THE ELDERLY AND DEMENTIA PATIENTS

Anticholinergic medications are widely prescribed among the elderly population (Carnahan et al., 2004). In the United States, 51% of the general population use anticholinergic medications (Cancelli et al., 2008). Depending on the sample characteristics and the definition of

anticholinergic medications used, the prevalence of anticholinergic drugs use in the community-dwelling elderly population varies from 6.9% to 47%. Due to this high prevalence, the patients may have a high potential for mental and physical impairment and hence they are inappropriate in the elder population. Elderly are more vulnerable to these drugs because of physiological and pathological changes that often accompany the aging process.

Anticholinergic medication use in dementia patients is of significant concern because of the pathophysiology of the disease and the mechanism of action of anticholinergic medications. Patients with dementia undergo progressive cognitive decline due to damage to the cholinergic neurons system, and the central adverse effects of anticholinergic medications can lead to worsening of cognitive function impairment (Kemper et al., 2007; Rudolph et al., 2008). Consequently, dementia patients are more vulnerable to develop anticholinergic medication-induced cognitive impairment and psychiatric adverse effects than general population (Roe et al., 2002; Chan et al., 2006). There are few previous studies that have shown the association of anticholinergic medications use and cognitive decline, delirium and dementia in elderly general population (Carriere et al., 2009, Campbell et al., 2011).

## STATEMENT OF PROBLEM

Potentially inappropriate medications (PIMs) continue to be prescribed for the most vulnerable elderly population, despite evidence of poor outcomes from their utilization in elderly. PIMs now form an integral part of policy and practice and are incorporated into several quality measures (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012). Although treatment guidelines such as the Beers criteria can be used to identify inappropriate medications in the elderly (Fick et al., 2004), 12% to 21% of older patients in the United States use such agents (Curtis et al., 2004; Pitkala et al., 2002).

Medications with anticholinergic properties have frequently been cited in the literature as causing an increase in adverse events due to inappropriate prescription. Such conditions often lead to consequences such as falls, impulsive behavior, and loss of independence. Higher rates of cognitive dysfunction and delirium are found in patients experiencing a greater anticholinergic load (Ancelin et al., 2006; Mulsant et al., 2003). The anticholinergic drugs constitute a high proportion in the list of potentially inappropriate medications. Some studies have determined the prevalence and predictors of inappropriate medication use but their findings are limited to specific populations and selected settings. However, no study has evaluated the prevalence of inappropriate anticholinergic medication and its predictors in nationally representative population. Identification of predictors will help us to optimize anticholinergic medication use in elderly and improve future prescribing patterns. The AGS 2012 Beers Criteria being the latest update, is the most ideal version to identify inappropriate medications. Since this update is built on an evidence-based approach, it is more strong and accurate in identifying the inappropriate medications.

As discussed earlier dementia patients are more vulnerable to develop anticholinergic medication-induced adverse effects than general population. There are studies that have found the prevalence and predictors of anticholinergic medication use in elderly dementia patients. However, the prevalence and predictors of inappropriate anticholinergic medication use in elderly dementia patients is still unknown. Identification of these predictors will help us to achieve appropriate anticholinergic medication use in elderly dementia population, thereby controlling further decline in their mental cognition.

## OBJECTIVES

The objectives of this study were to:

1) Determine the prevalence of inappropriate anticholinergic medication use in the elderly and elderly with dementia patients.
2) Determine the predictors of inappropriate anticholinergic medication use in the elderly
3) Determine the predictors of inappropriate anticholinergic medication use in elderly dementia patients.

# CHAPTER 2
# LITERATURE REVIEW

This chapter describes literature related to prevalence and predictors of potentially inappropriate medication prescriptions in general and anticholinergic medications in specific.

## POTENTIALLY INAPPROPRIATE MEDICATION PRESCRIPTIONS

### *Studies in The United States*

A study conducted by Piecoro et al., (2000) examined the prevalence of potentially inappropriate drug use in Medicaid recipients aged 65 years and older who received a prescription. This cross-sectional retrospective study found that 27% of patients received atleast one potentially inappropriate agent. Prevalence was higher for nursing home residents (33%) than for community dwellers (24%). Amitriptyline (7.6%), propoxyphene (6.5%), doxepin (4.0%), and indomethacin (2.3%) were the most prescribed potentially inappropriate agents. Out of these four drugs mentioned, amitriptyline and doxepin have strong anticholinergic properties. (Piecoro et al., 2000)

A study conducted by Lau et al. (2004) estimated the scope of potentially inappropriate medication prescriptions (PIRx) among elderly residents in U.S. nursing homes (NHs), and examined associated resident and facility characteristics. The 1996 Medical Expenditure Panel Survey (MEPS) Nursing Home Component was used wherein, the PIRx, defined by Beers criteria (1991, 1997), were identified using up to a year's worth of NH prescribed medicine data for each resident. The study found that 50% of all residents aged 65 or older, with an NH stay of three months or longer received at least one PIRx in 1996. The most common PIRx involved

propoxyphene, diphenhydramine, hydroxyzine, oxybutynin, amitriptyline, cyproheptadine, iron supplements, and ranitidine. Majority of these are highly anticholinergic in nature. Resident factors associated with greater odds of PIRx were Medicaid coverage, no high school diploma, and non-dementia mental disorders. Facility factors were more beds and lower RN-to-resident ratio.

Further, a study by Caterino et al., (2004) determined the national rate and trend of inappropriate medication administration to elderly emergency department (ED) patients. The secondary objectives were to identify risk factors for receiving an inappropriate medication and to determine whether administration is sometimes justified based on diagnosis. This retrospective study involved analysis of ED visits in the 1992–2000 National Hospital Ambulatory Medical Care Survey wherein the inappropriate medications were identified using Beers' 1997 explicit criteria. The study found that inappropriate medications were administered in about 12.6% of elderly ED visits from 1992 to 2000. There were six drugs that accounted for 70.8% of inappropriate administration: promethazine (22.2%), meperidine (18.0%), propoxyphene (17.2%), hydroxyzine (10.3%), diphenhydramine (7.1%), and diazepam (6.0%). Out of these, promethazine, hydroxyzine and diphenhydramine (46.5%) were associated with strong anticholinergic properties. The multivariate analysis indicated 'number of ED medications' as the strongest predictor of inappropriate medications. Diagnoses indicated that potentially appropriate uses of these medications were rarely present.

Another study by Curtis et al., (2004) determined the extent of potentially inappropriate outpatient prescribing for elderly patients, as defined by the Beers revised list of drugs (1997) to be avoided in elderly populations. This retrospective cohort study was conducted using the outpatient prescription claims database of a large, national pharmaceutical benefit manager. The

study found that amitriptyline and doxepin accounted for 23% of all claims for Beers list drugs, and 51% of those claims were for drugs with the potential for severe adverse effects. The most commonly prescribed classes were psychotropic drugs and neuromuscular agents. Both these classes are strongly anticholinergic in nature.

Another study by Lau et al. (2005) examined the association of potentially inappropriate medication prescribing (PIRx) with hospitalization and death among elderly long-stay nursing home residents. This study used data from the 1996 Medical Expenditure Panel Survey (MEPS) Nursing Home Component and defined PIRx using the combined version of the Beers criteria There were 3372 residents, 65 years and older, who had nursing home stays of 3 consecutive months or longer in 1996. The study found that residents who received any PIRx had greater risk of being hospitalized and greater risk of death in the following month than those receiving no PIRx. Therefore, it concluded that PIRx was associated with subsequent adverse outcomes (hospitalization and death).

Another study by Perri III et al. (2005) identified the prevalence of inappropriate medication use among elderly patients in Georgia nursing homes using the Beers criteria and identified the relationship between inappropriate drug use and the likelihood of an adverse health outcome. This cohort study used Medicaid data to review 1117 patient medical records in 15 nursing homes with a high risk of polypharmacy. The prevalence of inappropriate medication use was estimated, as defined by the Beers criteria and the adverse health outcomes of hospitalizations, emergency department visits, or deaths were identified from Medicaid claims. The study found that 46.5% patients received at least one inappropriate medication and 12.8% patients experienced atleast one adverse health outcome. Further analysis revealed that revealed that the total number of medications taken (OR 1.139, 95% CI 1.105 to 1.173) significantly

increased the likelihood of receiving an inappropriate drug, while having a diagnosis of "dementia" (OR 0.748, 95% CI 0.565 to 0.991) decreased the likelihood. Inappropriate medication use increased the likelihood of experiencing atleast one adverse health outcome more than twofold (OR 2.34, 95% CI 1.61 to 3.40). The study concluded that inappropriate use of medication in the elderly is associated with a higher risk of adverse health outcomes.

A very recent study by Jones et al. (2013) examined the Potentially Inappropriate Medication (PIM) prevalence in elderly patients with Chronic Kidney Disease (CKD). The study included around 100 patients with CKD above the age of 70 years between January 2008 and June 2008 at a University Teaching Hospital. PIMs were defined using the modified Beers' criteria and latest British National Formulary (BNF) guidance for prescribing in patients with renal impairment. The study found that 56 patients had one or more PIMs prescribed during the acute admission period. 81 out of the 622 medications prescribed were 'inappropriate'; therefore, the prevalence of PIMs prescribed in this case was 13%. The study therefore, concluded high prevalence of PIMs in elderly inpatients with CKD.

***Studies in Other Countries***

A study conducted by Dhalla et al. (2002) compared the prevalence of inappropriate prescribing before and after nursing home admission and determined patient and physician characteristics associated with it. This pre/post retrospective cohort study involved all the licensed nursing homes in Ontario, Canada. 19,911 individuals, aged 66 and older, newly admitted to nursing homes between April 1, 1997 and March 31, 1999 were included. For every patient, Beers' criteria was used to characterize and compare the prevalence of inappropriate prescribing before and after nursing home admission. The study found that the proportion of

patients receiving a prescription for at least one inappropriate drug decreased from 25.4% before nursing home admission to 20.8% afterward ($P < 0.001$). Significant predictors included patients younger than 85, having more than one prescriber, having a physician aged 50 years or older, having a male physician, having a nonspecialist physician, having a nonurban physician, and having a physician practicing outside the greater Ontario metropolitan area. The study concluded that prevalence of inappropriate prescriptions declined after nursing home admissions. Targeted interventions such as regionally based education programs or drug use restrictions could have reduced the prevalence of inappropriate prescribing.

Another study conducted by Apoteket et al. (2007) in Sweden evaluated drug therapy quality among elderly nursing home residents and compared quality in young and old elderly to determine whether number of prescribers affected quality of drug therapy. This cross-sectional population-based study included all nursing home residents, aged 65 years and older in the Gothenburg area using the multi-dose system. The outcome, that is, quality of drug therapy was assessed using five quality indicators for the elderly. The study found that over 70% of residents had one or more potentially inappropriate prescription. Younger nursing home residents (65-79 years) had significantly lower quality of drug therapy than older residents (>80 years). An increasing number of prescribers per resident were associated with a higher number of drugs prescribed and a lower quality of drug therapy. The study therefore, concluded that computerized quality assurance systems could provide support for healthcare providers.

***Summary of studies***

The above mentioned studies indicate a high prevalence of potentially inappropriate prescription of medications in elderly, ranging from 12.6% to 70%. This increased prevalence is

associated with higher risk of adverse health outcomes including greater risk for subsequent hospitalizations and death. Moreover, the predictor studies illustrate that inappropriate medication prescription is associated with increasing number of medications (polypharmacy), which is common in elderly and, that in turn increases the probability of adverse health outcomes. Other predictors include medicaid coverage, no high school diploma, non-dementia mental disorders, diagnosis of dementia, age > 85 years, more than one prescriber, physician aged 50 years or above, male physician, non-specialist physician, and non-urban physician. This is also mentioned in the literature that majority of the inappropriately prescribed medications were strongly anticholinergic in nature.

## ANTICHOLINERGIC MEDICATION USE

### *Studies in the United States*

In a study by Seifert et al. (1983), the Medicare Utilization Review Committee conducted a survey to determine the use of drugs with anticholinergic effects in confused elderly nursing home patients. It was found that 29 patients (34.5%) were receiving anticholinergic drugs, predominantly from the antidepressant and antipsychotic class. Thioridazine was the most frequently used antipsychotic. The study concluded that anticholinergics could increase the risk of or exacerbate existing confusion, and this possible anticholinergic activity of drugs should be considered when prescribing for elderly patients.

A study by Tune et al. (1992) investigated the anticholinergic effects of 25 drugs most frequently prescribed in the elderly using radioreceptor assay. While some of these drugs were typically associated with the anticholinergic side-effects, others were not. Fourteen had detectable anticholinergic drug levels; ten of these had levels that have been associated with impairments in memory and attention in normal elderly subjects. The results indicated that

patients taking multiple medications, usually elderly were at increased risk of side-effects for psychotropic drugs, most of which have anticholinergic effects. (Tune et al., 1992)

A study by Roe et al. (2002) compared the prevalence of anticholinergic use in community-based older adults with probable dementia as the treatment group and the group of older adults who were unlikely to have dementia as the comparison group. This comparison was done over a period of 3- to 12-month follow-up using Pharmacy Claim data. This study found that the prevalence of patients taking at least one anticholinergic drug was 33% for the treatment group and 23.4% for the comparison group. Whereas, the prevalence rate for patients with the multiple use of anticholinergic drugs over the entire follow-up period was 26.1% and 20.4% for treatment and comparison group respectively. Authors concluded that dementia older patients were prescribed more anticholinergics (Roe et al., 2002).

A study by Carnahan et al. (2004) measured the prevalence of anticholinergic use cross-sectionally in patients receiving cholinesterase inhibitors and described change in use of anticholinergics upon inception of cholinesterase inhibitor treatment. The study participants were Iowa Medicaid beneficiaries aged 50 and older with a pharmacy claim for a cholinesterase inhibitor during January 1997 through February 2000. Anticholinergic use was determined for all patients with a cholinesterase inhibitor pharmacy claim during January and February of 2000. The study found that out of 557 patients receiving a cholinesterase inhibitor, 197 (35.4%) received an anticholinergic concurrently. Of all anticholinergics, 74.5% (178/239) were identified as inappropriate for use in the elderly, 22.2% (53/239) under any circumstances. The study concluded that the concurrent use of anticholinergics and cholinesterase inhibitors is common although rarely appropriate.

Another study by Ness et al. (2006) assessed the prevalence of anticholinergic symptoms, corresponding symptom burden, and anticholinergic-related ADEs in a sample of community-dwelling elderly veterans. This prospective cohort study was conducted at the Veterans Affairs Medical Center (VAMC) primary care clinics with the sample size of 532 patients. The inclusion criterion for the study was the older patients taking ≥5 scheduled medications. This study found the prevalence of 27.1% for the use of anticholinergic medications in older veteran patients having intact cognitive function. The study concluded that elderly veterans with intact cognitive function were commonly using anticholinergic drugs and there were high prevalence of dry mouth and constipation with this drug use (Ness et al., 2006).

Another study by Kemper et al. (2007) determined prevalence of OTC and prescription medications use with potential anticholinergic side effects among 193 older adults (age >50 years) with memory problems. The study involved clients seen between October 1999 and April 2004 and performed a secondary analysis of the medications older adults (older than 50 years) were taking at their initial clinic visit. The findings revealed that 10.3% of these older adults were consuming one or more OTC or prescription medications with anticholinergic side effects. (Kemper et al., 2007)

Further, a cross-sectional study conducted by Kolanowski et al. (2009) described the anticholinergic burden experienced by dementia patients using the Anticholinergic Cognitive Burden (ACB) Scale. The results again indicated a high prevalence of anticholinergic use. 81.6% subjects were prescribed at least one drug with anticholinergic properties and 36.7% were prescribed at least one drug with severe anticholinergic properties.

Another study by Chatterjee et al. (2010) examined the anticholinergic medications utilization and factors associated with these medications use in elderly nursing home patients with dementia. The study used 2004 US National Nursing Home Survey (NHHS) data and identified anticholinergic drugs using the Anticholinergic Drug Scale (ADS) which classifies anticholinergic drugs into four levels in increasing order of their anticholinergic activity. The Anderson Behavioral Model was used to determine the factors associated with anticholinergic medications use. The study evaluated the prevalence rate 67.96% for level-1 drugs and 21.27% for level-2 or level-3 medications. The predictors that decreased the likelihood of receiving higher-level anticholinergic medications were age, dependence in decision making ability and behavioral symptoms whereas the predictors such as Medicaid as the source of payment, mood indicators, total number of medications and schizophrenia, anxiety and Parkinson's disease increased the likelihood of such medications (Chatterjee et al., 2010).

A recent study by Bhattacharya et al. (2011) studied patterns and predictors of prescribing anticholinergic drug in elderly outpatients with dementia from 2006-2007 using National Ambulatory Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) data. The anticholinergic drugs were identified using the Anticholinergic Drug Scale (ADS) with four levels (0-3) of drugs with anticholinergic activities. The study showed that 43% of the patients were prescribed at least one anticholinergic drug and 10.07% of the elderly were prescribed levels 2 and 3 anticholinergic medications. The predictors such as age, acetylcholinesterase inhibitor use and comorbid mood disorders were negatively associated with prescribing of anticholinergic medications. The number of medications prescribed increased the likelihood of receiving these prescriptions. The study concluded that one in 10 of outpatient

visits by elderly dementia person involved prescribing medications with anticholinergic properties (Bhattacharya et al., 2011).

Very recently, a systematic review by Gerretsen et al. (2011) aimed to provide a current perspective on the utilization and safety of anticholinergic medications. The review performed Medline and Pubmed literature searches (1966 - the present) using 'anticholinergic' and 'drug safety'. The expert opinion stated that the prescribers were required to be more vigilant for adverse anticholinergic effects, particularly in older patients. The symptoms, ranging from subtle cognitive impairment to delirium, could be attributed due to the cumulative effects of multiple medications of modest antimuscarinic activity.

***Studies in Other Countries***

A study in France by Carriere et al. (2009) in his 3-City study evaluated the effect of high intake of anticholinergic medications among community-dwelling elderly persons on the cognitive decline and dementia. The recruited population-based cohort included 4128 women and 2784 men with age 65 years or older. The anticholinergic use was observed at baseline and 2 and 4 years later. The result of this study found that at baseline, a total of 7.5% of the participants used anticholinergic medications of whom 6.9% were taking two drugs simultaneously and 1.5% was taking three medications. The main classes of drugs consisted of antispasmodics, antidepressants, antipsychotics, anxiolytics, antiasthmatics, and antiparkinsons (Carriere et al., 2009).

Another study by Jessen et al. (2010) in Germany examined the anticholinergic drug use using the data from the German Study in Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe) in Germany. The individuals with age >75 years were selected randomly

from the GP registries without dementia and were followed longitudinally for 54 months with three points of investigation at 18 months intervals. They found that 37% of the participants used anticholinergic drugs at least at one point of time. The most frequently anticholinergic drugs were cardiovascular agents, analgesics/anti-inflammatories, and antidepressants (Jessen et al., 2010).

A study conducted by Wawruch et al. (2011) evaluated anticholinergic medication use in elderly patients and identified the risk factors that increase their prescription. The study involved a sample of 1636 patients which were hospitalized in the three municipal hospitals during a period of one year (1 January 2008 to 31 December 2009) in Slovakia. For identifying the risk factors, they compared socio-demographic, clinical characteristics and comorbid conditions of users and non-users of such drugs and used binary logistic regression model for all the risk factors. The study demonstrated relatively high prevalence of 10.5% and 14.2% anticholinergic medications users at the time of hospital admission and discharge respectively. The study also found that the most important risk factors that increased the probability of use of such medications were immobilization, constipation, gastroduodenal ulcer disease, and psychiatric comorbidities like depression, epilepsy, Parkinson's disease (Wawruch et al., 2011).

Similarly, Kumpala et al. (2011) determined the prevalence and predictors of anticholinergic drug and the possible association between anticholinergic drug use and mortality among 53 long-term care wards in Helsiniki in 2003. This prospective cohort study determined the anticholinergic drugs using the Anticholinergic Risk Scale (ARS). The study found that 36% had a mild anticholinergic load (ARS score = 1-2) and 19% had high anticholinergic load (ARS score ≥3). Stroke, depression, other psychiatric illness and parkinson's disease were found to be predicting anticholinergic medication use. (Kumpala et al., 2011)

Recently, Fox et al. (2011) with the use of the Medical Research Council Cognitive Function and Ageing Study between 1991 and 1993 determined the possible and definite anticholinergic medication use in UK. This was a 2-year longitudinal study of 13,400 community-dwelling and institutionalized participants, aged 65 and older that determined the anticholinergic drugs with the help of Anticholinergic Cognitive Burden Scale. The study found that 47% of the population used the medications with possible anticholinergic properties and 4% used a drug with definite anticholinergic properties at baseline (Fox et al., 2011).

***Summary of Studies***

Overall, the prevalence studies provide us with a clear background of high percentage of anticholinergic medication utilization in the elderly, ranging from 7.5% to 81.6%. This prevalence has been obtained from specific data population groups, such as patients from Pharmacy Claims, Veterans Affairs Medical Center (VAMC) primary care clinics, long-term care facilities or nationally representative samples from NHHS and NAMCS & NHAMCS. There are four studies that examined the determinants of anticholinergic drugs use. Two out of four studies were performed in elderly dementia patients in US and other two studies were performed in Slovakia and Finland in elderly population. These studies found that several factors were associated with anticholinergic use. These include polypharmacy, dementia diagnosis, age, dependence in decision making ability and behavioral symptoms, medicaid as source of payment, mood indicators, schizophrenia, anxiety, parkinson's disease, immobilization, constipation, gastro-duodenal ulcers, depression, epilepsy, and stroke.

## GAPS IN LITERATURE

The fact that the prevalence of inappropriate prescribing remains alarmingly high for the elderly is incontrovertible, providing a critical challenge to the nation's health system. Since the elderly individuals currently make up over 12.5% of the U.S. population, the sustained high prevalence of inappropriate prescribing in the elderly constitutes a significant threat to public health, safety and cost-effective health care. Literature review identified that inappropriate prescribing leads to adverse drug reactions (ADRs), an important medical problem, resulting in hospitalizations. These hospitalizations are further associated with increased in-hospital costs and a substantial increase in morbidity and mortality. The updated 2012 AGS Beers' criteria is of great significance because it allows for accurate prescribing and closer monitoring of drug use. Literature also revealed that majority of inappropriate medications are strongly anticholinergic in nature. Hence, the need to study inappropriate prescription of anticholinergic medications in this population arises.

Furthermore, high utilization of anticholinergic medications in the elderly population is evident in the literature. Many studies have indicated high prevalence of patients taking many anticholinergic drugs concurrently. Their activity in the elderly necessitates thoughtful consideration before prescription. One of the studies stated 74.5% of all anticholinergics to be inappropriate for use in the elderly. Anticholinergic medications can lead to a confused state of mind as well as cause impairment in memory and attention in normal elderly. Here also, literature revealed numerous predictors for anticholinergic drug use that include polypharmacy, dementia diagnosis, age, dependence in decision making ability and behavioral symptoms, medicaid as source of payment, mood indicators, schizophrenia, anxiety, parkinson's disease,

immobilization, constipation, gastro-duodenal ulcers, depression, epilepsy, and stroke. Moreover, there are rarely any studies conducted on population-level data.

However, a substantial subset of the listed agents in the Beers' criteria does share a common pharmacologic property, in that they demonstrate anticholinergic activity. Considering that anticholinergic agents identified in the Beers List can all contribute to a similar constellation of adverse effects in the elderly (delirium, falls, low blood pressure, urinary retention, and cardiac arrhythmias), process measures that focus specifically on these potentially inappropriate anticholinergic agents may be effective in assessing quality of prescription drug use and also facilitate the development of effective, focused clinical interventions. Moreover, there is no existing literature regarding the inappropriate prescription of anticholinergic medications in the elderly. Also it is not clear that which anticholinergic medication should be regarded as inappropriate in the elderly population. So it is necessary to understand and operationalize the definition of inappropriate anticholinergic medications in the elderly population. Hence, it would be important to study the prevalence and predictors of inappropriate anticholinergic prescription in the elderly. A comprehensive model like Anderson Behavior Model will provide detailed information with regards to determinants that predict prescription of inappropriate anticholinergic medications in elderly.

Further, literature suggests that anticholinergic medications, that are associated with significant adverse effects, may lead to worsening of cognitive impairment, particularly in elderly dementia patients. Few studies have determined the prevalence and predictors of anticholinergic medications in elderly dementia patients. However, there is no literature regarding inappropriate prescription of anticholinergic medications in this vulnerable population. Given the fact that elderly dementia patients have increased sensitivity towards anticholinergic

drug use, it is important to know the extent and factors responsible for inappropriate anticholinergic medication use in this population.

# CHAPTER 3
# METHODS

This section describes the methodology used to achieve the study objectives including data source, study design and sample, operational definitions, conceptual model, data files and analytical approach. The study first determined the prevalence of inappropriate anticholinergic medications use in elderly and elderly dementia patients. Secondly, it determined the predictors of inappropriate anticholinergic medications use in elderly patients. Thirdly, it determined the predictors of inappropriate anticholinergic medications use in elderly dementia patients.

## DATA SOURCE

The Medical Expenditure Panel Survey (MEPS) is a national representative survey of health care utilization including medications, expenditures, sources of payment and insurance coverage for the US civilian non-institutionalized population. It is administered by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for Health Statistics (NCHS), the U.S. Department of Health and Human Services (DHHS). AHRQ conducted two surveys prior to MEPS: first was conducted in 1977, the National Medical Care Expenditure Surveys (NMCES), and second in 1987, the National Medical Expenditure Surveys (NMES). Since 1996, AHRQ started conducting MEPS to provide more timely information about the nation's changing health care system and it is conducted annually thereafter. MEPS is a multi-stage probability survey, which collects data on the health services that Americans use, frequency and cost of use, and costs associated and payment of the services, as well as data on the private health insurance available to the U.S. civilian non-institutionalized population. MEPS

from its probability sampling provide national level weights from which national level estimation can be made. The MEPS data is publicly available online at http://meps.ahrq.gov/mepsweb/; the most recent yearly data posted on the website is 2010.

The MEPS has two major components: the Household Component (HC) and Insurance Component (IC). It also has two other components: Medical Provider Component (MPC) and Nursing Home Component (NHC). The MEPS household sample, which provides the basis for HC and MPC data collection, is selected from participants in the previous year's National Health Interview Survey (NHIS) (Cohen et al., 2009)

The MEPS Household Component is the main survey designed to provide annual national estimates of the health care use, medical expenditures, sources of payment, and insurance coverage for the US civilian non-institutionalized population. Besides, it also provides data on individuals' health status, demographic characteristics, employment, access to health care and satisfaction with care which can be aggregated to obtain estimates for families and population subgroups of interest. MEPS involves a complex survey design involving oversampling of Blacks and Hispanics, which makes studying minority populations feasible. Oversampling aims at improving the precision of estimates for these subpopulations groups by increasing the sample size. The MEPS-HC consists of an overlapping panel design (Figure 3.1) in which any given sample panel is interviewed a total of 5 times in person over a period of about 30 months. As a result data for two calendar years is obtained. Data collection is done through computer-assisted personal interviewing technique. The data collection process is conducted every year on a new sample of households, thus providing overlapping panels of survey data when combined with the ongoing panel.

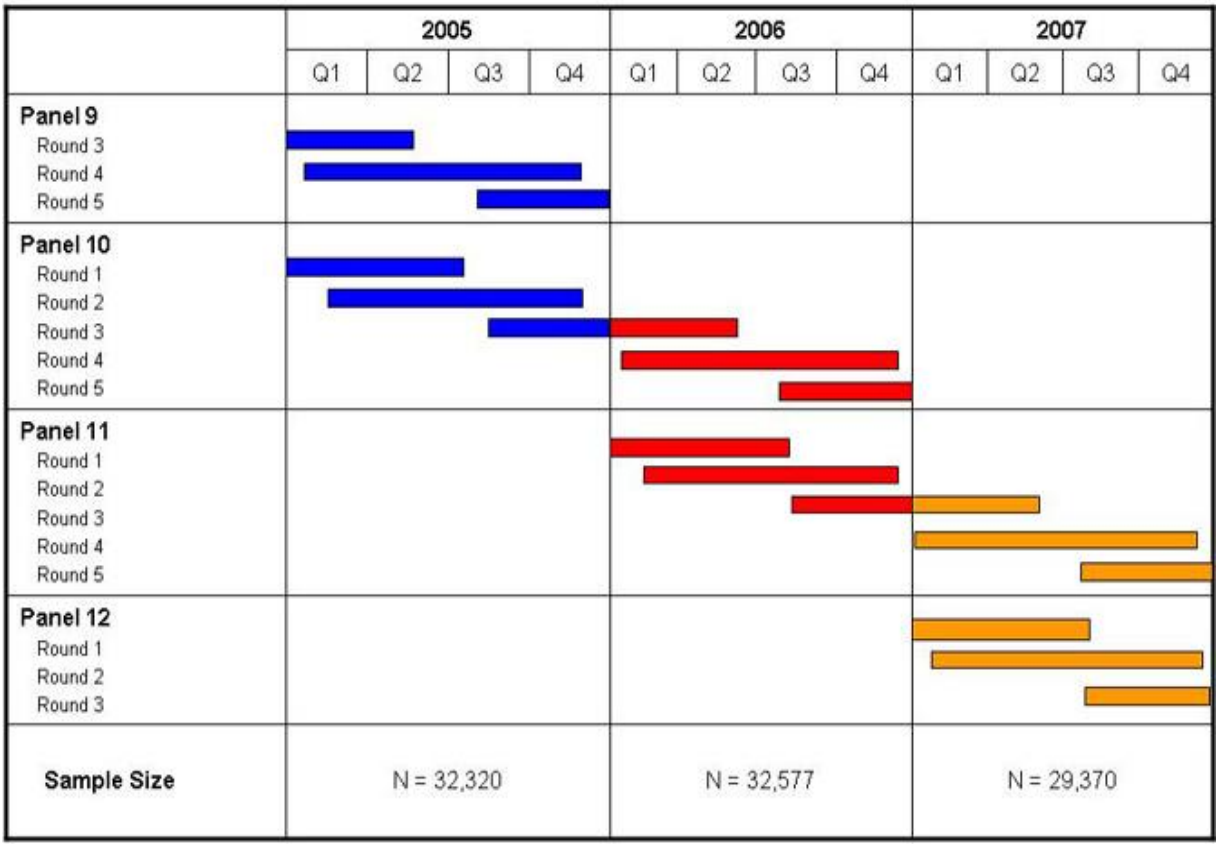


**Figure 3.1: MEPS panel design** (Source: www.meps.ahrq.gov)

The MEPS Medical Provider Component (MPC) is a supplement to the household component to confirm the information provided by the interviewer. It collects data from hospitals, physicians, home health care providers, and pharmacies identified by MEPS-HC participants. The MPC data collects information on charges, payments, diagnoses which are coded by ICD-9 CM (International Classification of Disease, the ninth edition, Clinical Modification) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, the fourth edition) codes, physician procedures which are classified by CPT-4 (Current Procedural Technology, the fourth version) codes, inpatients stays which are coded by DRG (Diagnosis-related Group) codes and prescribed medicines (medication names, national drug codes (NDC), strengths, quantities, dosages and dose forms, etc.). Upon completion of the household CAPI

interview and obtaining permission from the household survey respondents, a sample of medical providers are contacted by telephone to obtain information that household respondents cannot accurately provide.

The Insurance Component (IC) collects data from private and public sector employers the number and types of private health insurance plans offered, benefits associated with these plans, annual premiums, annual contributions by employers and employees, eligibility requirements, and employer characteristics. MEPS-IC selects the establishments based on the US Census bureau list. The main purpose of IC is to measure availability, enrollment, benefits and payment provisions and cost. The IC is not directly linked to the household survey. The data are collected by the Census Bureau and are protected under the confidentiality provisions of Title 13 (the Bureau's authorizing legislation). As a result, IC data are disseminated publicly only through summary data tables posted on the AHRQ website.

The Nursing Home Component (NHC) of MEPS was included only in 1996 on a sample of nursing homes and residents in the US. Information gathered consisted of the characteristics of the facilities and services offered; expenditures and sources of payment on an individual resident level; and resident characteristics, including functional limitation, cognitive impairment, age, income, and insurance coverage. The NHC also collected data on the availability and use of community-based care prior to admission to nursing homes. NHC data are available only at the Data Center located at AHRQ or one of the Census Bureau's Research Data Centers.

**Cross-Sectional And Longitudinal Analysis In MEPS** - Yearly data files of MEPS contain data collected from respondents during one calendar year, from January to December. Using these yearly files, both cross-sectional and longitudinal studies can be conducted. A unique

identifier is assigned to each respondent as well as the reported events. Panel file collects 2-years of information for each respondent; this data can be used for longitudinal analysis. A sampling weight variable is assigned to each respondent in order to generate national level estimates. For a larger analytical sample size multiple years and panel of MEPS data can be combined for both cross-sectional and longitudinal data analysis, respectively.

## DATA FILES AND DATA EDITING

Various files from MEPS Household Component were used in this study. Full-Year Consolidated data files and Medical Conditions files of MEPS-HC Full-Year files and Prescribed Medicines files of the MEPS-HC Event files were used for analysis. The Full-Year Consolidated data files are the main person-level files of the Household Component Full-Year files, which include all demographic and medical characteristics, as well as patient-reported responses to the main survey questions. Since the survey involves five interview rounds over the two-year panel, data from interview rounds 1, 2, and 3 are included for individuals in their first of two years, and data from interview rounds 3, 4, and 5 are included for individuals in their second of two years. The single-year consolidated data files can be thought of as the first half of one two-year panel survey stacked on top of the second half of another two-year panel survey. This file provided personal-level data on the following variables: survey administration, language of interview, demographics, parent identifiers, health status, disability days, access to care, employment, quality of care, patient satisfaction, health insurance, healthcare utilization, income and expenditure. There was also a person-level weight variable that was used to derive national estimates in order to assess the prevalence nationwide. To obtain analytic variables, the records on this file were linked to the MEPS public use data files using the sample person identifier (DUPERSID), which is a combination of dwelling unit id (DUID) and person id (PERSID).

The Medical Conditions files of the Household Component Full-Year files set provide information on the household-reported medical conditions along with the ICD-9-CM codes (International Classification of Diseases, Ninth Revision, Clinical Modification) and Clinical Classification codes. The patients having diagnoses of diseases that are positively and negatively related with anticholinergic medication use were identified using three digit ICD 9-CM codes and the Clinical Classification codes. The diseases that are positively related with anticholinergic medication use are the diseases where prescription of anticholinergic medications is essential for the treatment. However, diseases that are negatively related with anticholinergic medication use are the diseases where prescription of anticholinergic medications can worsen/exacerbate the diseased condition of any patient.

The Prescribed Medicines files of the Household Component Event files were used to identify the adults who received inappropriate anticholinergic drugs. Prescription medicines files are the event-level where each record represents a prescription medicine that has been purchased/obtained by the household respondent. Data in the prescription medication file of MEPS is self-reported by survey participants, and the information is validated by the pharmacy where the prescription was purchased. The medication prescription file of MEPS was used to identify prescription medications received by the patients.

Prescription medicines are coded in event file using National Drug Codes (NDC). Multum lexicon variables are included for therapeutic classification of medications. Medications in MEPS prescription event files data were classified according to Multum Lexicon Code system, where medications were categorized in large therapeutic classes and then in therapeutic subclasses and then in sub-subclasses, if any. National Drug Codes (NDC) was used to select inappropriate anticholinergic drugs users from the prescription medicine files. Multum Lexicon

Addendum file was used to identify NDC codes and then it was merged with MEPS prescription medicine file.

**OPERATIONAL DEFINITIONS**

- The elderly patients were defined as an individual 65 years or older.
- The inappropriate medications were identified using the American Geriatrics Society 2012 Beers Criteria which are divided into three categories: potentially inappropriate medications and classes to avoid in older adults, potentially inappropriate medications and classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate, and finally medications to be used with caution in older adults. The disease-independent inappropriate anticholinergic medications (irrespective of diagnosis) were defined as drugs/medications that were recommended to avoid in elderly due to their strong anticholinergic properties. However, the disease-dependent inappropriate anticholinergic medications (with respect to diagnosis) in elderly were defined as drugs/medications that were recommended to avoid in elderly because their strong anticholinergic properties could exacerbate the existing diseased condition. These drugs were identified using National Drug Codes (NDC); NDC codes were identified from Multum Lexicon Addendum File. Table 3.1 and 3.2 below, show inappropriate anticholinergic medications in elderly and elderly dementia patients respectively.
- All dementia patients were identified using ICD-9 CM codes of 290.XX, 294.XX or 331.XX or patients taking Cholinesterase Inhibitors or Memantine. Cholinesterase inhibitors and Memantine were identified from prescription medicines file using Multum Lexicon therapeutic classification code of 313 and prescription drug name respectively.

**Table 3.1: Inappropriate anticholinergic medications (disease-independent) for Elderly Patients as per 2012-AGS Beers' Criteria**

| Therapeutic Category of Drugs | Drugs |
|---|---|
| **Antihistamines** | Brompheniramine Carbinoxamine<br>Chlorpheniramine Clemastine<br>Cyproheptadine Dexbrompheniramine<br>Dexchlorpheniramine Diphenhydramine (oral)<br>Doxylamine Hydroxyzine<br>Promethazine Triprolidine |
| **Antiparkinson's** | Benztropine (oral) Trihexyphenidyl |
| **Antispasmodics** | Atropine Products Belladonna alkaloids<br>Dicyclomine Hyoscyamine<br>Propantheline Scopolamine<br>Clidinium-chlordiazepoxide |
| **Tertiary TCAs** | Amitriptyline Chlordiazepoxide-amitriptyline<br>Clomipramine Doxepin<br>Imipramine Perphenazine-amitriptyline<br>Trimipramine |
| **Antipsychotics** | Thioridazine Mesoridazine |
| **Skeletal Muscle Relaxants** | Carisoprodol Chlorzoxazone<br>Cyclobenzaprine Metaxalone<br>Methocarbamol Orphenadrine |
| **Antiarrhythmics** | Disopyramide |

**Table 3.2: Inappropriate anticholinergic medications for Elderly Dementia Patients as per 2012-AGS Beers' Criteria**

| Therapeutic Category of Drugs | Drugs | |
|---|---|---|
| **Antihistamines** | Brompheniramine<br>Chlorpheniramine<br>Cyproheptadine<br>Dexchlorpheniramine<br>Doxylamine<br>Dimenhydrinate<br>Loratidine | Carbinoxamine<br>Clemastine<br>Dexbrompheniramine<br>Diphenhydramine (oral)<br>Hydroxyzine<br>Triprolidine<br>Meclizine |
| **Antiparkinson's** | Benztropine (oral) | Trihexyphenidyl |
| **Antispasmodics** | Atropine Products<br>Atropine<br>Homatropine | Belladonna alkaloids<br>Dicyclomine<br>Hyoscyamine<br>Scopolamine<br>Propantheline<br>Clidinium-chlordiazepoxide |
| **Tertiary TCAs** | Amitriptyline<br>Nortriptyline<br>Protriptyline<br>Doxepin<br>Paroxetine<br>Amoxapine | Clomipramine<br>Imipramine<br>Trimipramine<br>Desipramine<br>Chlordiazepoxide-amitriptyline<br>Perphenazine-amitriptyline |
| **Antipsychotics** | Thioridazine<br>Thiothixene<br>Chlorpromazine<br>Fluphenazine<br>Olanzapine<br>Pimozide<br>Promethazine | Mesoridazine<br>Trifluoperazine<br>Clozapine<br>Loxapine<br>Perphenazine<br>Prochlorperazine |
| **Skeletal Muscle Relaxants** | Carisoprodol<br>Cyclobenzaprine<br>Methocarbamol<br>Tizanidine | Chlorzoxazone<br>Metaxalone<br>Orphenadrine |
| **Antimuscarinics** | Darifenacin<br>Oxybutynin<br>Tolterodine<br>Flavoxate | Fesoterodine<br>Solifenacin<br>Trospium |
| **Antiarrhythmics** | Disopyramide | |

## STUDY DESIGN AND POPULATION

A retrospective cross-sectional design was used to estimate the prevalence and determinants of inappropriate anticholinergic medications use in the elderly patients as well as elderly dementia patients. The cohort for all three objectives comprised of participants of panel 13, 14 and 15 collected during calendar years 2009 and 2010 respectively. National estimates of inappropriate anticholinergic medications use were assessed by using sampling weights available from MEPS data. AHRQ recommends an un-weighted sample size of 100 or greater and a relative standard error no greater than 30% in any domain analysis for reliable national estimates.

The updated 2012 AGS Beers' Criteria was accomplished through the support of American Geriatrics Society (AGS) and the work involved an interdisciplinary panel of 11 experts in geriatric care and pharmacotherapy. It included the use of an evidence-based approach based on the Institute of Medicine standards and the development of a partnership to regularly update the Criteria. As, mentioned earlier the inappropriate anticholinergics were identified from these criteria. Inappropriate anticholinergic medications (disease-independent) were divided into seven categories: antihistamines, antiparkinson's, antispasmodics, tertiary TCAs, antipsychotics, skeletal muscle relaxants, antiarrhythmics.

The objectives of this study used cross-sectional MEPS data from 2009-2010. Analytical sample included all elderly patients from 2009-2010 for the first and second objective whereas, analytical sample included all elderly dementia patients from 2009-2010 for the third objective. Combining multiple year data provided a sufficient sample size to examine the prevalence and predictors of inappropriate anticholinergic use. The second and third objective examined the predictors of inappropriate anticholinergic medications in the elderly and elderly dementia

patients respectively. For the third objective, the inclusion criteria was the elderly patients with a diagnosis of dementia in 2009-2010.

## THE CONCEPTUAL FRAMEWORK

### *Andersen Behavioral Model*

Andersen Behavioral Model (ABM) of health services research was used in this study to examine the determinants of inappropriate anticholinergic medications use. The original model was developed in the late 1960s to assist the understanding of why families use health services, to define and measure equitable access to health care, to assist in developing policies to promote equitable access (Andersen, 1968; Anderson, 1995). However, in 1973 it was extended to the individual level where the unit of analysis was individual instead of a family. This was because of the difficulty in developing measures at the family level that take into account the potential heterogeneity of the family members (Andersen et al., 1973). Since then it has been widely used to assess health care use in services ranging from vaccination and physician care to hospitalizations and home health care services. The model suggests that use is a function of a predisposition by people to use health services, factors that enable or impede such use, and people's need for care (Andersen, 1968; Anderson, 1995). Figure 3.2 describes the model in brief.

Predisposing factors are the characteristics of an individual that were in existence before the illness. It describes the propensity of an individual to use health care services. The following variables were included as predisposing characteristics determining inappropriate anticholinergic medications use: demographics (age, race/ethnicity, gender, and marital status) and social structure (education).

Enabling characteristics illustrate the logistical aspects of obtaining care. It describes ability of an individual to secure health care services and can be at both personal and community level. It included following variables in the model: income, health insurance coverage, usual source of care, metropolitan status area (MSA), and region.

Need characteristics reflect the most immediate cause of health service use, from functional and health problems that generate the need for health care services. It describes perceived and actual health status of an individual. It included following variables in the final model: self-reported health status, chronic conditions (diagnoses of positively-related and negatively-related diseased conditions), activities of daily living (ADL), and instrumental activities of daily living limitations (IADL). Yearly dummies were included as covariate because we pooled data from multiple years, 2009 and 2010.

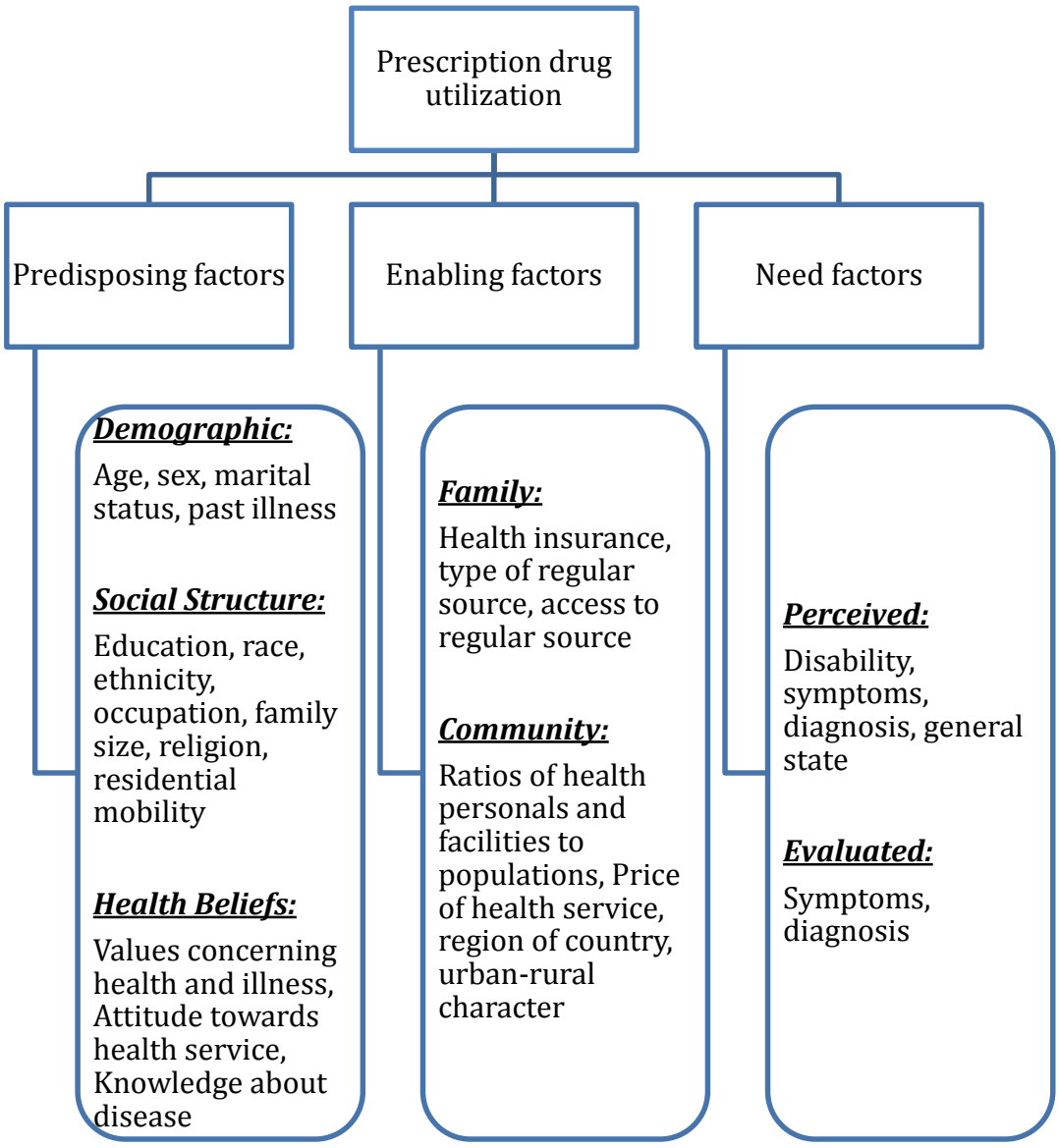


**Figure 3.2: Anderson Behavioral Model of individual determinants of health service utilization** (Source: R Andersen and Newman, 1973)

## STUDY VARIABLES

**Objective 2**: To determine predictors of inappropriate anticholinergic medications use in elderly patients.

Dependent variable: A dichotomous variable for elderly patients who had received inappropriate anticholinergic medications coded as 1 versus elderly patients who did not receive any inappropriate anticholinergic medications coded as 0.

**Objective 3:** To determine predictors of inappropriate anticholinergic medications use in elderly dementia patients.

Dependent variable: A dichotomous variable for elderly dementia patients who had receive inappropriate anticholinergic medications coded as 1 versus elderly dementia patients who did not receive any inappropriate anticholinergic medications coded as 0.

**Independent variables (Objective 2 & 3):**

They were defined using Andersen's behavior model as it is widely used in health care utilization studies. As described before, Andersen behavior model categorizes variables as predisposing, enabling and need factors.

Predisposing Variables

- Age: Age was categorized as 65-74 years, 75-84 years and ≥85 years.
- Gender: Gender was categorized as Male and Female.
- Race/Ethnicity: Self-reported ethnicity/race was categorized as Non-Hispanic Asians, Non-Hispanic Blacks, Hispanic, and others.

- Marital Status: Marital Status in MEPS is recorded as married, widowed, divorced, separated and never married. For this study, marital status was dichotomized as married and others. (others included widowed, divorced, separated and never married)
- Education: Education was categorized as <12 years (less than high school), 12 -15 years (high school diploma) and >15 years (college degree or higher).

Enabling factors

- Family Income: Family Income was categorized as poor (≤ 100% FPL), low income (100% - ≤ 200% FPL), middle income (200% - ≤ 400% FPL) and high income (> 400% FPL)
- Insurance: Health insurance was divided into three categories: Private, Public and Uninsured. Public insurance included individuals that only public insurance any time during the study period (Medicare, Medicaid /SCHIP, Medicaid waiver programs). Private insurance included individuals that had any private insurance coverage any time during the study period (employer-provided coverage, non-employer-provided coverage, TRICARE/CHAMPVA).
- Usual Source of Care (USC): USC was dichotomized as yes /no
- Metropolitan Status Area (MSA): MSA was categorized as non-MSA and MSA
- Region: Region was categorized as Northeast, Midwest, South and West.

Need Factors

- Activities of Daily Living (ADL): ADL was dichotomized as yes /no.
- Instrumental Activities of Daily Living (IADL): IADL was dichotomized as yes/no.
- General Health Status: General health status was grouped into three categories: Excellent, Very Good or Good and Fair or Poor.

- Mental Health Status: Mental health status was grouped into three categories: Excellent, Very Good or Good and Fair or Poor.
- Chronic Conditions:
    - ***For objective 2***: Medical conditions positively-related with anticholinergic prescription include: Schizophrenia, Bipolar disorder, Anxiety, Insomnia, Urinary incontinence, Gastroesophageal reflux disease, Secondary parkinsonism, Acute dystonia due to drugs, Abnormal involuntary movements, Irritable bowel syndrome, Depression, Neuropathic pain, Muscle spasms/low back pain. Medical conditions negatively-related with anticholinergic prescription include Syncope, Chronic Seizures and Epilepsy, Delirium, Dementia, Falls, Fractures, Parkinson's disease, Chronic Constipation, Benign prostatic hyperplasia, Myasthenia gravis, Hyperthyroidism, Narrow angle glaucoma, Heart failure, Arrhythmias, Prior myocardial infarction.
    - ***For objective 3***: Co-morbidities and medical conditions positively-related with anticholinergic prescription include: Schizophrenia, Bipolar disorder, Anxiety, Insomnia, Urinary incontinence, Gastroesophageal reflux disease, Secondary parkinsonism, Acute dystonia due to drugs, Abnormal involuntary movements, Irritable bowel syndrome, Depression, Neuropathic pain, Muscle spasms/low back pain. Medical conditions negatively-related with anticholinergic prescription include Syncope, Chronic Seizures and Epilepsy, Delirium, Dementia, Falls, Fractures, Parkinson's disease, Chronic Constipation, Benign prostatic hyperplasia, Myasthenia gravis, Hyperthyroidism, Narrow angle glaucoma, Heart failure, Arrhythmias, Prior myocardial infarction.

The underlined medical conditions could not be included in the analysis because of coding limitations. Bipolar mania and depression were grouped together as mood disorders because of small sample size. Due to the small sample size syncope, delirium, secondary parkinsonism, schizophrenia, hyperthyroidism and prior myocardial infarction could not be included for Objective 2. Similarly, syncope, epilepsy, delirium, benign prostatic hyperplasia, secondary parkinsonism, schizophrenia, hyperthyroidism, urinary incontinence and prior myocardial infarction were excluded from Objective 3 due to small sample sizes.

## STATISTICAL ANALYSIS

MEPS public use data files from 2009 and 2010 were used for the purpose of analysis. National estimates for the US non-institutionalized population were obtained using MEPS sampling weights that adjusted for complex sample design and non-response. SAS 9.3 (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis since it enables such complex survey data analyses, while accounting for weights. A significance level of $\alpha = 0.05$ was observed for the analyses.

### *Objective 1*

Descriptive statistics for the prevalence of inappropriate anticholinergic medications use were performed using domain analysis among elderly patients. This prevalence was calculated among the elderly patients irrespective of any diagnoses. Besides, a sub-group analysis of inappropriate anticholinergics was also done. Frequencies and percentages were calculated for various inappropriate anticholinergic medications to determine the most frequently prescribed inappropriate anticholinergic drug in the elderly patients. SAS procedure PROC SURVEYFREQ was used to perform these analyses.

***Objective 2***

Weighted frequency analyses (PROC SURVEYFREQ) were performed to describe the study sample. Multivariate logistic regression analyses were used to determine the predictors of inappropriate anticholinergic medications use among elderly patients (irrespective of diagnoses). PROC SURVEYLOGISTIC was used for these analyses.

- Dependent Variable: A dichotomous variable for elderly patients who had received inappropriate anticholinergic medications were coded as1 otherwise coded as 0.
- Independent Variables: All variables according to ABM model of health service utilization (predisposing, enabling and need factors) were included.

Probability of the outcome was modeled using the logarithmic odds as a linear function of the predictor variables. The mathematical expression of the logistic regression model is:

$$\log \frac{p}{1-p} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots\ldots\ldots\ldots\ldots + \beta_k X_k$$

Where $X_1$..... $X_k$ were predictor variables (predisposing, enabling and need variables), and *p* was the probability of the occurrence of the outcome, use of inappropriate anticholinergic level 2 or 3 medications use. The risk ratio was referred to as the Odds Ratio (OR); beta coefficients were interpreted as OR.

***Objective 3***

Multivariate logistic regression analyses were also used to determine the predictors of inappropriate anticholinergic medications use among elderly dementia patients. PROC SURVEYLOGISTIC was used for these analyses.

- Dependent Variable: A dichotomous variable for elderly dementia patients who had received inappropriate anticholinergic medications were coded as1 otherwise coded as 0.
- Independent Variables: All variables according to ABM model of health service utilization (predisposing, enabling and need factors) were included.

Probability of the outcome was modeled using the logarithmic odds as a linear function of the predictor variables. The mathematical expression of the logistic regression model is: :

$$\log\frac{p}{1-p} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots\ldots\ldots\ldots\ldots + \beta_k X_k$$

Where $X_1$..... $X_k$ were predictor variables (predisposing, enabling and need variables), and *p* was the probability of the occurrence of the outcome, use of inappropriate anticholinergic level 2 or 3 medications use. The risk ratio was referred to as the Odds Ratio (OR); beta coefficients were interpreted as OR.

# CHAPTER 4
# RESULTS

## PREVALENCE OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY

All results were presented as weighted annualized estimates. Analysis of 2009 - 2010 MEPS reported an actual estimate of 7,352 elderly participants which has been extrapolated to estimate of 78.60 million (95% CI: 73.72 million to 83.49 million) elderly individuals in the US (12.78% of US population). Out of this, 721 elderly participants received inappropriate anticholinergics, which was extrapolated to an estimated 7.51 million (95% CI: 6.65 million to 8.38 million) elderly individuals in the U.S. receiving inappropriate anticholinergics; thereby giving a prevalence of 9.56%.

Weighted descriptive statistics for the analytical sample reflecting sampling weights have been summarized in **Table 4.1**. Most of patients were 65 - 74 years (54.08%) old, female (56.52%), non-Hispanic others (80.66%), married (55.19%) and had 12-15 years of education (54.71). More than 93% of patients had a usual source of care and almost 48% of the patients had only public health insurance. Almost nine out of 10 patients reported good, very good, or excellent general health status. Also, 9.50% and 17.85% people needed assistance in performing ADLs and IADLs, respectively. Results showed that 10.80% had a diagnosis of mood disorder, 8.76 had cardiac arrhythmias, 8.45% had anxiety, 4.81% had dementia, 4.52 had fractures, 3.74% had urinary incontinence and 3.46 had benign prostatic hyperplasia.

**Table 4.2** reports a list of the most frequently prescribed inappropriate anticholinergic drugs among the elderly patients along with unweighted and weighted statistics. Overall, 9.56% of the elderly patients used at least one inappropriate anticholinergic drug. The most frequently

prescribed drugs were found to be cyclobenzaprine accounting for 2.08% (95% CI: 1.64, 2.52) followed by promethazine (1.75%, 95% CI: 1.27, 2.23), amitriptyline (1.47%, 95% CI: 1.10, 1.85), hydroxyzine (0.95%, 95% CI: 0.63, 1.26), and dicyclomine (0.84%, 95% CI: 0.53, 1.15). Other inappropriate anticholinergic drugs prescribed are mentioned below in the decreasing order of their prescribing frequencies.

**Table 4.1: Patient characteristics of elderly in the United States**

| Category | Variables | Unweighted Frequency Total= 7,352 | Weighted Frequency Total= 78,601,667 | Percentage |
|---|---|---|---|---|
| ***Predisposing Characteristics*** | | | | |
| **Age** | 65 – 74 | 4,066 | 42,505,054 | 54.08 |
| | 75 – 84 | 2,393 | 26,379,729 | 33.56 |
| | >= 85 | 893 | 9,716,885 | 12.36 |
| **Sex** | Male | 3,135 | 34,176,879 | 43.48 |
| | Female | 4,217 | 44,424,788 | 56.52 |
| **Race/Ethnicity** | Hispanic | 936 | 5,711,807 | 7.27 |
| | NH Black | 1,269 | 6,661,682 | 8.48 |
| | NH Asian | 487 | 2,825,763 | 3.60 |
| | NH Other | 4,660 | 63,402,415 | 80.66 |
| **Marital status** | Married | 3,861 | 43,383,771 | 55.19 |
| | Unmarried | 3,491 | 35,217,896 | 44.81 |
| **Education*** | < 12 years | 2,151 | 16,780,648 | 21.55 |
| | 12 - 15 years | 3,664 | 42,609,009 | 54.71 |
| | > 15 years | 1,426 | 18,487,613 | 23.74 |
| ***Enabling Characteristics*** | | | | |
| **Family income** | < 100% FPL | 1,123 | 7,093,036 | 9.02 |
| | 100% to 200% FPL | 1,839 | 19,056,283 | 24.24 |

| | | | | |
|---|---|---|---|---|
| | > 200% FPL | 4,390 | 52,452,348 | 66.73 |
| **Health insurance coverage** | Any Private | 3,356 | 40,670,538 | 51.74 |
| | Public Only | 3,934 | 37,602,273 | 47.84 |
| | Uninsured | 62 | 328,856 | 0.42 |
| **Usual source of health care*** | Yes | 6,670 | 72,502,801 | 93.19 |
| | No | 578 | 5,296,561 | 6.81 |
| **Urban residence** | MSA | 5,833 | 63,765,513 | 81.12 |
| | Non-MSA | 1,519 | 14,836,154 | 18.88 |
| **Region** | Northeast | 1,194 | 15,495,892 | 19.71 |
| | Midwest | 1,528 | 17,442,303 | 22.19 |
| | South | 2,874 | 28,749,519 | 36.58 |
| | West | 1,756 | 16,913,952 | 21.52 |
| ***Need Characteristics*** | | | | |
| **ADL*** | Yes | 768 | 7,405,664 | 9.50 |
| | No | 6,513 | 70,569,353 | 90.50 |
| **IADL*** | Yes | 1,410 | 13,940,938 | 17.85 |
| | No | 5,881 | 64,148,001 | 82.15 |
| **General health status** | Excellent | 1,835 | 21,529,616 | 27.39 |
| | Good | 4,572 | 48,486,508 | 61.69 |
| | Fair/Poor | 945 | 8,585,543 | 10.92 |
| **Mental health status** | Excellent | 3,399 | 39,374,358 | 50.09 |
| | Good | 3,615 | 36,281,037 | 46.16 |
| | Fair/Poor | 338 | 2,946,271 | 3.75 |
| **Diagnoses*** | **Negatively related** | | | |
| | Syncope | 38 | 387,018 | 0.51 |
| | Epilepsy | 87 | 904,568 | 1.18 |

| | | | | |
|---|---|---|---|---|
| | Delirium | - | - | - |
| | Dementia | 394 | 3,777,204 | 4.81 |
| | Fractures | 283 | 3,459,174 | 4.52 |
| | Parkinson's | 70 | 767,163 | 1.00 |
| | Benign Prostatic Hyperplasia | 217 | 2,646,572 | 3.46 |
| | Hyperthyroidism | 65 | 806,957 | 1.05 |
| | Heart failure | 199 | 2,201,236 | 2.88 |
| | Cardiac Arrhythmia | 548 | 6,704,786 | 8.76 |
| | Prior Myocardial Infarction | - | - | - |
| | **Positively related** | | | |
| | Schizophrenia | 09 | 62,267 | 0.08 |
| | Mood disorders | 727 | 8,265,546 | 10.80 |
| | Anxiety | 602 | 6,471,453 | 8.45 |
| | Secondary Parkinsonism | 09 | 112,015 | 0.15 |
| | Urinary Incontinence | 241 | 2,865,577 | 3.74 |
| [*]% did not add up to 100 due to missing values | | | | |

**Table 4.2: Estimated National Prevalence of Inappropriate Anticholinergic medication use by elderly patients in the United States, 2009 – 2010**

| | | Elderly Patients | |
|---|---|---|---|
| **Medication** | **Unweighted Frequency** | **Weighted Frequency** | **%[a]** |
| **Overall Inappropriate Anticholinergic use** | 721 | 7,512,054 | 9.56% |
| **Cyclobenzaprine** | 163 | 1,636,117 | 2.08 |
| **Promethazine** | 130 | 1,373,712 | 1.75 |
| **Amitriptyline** | 102 | 1,158,588 | 1.47 |
| **Hydroxyzine** | 80 | 743,655 | 0.95 |
| **Dicyclomine** | 58 | 662,233 | 0.84 |
| **Carisoprodol** | 49 | 573,146 | 0.73 |
| **Methocarbamol** | 39 | 385,134 | 0.49 |
| **Doxepin** | 23 | 260,608 | 0.33 |
| **Diphenhydramine** | 24 | 234,757 | 0.30 |
| **Hyoscyamine** | 23 | 225,076 | 0.29 |
| **Imipramine** | 16 | 212,850 | 0.27 |
| **Metaxalone** | 15 | 165,736 | 0.21 |
| **Atropine** | 13 | 153,010 | 0.19 |
| **Scopolamine** | 13 | 120,386 | 0.15 |
| **Cyproheptadine** | 13 | 86,017 | 0.11 |
| **Chlorpheniramine** | 09 | 85,973 | 0.11 |
| **Homatropine** | 06 | 85,460 | 0.11 |
| **Benztropine** | 08 | 45,546 | 0.06 |
| **Disopyramide** | 02 | 41,240 | 0.05 |
| **Orphenadrine** | 04 | 39,114 | 0.05 |
| **Chlorzoxazone** | 05 | 30,397 | 0.04 |
| **Brompheniramine** | 02 | 20,432 | 0.03 |
| **Clomipramine** | 03 | 15,380 | 0.02 |
| **Propantheline** | 01 | 13,963 | 0.02 |
| **Clemastine** | 01 | 11,236 | 0.01 |
| **Trihexyphenidyl** | 01 | 5,691 | 0.01 |
| **[a] Denominator for calculation of individual drug percentage values is overall elderly population (N =78,601,667)** | | | |

## PREDICTORS OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY

**Table 4.3** reports the adjusted odds ratios (ORs) along with 95% CI for multivariate logistic regression results, where the dependent variable was use of inappropriate anticholinergic drugs. The multivariate logistic regression included predisposing, enabling and need factors. Of the predisposing factors, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly lower for patients between 75 to 84 years of age (OR: 0.64; 95% CI: 0.49 – 0.85) compared to the reference group, 65 to 74 years of age. Further, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly much lower for patients >=85 years of age (OR: 0.52; 95% CI: 0.33 – 0.81) compared to the reference group, 65 to 74 years of age. The odds of receiving inappropriate anticholinergic drugs in elderly were significantly higher for female patients (OR: 1.37; 95% CI: 1.06 – 1.77) compared to the male reference group. Also, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly lower for patients having >15 years of education (OR: 0.54; 95% CI: 0.35 – 0.84) compared to the reference group, <12 years of education. Of the enabling factors, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly higher for patients who resided in the South region (OR: 1.88; 95% CI: 1.25 – 2.84) compared to the reference group, Northeast. Among the need factors, elderly patients suffering from anxiety (OR: 2.15; 95% CI: 1.57 - 2.94) were more likely to use inappropriate anticholinergic drugs. None of the other factors were significantly associated with the use of inappropriate anticholinergic drugs in elderly patients.

**Table 4.3: Factors associated with the use of Inappropriate Anticholinergic medications in the elderly patients – Multivariate Logistic Regression**

| Category | Variables | Odds Ratio | 95% CI |
|---|---|---|---|
| ***Predisposing Characteristics*** | | | |
| **Age** | 65 – 74 | Reference | - |
| | 75 – 84* | 0.64 | 0.49 - 0.85 |
| | >= 85* | 0.52 | 0.33 – 0.81 |
| **Sex** | Male | Reference | - |
| | Female* | 1.37 | 1.06 - 1.77 |
| **Race/Ethnicity** | Hispanic | Reference | - |
| | NH Black | 1.16 | 0.78 - 1.73 |
| | NH Asian | 1.24 | 0.71 - 2.16 |
| | NH Other | 1.44 | 0.99 – 2.11 |
| **Marital status** | Married | Reference | - |
| | Unmarried | 1.26 | 0.95 - 1.66 |
| **Education** | < 12 years | Reference | - |
| | 12 - 15 years | 0.85 | 0.64 - 1.13 |
| | > 15 years* | 0.54 | 0.35 – 0.84 |
| ***Enabling Characteristics*** | | | |
| **Family income** | < 100% FPL | Reference | - |
| | 100% to 200% FPL | 1.21 | 0.84 - 1.74 |
| | > 200% FPL | 1.32 | 0.97 - 1.80 |
| **Usual source of health care** | Yes | Reference | - |
| | No | 0.69 | 0.39 - 1.24 |
| **Urban residence** | MSA | Reference | - |
| | Non-MSA | 0.94 | 0.72 - 1.21 |
| **Region** | Northeast | Reference | - |
| | Midwest | 1.21 | 0.79 – 1.85 |

| | | | |
|---|---|---|---|
| | South* | 1.88 | 1.25 - 2.84 |
| | West | 1.19 | 0.73 - 1.94 |
| ***Need Characteristics*** | | | |
| **ADL** | Yes | Reference | - |
| | No | 1.18 | 0.85 - 1.65 |
| **IADL** | Yes | Reference | - |
| | No | 0.84 | 0.60 - 1.17 |
| **General health status** | Excellent | Reference | - |
| | Good | 1.05 | 0.78 - 1.42 |
| | Fair/Poor | 1.40 | 0.95 - 2.06 |
| **Mental health status** | Excellent | Reference | - |
| | Good | 1.13 | 0.89 - 1.44 |
| | Fair/Poor | 0.89 | 0.48 - 1.63 |
| **Diagnoses** | **Negatively related** | | |
| | Epilepsy | 1.55 | 0.64 - 3.76 |
| | Dementia | 1.30 | 0.74 - 2.31 |
| | Fractures | 1.08 | 0.70 - 1.67 |
| | Parkinson's | 1.25 | 0.53 - 2.96 |
| | Benign Prostatic Hyperplasia | 1.42 | 0.78 - 2.62 |
| | Heart failure | 1.48 | 0.88 - 2.47 |
| | Cardiac Arrhythmia | 1.45 | 0.98 - 2.15 |
| | **Positively related** | | |
| | Mood disorders | 1.25 | 0.92 - 1.69 |
| | Anxiety* | 2.15 | 1.57 - 2.94 |
| | Urinary Incontinence | 1.44 | 0.91 - 2.26 |
| *** Significance at p<0.05** | | | |

## PREVALENCE OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY DEMENTIA PATIENTS

A total of 394 elderly patients, extrapolated to 3.78 million (95% CI: 3.17 million to 4.38 million) elderly patients were found to have been diagnosed with dementia; the dementia prevalence of 4.81%. Of those, 99 dementia patients, extrapolated to 1.02 million dementia patients (95% CI: 0.70 million to 1.33 million) were reported to use inappropriate anticholinergic medications; thereby giving a prevalence of 26.95%.

Weighted descriptive statistics for the analytical sample (elderly dementia patients) based on sampling weights have been summarized in **Table 4.4**. Most of patients were 75–84 years (47.16%) old, female (57.05%), non-Hispanic others (76.95%), unmarried (53.72%) and had 12-15 years of education (54.99%). More than 94% of patients had a usual source of care and almost 60% of the patients had public health insurance only. Approximately 7 out of 10 patients reported good, very good, or excellent general health status and, 42.39% and 65.10% people needed assistance in performing ADLs and IADLs, respectively. Results showed that 17.31% had a diagnosis of mood disorder, 15.26% had anxiety, 5.68% had urinary incontinence and 3.98% had parkinson's disease.

**Table 4.5** reports a list of the most frequently prescribed inappropriate anticholinergic drugs among the elderly dementia patients along with unweighted and weighted characteristics. Overall, 26.95% of the elderly dementia patients used at least one inappropriate anticholinergic drug. The most frequently prescribed drugs were found to be oxybutynin accounting for 4.54% (95% CI: 1.41, 7.67) followed by solifenacin 4.48% (95% CI: 2.07, 6.89), paroxetine 2.81% (95% CI: 0.23, 5.39), tolterodine 2.47% (95% CI: 0.61, 4.33) and promethazine 2.41% (95% CI:

0.19, 4.63). Other inappropriate anticholinergic drugs prescribed are mentioned below in the decreasing order of their prescribing frequencies.

**Table 4.4: Patient characteristics of elderly dementia patients in the United States**

| Category | Variables | Unweighted Frequency Total= 394 | Weighted Frequency Total= 3,689,902 | Percentage |
|---|---|---|---|---|
| ***Predisposing Characteristics*** | | | | |
| **Age** | 65 – 74 | 94 | 889,961 | 23.56 |
| | 75 – 84 | 183 | 1,781,364 | 47.16 |
| | >= 85 | 117 | 1,105,879 | 29.28 |
| **Sex** | Male | 155 | 1,622,204 | 42.95 |
| | Female | 239 | 2,155,000 | 57.05 |
| **Race/Ethnicity** | Hispanic | 52 | 309,668 | 8.20 |
| | NH Black | 89 | 437,675 | 11.59 |
| | NH White | 19 | 123,324 | 3.26 |
| | NH Other | 234 | 2,906,537 | 76.95 |
| **Marital status** | Married | 165 | 1,748,089 | 46.28 |
| | Unmarried | 229 | 2,029,116 | 53.72 |
| **Education*** | < 12 years | 141 | 1,034,034 | 27.92 |
| | 12 - 15 years | 190 | 2,036,797 | 55.00 |
| | > 15 years | 50 | 632,739 | 17.08 |
| ***Enabling Characteristics*** | | | | |
| **Family income** | < 100% FPL | 82 | 513,597 | 13.60 |
| | 100% to 200% FPL | 101 | 1,019,071 | 26.98 |
| | > 200% FPL | 211 | 2,244,536 | 59.42 |
| **Health insurance coverage** | Any Private | 132 | 1,526,924 | 40.42 |

| | | | | |
|---|---|---|---|---|
| | Public only | 262 | 2,250,280 | 59.58 |
| | Uninsured | - | - | - |
| **Usual source of health care*** | Yes | 366 | 3,527,037 | 94.49 |
| | No | 23 | 205,625 | 5.51 |
| **Urban residence** | MSA | 299 | 2,889,095 | 76.49 |
| | Non-MSA | 95 | 888,110 | 23.51 |
| **Region** | Northeast | 51 | 552,984 | 14.64 |
| | Midwest | 68 | 712,136 | 18.85 |
| | South | 184 | 1,630,144 | 43.16 |
| | West | 91 | 881,941 | 23.35 |
| ***Need Characteristics*** | | | | |
| **ADL*** | Yes | 183 | 1,597,498 | 42.39 |
| | No | 210 | 2,170,934 | 57.61 |
| **IADL*** | Yes | 269 | 2,453,309 | 65.10 |
| | No | 124 | 1,315,185 | 34.90 |
| **General health status** | Excellent | 59 | 554,690 | 14.68 |
| | Good | 220 | 2,270,378 | 60.11 |
| | Fair/Poor | 115 | 952,137 | 25.21 |
| **Mental health status** | Excellent | 65 | 684,545 | 18.12 |
| | Good | 178 | 1,819,884 | 48.18 |
| | Fair/Poor | 151 | 1,272,775 | 33.70 |
| **Diagnoses*** | **Negatively related** | | | |
| | Syncope | 04 | 62,493 | 1.65 |
| | Epilepsy | 14 | 133,370 | 3.53 |
| | Delirium | - | - | - |
| | Fractures | 20 | 180,398 | 4.78 |

| | | | | |
|---|---|---|---|---|
| | Parkinson's | 19 | 150,286 | 3.98 |
| | Benign Prostatic Hyperplasia | 16 | 135,584 | 3.59 |
| | Hyperthyroidism | 04 | 58,003 | 1.54 |
| | Heart Failure | 18 | 142,762 | 3.78 |
| | Cardiac Arrhythmias | 37 | 409,076 | 10.83 |
| | Prior Myocardial Infarction | - | - | - |
| | **Positively related** | | | |
| | Schizophrenia | - | - | - |
| | Mood Disorders | 69 | 653,790 | 17.31 |
| | Anxiety | 57 | 576,348 | 15.26 |
| | Secondary Parkinsonism | 03 | 27,037 | 0.72 |
| | Urinary Incontinence | 23 | 214,478 | 5.68 |
| *% did not add up to 100 due to missing values | | | | |

**Table 4.5: Estimated National Prevalence of Inappropriate Anticholinergic medication use by elderly dementia patients in the United States, 2009 – 2010**

| | | Elderly Dementia Patients | |
|---|---|---|---|
| **Medication** | **Unweighted Frequency** | **Weighted Frequency** | **%[a]** |
| **Overall Inappropriate Anticholinergic use** | 99 | 1,017,800 | 26.95% |
| **Oxybutynin** | 14 | 171,543 | 4,54 |
| **Solifenacin** | 15 | 169,156 | 4.48 |
| **Paroxetine** | 08 | 106,128 | 2.81 |
| **Tolterodine** | 14 | 93,382 | 2.47 |
| **Promethazine** | 08 | 91,008 | 2.41 |
| **Cyclobenzaprine** | 09 | 87,530 | 2.32 |
| **Carisoprodol** | 05 | 79,065 | 2.09 |
| **Darifenacin** | 04 | 47,070 | 1.25 |
| **Meclizine** | 06 | 43,236 | 1.44 |
| **Olanzapine** | 05 | 41,648 | 1.10 |
| **Methocarbamol** | 04 | 40,591 | 1.07 |
| **Tizanidine** | 02 | 39,045 | 1.03 |
| **Homatropine** | 02 | 39,045 | 1.03 |
| **Atropine** | 02 | 37,920 | 1.00 |
| **Dicyclomine** | 06 | 34,147 | 0.90 |
| **Nortriptyline** | 02 | 27,123 | 0.72 |
| **Hydroxyzine** | 05 | 26,644 | 0.71 |
| **Doxepin** | 02 | 21,758 | 0.58 |
| **Metaxalone** | 02 | 19,401 | 0.51 |
| **Hyoscyamine** | 03 | 19,140 | 0.51 |
| **Diphenhydramine** | 03 | 17,178 | 0.45 |
| **Chlorpromazine** | 02 | 16,599 | 0.44 |
| **Benztropine** | 01 | 13,866 | 0.37 |
| **Amitriptyline** | 03 | 13,649 | 0.36 |
| **Brompheniramine** | 01 | 8,468 | 0.22 |
| **Clomipramine** | 01 | 8,384 | 0.22 |
| **Imipramine** | 01 | 3,204 | 0.08 |
| **[a] Denominator for calculation of individual drug percentage values is overall elderly dementia population (N =3,777,204)** | | | |

## PREDICTORS OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY DEMENTIA PATIENTS

**Table 4.6** reports the adjusted odds ratios (ORs) along with 95% CI for multivariate logistic regression results, where the dependent variable was use of inappropriate anticholinergic drugs in elderly dementia patients. The multivariate logistic regression included predisposing, enabling and need factors. Of the predisposing factors, the odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly lower for patients between 75 - 84 years of age (OR: 0.35; 95% CI: 0.15 - 0.81) compared to the reference group, 65 - 74 years of age. Of the need factors, the odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly higher for patients having fair/poor general health status (OR: 5.09; 95% CI: 1.36 - 19.08) compared to the reference group, patients having excellent general health status The odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly higher for patients suffering from anxiety (OR: 3.02; 95% CI: 1.21 - 7.54) and patients suffering from mood disorder (OR: 4.15; 95% CI: 1.87 - 9.22). None of the other factors were significantly associated with the use of inappropriate anticholinergic drugs in elderly dementia patients.

**Table 4.6: Factors associated with the use of Inappropriate Anticholinergic medications in the elderly dementia patients – Multivariate Logistic Regression**

| Category | Variables | Odds Ratio | 95% CI |
|---|---|---|---|
| ***Predisposing Characteristics*** | | | |
| **Age** | 65 – 74 | Reference | - |
| | 75 – 84* | 0.35 | 0.15 - 0.81 |
| | >= 85 | 0.44 | 0.16 - 1.20 |
| **Sex** | Male | Reference | - |
| | Female | 1.43 | 0.63 - 3.24 |

| | | | |
|---|---|---|---|
| **Marital status** | Married | Reference | - |
| | Unmarried | 0.94 | 0.36 - 2.47 |
| **Family income** | < 100% FPL | Reference | - |
| | 100% to 200% FPL | 1.31 | 0.51 - 3.37 |
| | > 200% FPL | 1.23 | 0.46 - 3.26 |
| **Usual source of health care** | Yes | Reference | - |
| | No | 0.49 | 0.13 - 1.87 |
| **Urban residence** | MSA | Reference | - |
| | Non-MSA | 1.15 | 0.58 - 2.30 |
| **ADL** | Yes | Reference | - |
| | No | 0.93 | 0.43 - 2.01 |
| **IADL** | Yes | Reference | - |
| | No | 1.20 | 0.56 - 2.60 |
| **General health status** | Excellent | Reference | - |
| | Good | 1.63 | 0.59 - 4.50 |
| | Fair/Poor* | 5.09 | 1.36 - 19.08 |
| **Mental health status** | Excellent | Reference | - |
| | Good | 1.84 | 0.76 - 4.48 |
| | Fair/Poor | 0.54 | 0.19 - 1.53 |
| **Diagnoses** | **Negatively-related** | | |
| | Fractures | 1.49 | 0.42 - 5.27 |
| | Parkinson's | 0.62 | 0.13 - 2.88 |
| | Heart Failure | 1.88 | 0.38 - 9.32 |
| | Cardiac Arrhythmias | 0.44 | 0.18 - 1.10 |
| | **Positively-related** | | |
| | Mood Disorder* | 4.15 | 1.87 - 9.22 |
| | Anxiety* | 3.02 | 1.21 - 7.54 |
| *** Significance at p<0.05** | | | |

# CHAPTER 5

# DISCUSSION

## PREVALENCE OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY

To our knowledge, this is the first study to identify the prevalence and predictors of inappropriate anticholinergic medications use in elderly patients as well as elderly dementia patients at population based national level using 2012 AGS criteria. Analysis of 2009-2010 MEPS data showed that 9.56% of elderly patients used at least one inappropriate anticholinergic drug. This prevalence was less than the range of 12.6% to 70% reported in the previous studies. [Caterino et al., 2004; Apoteket, 2007] However, this range reported in the literature is for all potentially inappropriate medication prescriptions (PIRx) among elderly. Inappropriate anticholinergic medication prevalence found in the current study (9.56%) was less than inappropriate medication prevalence (12.6%) identified by Caterino et al. in the emergency department visits in elderly patients. Caterino et al., used National Hospital Ambulatory Medical Care Survey (NHAMCS) to analyze emergency department visits from 1992-2000 wherein the inappropriate medications were identified using Beers' 1997 explicit criteria. [Caterino et al., 2004] Inappropriate anticholinergic medication prevalence found in the current study (9.56%) was much lesser than inappropriate medication prevalence (70%) identified by Apoteket among the nursing home residents using the multi-dose system. Apoteket performed a cross-sectional study on a total of 7,904 nursing home residents (All multi-dose users aged 65 or above) in June, 2003 using drug-specific and diagnosis-specific Beers' Criteria 1997. [Apoteket, 2007] Further, inappropriate anticholinergic medication prevalence found in the current study (9.56%) was also

less than inappropriate medication prevalence identified by Piecoro et al., (27%), Lau et al., (50%), Perii III et al., (46.5%). [Piecoro et al., 2000; Lau et al., 2004; Perii III et al., 2005] This variation in the prevalence values can majorly be attributed to the fact that most studies examined all potentially inappropriate medication prescriptions (PIRx) among elderly as compared to the current study where the prevalence values have been calculated only for one category of medications among the inappropriate medications – inappropriate anticholinergic medications. The methodological differences in identifying inappropriate anticholinergic drugs and their utilization along with the study settings can also account for minor variations. Further, since 1997 the Beers' Criteria has updated twice - in 2003 and 2012. The current study used the latest updated 2012 AGS Beers' Criteria.

The current study found that among all the inappropriate anticholinergic medications as per the Beers' Criteria, cyclobenzaprine is the most frequently used accounting for 21.8% of the overall burden by inappropriate anticholinergic medications. This is followed by promethazine (18.3%) amitriptyline (15.4%), hydroxyzine (9.9%), dicyclomine (8.8%) and carisoprodol (7.6%) Other drugs that were found to contribute to this burden of inappropriate anticholinergic medications to a lesser degree included methocarbamol, doxepin, diphenhydramine, hyoscyamine, imipramine, metaxalone, atropine, scopolamine, cyproheptadine, chlorpheniramine, homatropine, benztropine, disopyramide, orphenadrine, chlorzoxazone, brompheniramine, clomipramine, propantheline, clemastine, trihexyphenidyl. This situation is `concerning because elderly patients are at high risk for complications caused by the inappropriate prescribing of medications and these complications may lead to serious drug-related morbidities or drug-related mortalities. These drugs from the current study are somewhat consistent with the inappropriately prescribed drugs mentioned in the literature. Amitriptyline

and doxepin have been identified by Piecoro et al. and Curtis et al. to contribute 11.6% and 23% respectively to potentially inappropriate medications. [Piecoro et al., 2000; Curtis et al., 2004] The most common inappropriate drugs as per Lau et al., included diphenhydramine, hydroxyzine, amitriptyline, and cyproheptadine. [Lau et al., 2004] Caterino et al., identified promethazine, hydroxyzine and diphenhydramine as inappropriately prescribed medications in his study. [Caterino et al., 2004] The high utilization of drugs like cyclobenzaprine, promethazine or amitriptyline raises concerns because certain alternatives are available for these agents with less anticholinergic activities. The Beer's criteria suggests that higher level of anticholinergic medications like amitriptyline, cyclobenzaprine, hydroxyzine, atropine, imipramine and cyproheptadine should be avoided in the elderly patients irrespective of diagnoses. [Beers et al., 1991; Beers et al., 1997; Fick et al., 2003; Lau et al., 2004] One of the qualities of care indicators in the Accessing Care of Vulnerable Elders (ACOVE) is to avoid drugs with strong anticholinergic properties. [Shrank et al., 2007] Hence, it is important to optimize the use of these drugs in the elderly patients in order to minimize the risk of cognitive impairment.

## PREDICTORS OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY

Results from the multivariate logistic regression revealed that age, sex, education, region and anxiety were associated with the use of inappropriate anticholinergic medications in elderly patients. Among the predisposing factors, patients between 75 to 84 years of age and those >=85 years of age were negatively associated with the use of inappropriate anticholinergic drugs compared to the patients between 65 to 74 years of age. This means that elderly patients between 75 to 84 years of age were 36% less likely to use inappropriate anticholinergic medications and

those >=85 years of age were 48% less likely to use inappropriate anticholinergic medications compared to patients between 65 to 74 years of age. This suggests that with increasing age, physicians and other prescribers are more careful and aware while prescribing anticholinergic medications to elderly, keeping in mind their potential central and peripheral side-effects. It was also found that elderly female patients were 37% more likely to use inappropriate anticholinergic medications compared to the elderly male patients. Further, elderly patients with >15 years of education were found to be 46% less likely to use inappropriate anticholinergic medications compared to elderly patients with <12 years of education. This clearly indicates that with better education, patients can be more aware and careful towards the medications they are using for their conditions.

Among the enabling factors, patients in the south region were positively associated with the use inappropriate anticholinergic drugs compared to northwest region. This means that elderly patients in the south region were 88% more likely to use inappropriate anticholinergic drugs compared to the northwest region. This suggests that there exists variation in inappropriate anticholinergic use due to geographic region. There is evidence in literature that a regional variation exists in prescribing of drugs that are included in the Beer's criteria, especially for high-risk drugs, and it has been found that Medicare beneficiaries residing in the South were more likely to receive high-risk medications compared to their counterparts in Northeast region.[71,72] However, it should be noted that the current study findings are based on patient-level analysis and cannot be directly compared with the existing literature due to differences in the population characteristics that affect prescribing patterns. The observed finding in the current study with respect to regional variation in inappropriate anticholinergic medication use can be

attributed to the differences in prescribing practices, patient preferences, or formulary structure across geographic regions.

Among need factors, patients with anxiety had 2.15 times greater likelihood of receiving inappropriate anticholinergic drugs. Anxiety is one of the common medical conditions among elderly patients associated with reducing overall health and quality of life. It requires the prescription of anticholinergic medications for their cure, for example - anticholinergic tricyclic antidepressants. Therefore, the probability of an inappropriate anticholinergic drug being prescribed in elderly with anxiety could be more. It is imperative for physicians, nurses and other prescribers to be aware of the anticholinergic medication profile, which includes the required drug effects and respective side-effects (central and peripheral). Besides, they should also consider the patient's history, anticholinergic burden and cognitive impairment prior to prescribing any other medications.

## PREVALENCE OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY DEMENTIA PATIENTS

Analysis of 2009-2010 MEPS data showed that 26.95% of elderly patients with dementia used at least one inappropriate anticholinergic drug. This prevalence is within the range of 10.3% to 67.9% reported in the previous studies. [Kemper et al., 2007; Ness et al., 2006; Chatterjee et al., 2010; Bhattacharya et al., 2011] However, it should be noted that all these studies have reported the prevalence of anticholinergic medication use in elderly. Inappropriate anticholinergic medication prevalence in elderly dementia patients found in the current study (26.95%) was less than 42.9% prevalence of anticholinergic medication use identified by Bhattacharya et al. in the outpatient settings. Bhattacharya et al. used NAMCS and NHAMCS

data, and performed visit level analysis rather than patient level. [Bhattacharya et al., 2011] Inappropriate anticholinergic medication prevalence in elderly dementia patients found in the current study (26.95%) was much lesser than the prevalence of anticholinergic medication use (74%) identified by Chatterjee et al. in the nursing home residents [Chatterjee et al., 2010] and the prevalence of anticholinergic medication use (82%) identified by Kolanowski et al. based on the data from nine nursing homes in one US state. [Kolanowski et al., 2009]. This variation in the prevalence values can majorly be attributed to the fact that they are calculated for anticholinergic medication use among elderly dementia patients as compared to the current study where the prevalence values have been calculated for inappropriate anticholinergic medication use among elderly dementia patients. Further, methodological differences in study design and settings, sample characteristics and definitions used to identify dementia patients as well as inappropriate anticholinergic medications can also account for differences in the prevalence estimates.

The current study found that among all the inappropriate anticholinergic medications as per the Beers' Criteria, oxybutynin is the most frequently used accounting for 16.8% of the overall burden by inappropriate anticholinergic medications in elderly dementia patients. This is followed by solifenacin (16.6%) paroxetine (10.4%), tolterodine (9.2%), promethazine (8.9%) and cyclobenzaprine (8.6%). Other drugs that were found to contribute to this burden of inappropriate anticholinergic medications to a lesser degree included carisoprodol, darifenacin, meclizine, olanzapine, methocarbamol, tizanidine, homatropine, atropine, dicyclomine, nortriptyline, hydroxyzine, doxepin, metaxalone, hyoscyamine, diphenhydramine, chlorpromazine, benztropine, amitriptyline, brompheniramine, clomipramine, imipramine. This situation is concerning because elderly dementia patients are highly sensitive to anticholinergic-

induced cognitive impairment and other anticholinergic-induced complications that may lead to serious drug-related morbidities or drug-related mortalities. These drugs from the current study are somewhat consistent with the inappropriately prescribed drugs mentioned in the literature. The high utilization of antimuscarinic agents like oxybutynin, solifenacin, tolterodine and darifenacin indicates the presence of urinary incontinence in the elderly dementia patients. However, these medications are non-substitutable. The presence of antidepressants like paroxetine, nortriptyline, doxepin, amitriptyline, clomipramine, and imipramine could be an indication of neuropathic pain in the older people. This raises concerns because safer non-anticholinergic alternatives are available. Hence, it is important to optimize the use of these drugs in the elderly dementia patients, given their increased sensitivity in order to minimize the risk of cognitive impairment.

## PREDICTORS OF INAPPROPRIATE ANTICHOLINERGIC MEDICATIONS USE IN ELDERLY DEMENTIA PATIENTS

Results from the multivariate logistic regression revealed that age, general health status, anxiety and mood disorders were associated with the use of inappropriate anticholinergic medications in elderly dementia patients. Among the predisposing factors, patients between 75 to 84 years of age were negatively associated with the use of inappropriate anticholinergic drugs compared to the patients between 65 to 74 years of age. This means that elderly dementia patients between 75 to 84 years of age were 65% less likely to use inappropriate anticholinergic medications compared to elderly dementia patients between 65 to 74 years of age. This might be attributed to prescriber awareness regarding use of anticholinergic medications to elderly dementia patients, keeping in mind their potential central and peripheral side-effects.

Among the need factors, elderly dementia patients with fair/poor general health status had 5.09 times greater likelihood of receiving inappropriate anticholinergic medications compared to elderly dementia patients with excellent general health status. A possible explanation for this could be related to the finding of most frequently used inappropriate anticholinergic medications in elderly dementia patients in our sample. The most frequently prescribed inappropriate anticholinergic drugs in our sample included oxybutynin, solifenacin and tolterodine, suggesting that the study sample were being treated for urinary incontinence. The fair/poor general health status can be attributed to the presence of urinary incontinence along with dementia that necessitates the use of inappropriate anticholinergic medications.

Elderly dementia patients suffering from mood disorders and anxiety had 4.15 times and 3.02 times respectively, greater likelihood of receiving inappropriate anticholinergic medications. Mood disorders and anxiety are common conditions among elderly dementia patients and are associated with excessive disability, increased caregiver burden, and greater mortality. The treatment of these conditions sometimes requires prescription of drugs like paroxetine, promethazine (anticholinergic in nature) that can lead to increased inappropriate anticholinergic medications. This finding could also be related to an increased number of comorbidities that could be related to polypharmacy, which as per literature evidences is positively associated with increased inappropriate prescriptions

Given the increased sensitivity of elderly dementia patients to anticholinergic-induced cognitive impairment, medications possessing anticholinergic activity should be avoided when possible. It is important to assess patient-specific characteristics such as total anticholinergic load, baseline cognitive function and individual patient variability, all of which are risk factors

for anticholinergic-induced cognitive adverse effects, prior to prescribing anticholinergic medications in this patient population (Carnahan et al., 2002).

In order to minimize the inappropriate anticholinergic medications related adverse events in elderly as well as elderly dementia patients, physicians need to be cautious while prescribing. Hence, there is a need of medication therapy management for polypharmacy and optimizing the prescribing of anticholinergic medications in elderly as well as elderly dementia patients. Medication use criteria like Beer's criteria and ACOVE are used to assess quality of prescribing medications in the elderly population suggesting the avoidance of anticholinergic medications in the elderly. These criteria have also recommended the use of safer alternatives in place of anticholinergic medications. Physicians and other health care providers should consider the non-pharmacological treatments and prescribe drugs without anticholinergic side effects to treat medical conditions wherever possible instead of pharmacological interventions which may cause variety of unwarranted side effects. Concurrent prescribing of two or more anticholinergic agents should be avoided when possible. Prescribers should also consider dose-reductions and close monitoring of patients receiving such medications, especially in elderly dementia patients concomitantly diagnosed with anxiety or mood disorders. This approach might help in reducing the inappropriate medication-related morbidity, mortality and improve health related quality of life.

## STRENGTHS AND LIMITATIONS

The strengths of our study include high generalizability due to the use of nationally representative data involving non-institutionalized patients. MEPS collect information on prescription medication that is validated by the pharmacy stores where the prescriptions were

purchased, enhancing the validity of these data over standard survey data (Zhang et al., 1985). Therefore, MEPS is considered to be one of the best data source to study prescription drug utilization at national level (Curtis et al., 2004).

Although the current study revealed important findings, it has several limitations. The study used cross-sectional data and therefore causal relationship cannot be established between socio-demographic factors and inappropriate anticholinergic medication use. The quality of care outcomes used in the study are patient-reported outcomes which can be subjected to recall bias. Since the study used secondary dataset, possibility of errors in data collection or data entry cannot be ruled out. The selection of enabling, predisposing and need factors that were used in the regression models, though based on previous literature, were limited to variables available in the data. Other variables of ABM such as belief constructs or patient perceptions, prescriber characteristics and other local area characteristics could not be studied. Furthermore, due to small sample size, we cannot control some variables in the dataset such as certain co-morbidities.

## FUTURE RESEARCH

Future study should address the impact of inappropriate anticholinergic medications use on HRQoL. Further, they should determine the association of inappropriate anticholinergic medication use and medications-induced morbidity as well as health care consequences such as hospitalization. Future studies should also aim to understand regional variations in inappropriate anticholinergic use and how can they help to improve the quality of care in the elderly population.

# CHAPTER 6
# SUMMARY AND CONCLUSION

The study examined prevalence and predictors of inappropriate anticholinergic medications use in elderly as well as elderly dementia patients. The Medical Expenditure Panel Survey (MEPS) data from the 2009 to 2010 was used for the analysis. The MEPS is a multistage probability survey which collects data on the health services that Americans use, frequency and cost of use, and payment for these services, as well as data on the private health insurance available to the U.S. population. Descriptive statistics were performed to determine the prevalence of inappropriate anticholinergic medications use in elderly and elderly dementia patients. Multivariate logistic regression was used to determine the predictors of inappropriate anticholinergic medications use in both the populations after adjusting for predisposing, enabling and need factors based on Andersen's behavioral model. Weighted analyses were performed for prevalence and predictors of inappropriate anticholinergic medications use.

The study results showed an annual estimates of approximately 78.60 million (95% CI: 73.71, 83.49) elderly patients; of which about, 7.51 million (95% CI: 6.64, 8.38) were reported to use inappropriate anticholinergic medications. The overall prevalence of inappropriate anticholinergic medications use in the elderly patients was 9.56% (95% CI: 8.52, 10.59). Approximately 3.78 million (95% CI: 3.17, 4.38) elderly patients were found to have been diagnosed with dementia; the dementia prevalence of 4.81% (95% CI: 4.08, 5.54). Of those dementia patients, about 1.02 million (95% CI: 0.70, 1.33) were reported to use inappropriate anticholinergic medications for an overall prevalence of 26.95% (95% CI: 20.10, 33.79).

The most frequently prescribed drugs among the elderly were found to be cyclobenzaprine (2.08%), promethazine (1.75%), amitriptyline (1.47%), hydroxyzine (0.95%),

and dicyclomine (0.84%). Of the predisposing factors, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly lower for patients between 75 to 84 years of age (OR: 0.64; 95% CI: 0.49 – 0.85) compared to the reference group, 65 to 74 years of age. Further, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly much lower for patients >=85 years of age (OR: 0.52; 95% CI: 0.33 – 0.81) compared to the reference group, 65 to 74 years of age. The odds of receiving inappropriate anticholinergic drugs in the elderly were significantly higher for female patients (OR: 1.37; 95% CI: 1.06 – 1.77) compared to the male reference group. Also, the odds of receiving inappropriate anticholinergic drugs in the elderly were significantly lower for patients having >15 years of education (OR: 0.54; 95% CI: 0.35 – 0.84) compared to the reference group, <12 years of education. Of the enabling factors, the odds of receiving inappropriate anticholinergic drugs in elderly were significantly higher for patients who resided in the South region (OR: 1.88; 95% CI: 1.25 – 2.84) compared to the reference group, Northeast. Among the need factors, elderly patients suffering from anxiety (OR: 2.15; 95% CI: 1.57 - 2.94) were more likely to use inappropriate anticholinergic drugs.

Among the elderly dementia patients, the most frequently prescribed drugs were found to be oxybutynin (4.54%), solifenacin (4.48%), paroxetine (2.81%), tolterodine (2.47%) and promethazine (2.41%). Of the predisposing factors, the odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly lower for patients between 75 - 84 years of age (OR: 0.35; 95% CI: 0.15 - 0.81) compared to the reference group, 65 - 74 years of age. Of the need factors, the odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly higher for patients having fair/poor general health status (OR: 5.09; 95% CI: 1.36 - 19.08) compared to the reference group, patients having

excellent general health status The odds of receiving inappropriate anticholinergic drugs in elderly dementia patients were significantly higher for patients suffering from anxiety (OR: 3.02; 95% CI: 1.21 - 7.54) and patients suffering from mood disorder (OR: 4.15; 95% CI: 1.87 - 9.22). None of the enabling factors were significantly associated with the use of inappropriate anticholinergic drugs in elderly dementia patients.

**CONCLUSIONS**

The study found that approximately one in ten elderly patients used inappropriate anticholinergic medications. Female gender, south region and anxiety increased the likelihood of receiving inappropriate anticholinergic medications whereas age between 75 to 84 years, age >=85 years and >15 years of education decreased the likelihood of receiving inappropriate anticholinergic medications. However, the study found that approximately one in four elderly dementia patients used inappropriate anticholinergic medications. While, fair/poor general health status, anxiety and mood disorder increased the likelihood of receiving inappropriate anticholinergic medications, age between 75 to 84 years decreased the likelihood of receiving inappropriate anticholinergic medications. Drugs with anticholinergic properties are associated with central and peripheral adverse effects in vulnerable elderly populations. Hence, there is urgent need to optimize anticholinergic use in elderly patients. Both educational and regulatory approaches are needed to improve inappropriate prescribing practices to optimize appropriate anticholinergic medication use in elderly as well as elderly dementia patients.

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