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EFFECT OF BEERS CRITERIA ON HEALTHCARE UTILIZATION AND COST IN COMMUNITY-DWELLING ELDERLY PATIENTS

by

Courtney O'Neill Roldan, MHA

A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Health Professions

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Approved by:

Chair, Project Committee	Kit N. Simpson, DrPH	Date 4/23/18
Member, Project Committee	Annie N. Simpson, PhD	Date 4/23/18
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Chairperson: Kit N. Simpson, DrPH
Committee: Annie N. Simpson, PhD
William P. Moran, MD, MS
David J. Taber, PharmD, BCPS

This retrospective cohort study uses 2013 Marketscan® claims data to quantify healthcare resource utilization and national healthcare costs attributable to using potentially inappropriate medications represented in 2012 Beers Criteria. We compare hospital admissions, days spent in the hospital, and total healthcare costs generated from inpatient and outpatient visits and prescription medication use for community-dwelling Medicare patients that received medications in Beers Criteria compared to a well-matched group of patients that received medications not included in Beers Criteria. Using Beers Criteria medications is associated with greater odds of hospital admission. Of those that are hospitalized, patients using Beers Criteria medications experience a greater number of hospital admissions and spend more days in the hospital compared to patients treated with medications not in Beers Criteria. We found total inpatient, outpatient, and prescription drug costs to be higher on average for patients that received Beers Criteria medications, and these patients were responsible for significantly higher annual healthcare costs in 2013. This study suggests the importance reducing the risk of unnecessary hospitalizations attributed to using inappropriate medications to minimize the burden the elderly population will have on our national healthcare system in the future.

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Abbreviations

ADE	Adverse Drug Event
CPOE	Computerized Order Entry Warning
ED	Emergency Department
ICD	International Classification of Diseases
IPET	Improved Prescribing in the Elderly Tool
LTC	Long Term Care
MAI	Medication Appropriateness Index
NDC	National Drug Code
NSAIDs	Nonsteroidal anti-inflammatory drugs
PIM	Potentially Inappropriate Medication
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Persons' Prescriptions

I. INTRODUCTION

Over the last century, the human life span in the United States has increased from 47 years to more than 75 years, and this number will continue to rise through the year 2050 (Anderson, 1999). The increase in the number of adults over the age of 65 is a major public health concern, with healthcare spending expected to increase 25% by the year 2030 due largely to the aging population (Centers for Disease Control and Prevention, 2013). Factors that contribute to the high cost of healthcare in the elderly population include deterioration of health and increased use of medications to treat a growing number of health problems as they age.

More than 90% of non-institutionalized adults aged 65 and older use at least one medication per week, and more than 40% use five or more different medications each week (Field et al., 2004). Many of these medications are not medically necessary, thus making polypharmacy a major issue of concern that is associated with prescription drug use in the elderly population. Consequences of polypharmacy are associated with rising healthcare costs, an increase in hospitalization rates (which also, in turn, impact growing costs), and a negative impact on functional status and quality of life (Maher, Hanlon, & Hajjar, 2013).

It was estimated that over $7 billion in annual incremental healthcare expenditures in 2001 were related to inappropriate medication use in community dwelling individuals over the age of 65 (Fu et al., 2007). The term inappropriate medication is generally used to describe those medications in which the risk of experiencing an adverse drug event (ADE) is greater than the potential benefit of that medication (Beers et al., 1991). As the elderly

population continues to grow, and as people continue to live longer, this population will require more medications to manage a growing list of multiple health problems, indicating that polypharmacy will continue to be an issue in the years to come.

As the number of medications consumed by the elderly increases, there is a greater risk of experiencing an ADE compared to those patients taking fewer medications (Maher et al., 2013). ADEs are a leading cause of poor health and death in the U.S. (Center for Drug Evaluation and Research, 2016). ADEs require preventable hospitalizations or may require patients to live out their remaining years in a long-term care (LTC) facility. Unfortunately, these consequences do not allow patients to maintain healthy, independent lives as they age.

One strategy that will address increasing healthcare costs prevalent in older adults is to reduce unnecessary healthcare utilization associated with PIMs included in Beers Criteria. This criteria includes PIMs or medication classes in which the increased risks of experiencing a negative health outcome outweigh potential benefits for adults over the age of 65 (American Geriatrics Society, 2012). The criteria are intended to be used by prescribing clinicians and pharmacists, and, if used appropriately, can help minimize polypharmacy and unnecessary negative health events in the elderly (American Geriatrics Society, 2015). At its initial development, the list was intended to serve as a tool to enable clinicians to identify those medications that should be avoided specifically in nursing home patients (Beers et al., 1991). Beers Criteria was updated in 1997 (Beers, 1997), 2003 (Fick et al., 2003), 2012 (American Geriatrics Society, 2012), and most recently in 2015 (American Geriatrics Society, 2015). These updates now encompass PIMs for all patients

over the age of 65 regardless of where they reside or receive care. A detailed history of the development and iterations of Beers Criteria is included in chapter two.

Despite the adoption of Beers Criteria among a variety of healthcare professionals and settings associated with geriatric care, PIM prescribing in the elderly remains prevalent (Page, Linnebur, Bryant, & Ruscin, 2010). Previous research of PIMs has focused on the prevalence, potential risk factors, and health outcomes associated with PIM use in the elderly. Few studies have included an economic outcome measure related to PIM use. Risk of hospitalization, hospitalization rates, days admitted to the hospital, and total costs associated with using PIMs listed in Beers Criteria have not been previously quantified. Previous studies of retrospective claims data have included only a select number of PIMs in Beers Criteria or have failed to address cost implications associated with healthcare resource utilization while accounting for all Beers Criteria medications classified as potentially inappropriate in older adults.

The goal of this study was to quantify healthcare resource utilization and national healthcare costs attributable to Beers Criteria medication use. This retrospective cohort study used research strategies not previously included in cost analyses of medication classes represented in 2012 Beers Criteria. We compared hospital admissions, days spent in the hospital, and total healthcare costs for patients that received medications in Beers Criteria compared to a well-matched group of patients that received medications not included in Beers Criteria. Community-dwelling Medicare patients with private supplementary insurance were included in the study, and healthcare utilization and costs were analyzed using 2013 Truven Health Marketscan® Commercial Claims and Encounters Database (Truven Health Analytics, 2017). Marketscan® is a nationally

representative database that consists of de-identified, standardized medical and pharmaceutical claims data (Truven Health Analytics, 2017). We identified inpatient visits, outpatient visits, and prescription medication costs for patients that received medications included in Beers Criteria as well as patients that received medications not included in Beers Criteria. Total healthcare costs were compared. Patients that received medications that are contraindicated due to Beers Criteria were matched to patients that received medications not included in Beers Criteria. This was the first study to analyze healthcare utilization and total healthcare costs for patients that were prescribed medications that adhere to Beers Criteria versus patients with similar health conditions that were prescribed medications that do not adhere to Beers Criteria.

Findings from this study will be of assistance to clinicians (i.e. primary care providers, psychiatrists, and other specialists), pharmacists that work with the elderly population, the elderly, and payers. Healthcare administrators and policy makers are also important stakeholders. Considering the consequences that PIM use has on healthcare spending, and considering the likelihood for increased healthcare costs in the near future due to an aging population, this group will be influential in guiding policy changes necessary to influence clinical practice to reduce unnecessary hospitalizations attributed to inappropriate prescribing behaviors in this population. Before we can expect a clinical change in medication management in the elderly population, we first needed to understand the hospitalization rates and cost implications of using PIMs listed in Beers Criteria (compared to using alternative medications not listed in Beers Criteria) and the overall impact on annual healthcare costs. It is critical that clinicians prescribe the right medication to the right patient at the right time. Beers Criteria may help with that. Elderly patients and

their caregivers need to be engaged and aware of the risks of Beers Criteria medications so they can become actively involved in the care they receive. Minimizing unnecessary hospitalizations will allow patients to maintain healthy, independent lives as they age and help alleviate rising healthcare costs.

Aim 1

To examine the healthcare resource utilization for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria.

Hypotheses

H1: The odds of hospital admission in a group of patients who receive Beers Criteria medications is greater than the odds of hospital admission in a group of patients who do not receive Beers Criteria medications.

H0: OR Hospital Admissions (Beers Criteria group) = OR Hospital Admissions (Control group)

Ha: OR Hospital Admissions (Beers Criteria group) ≥ OR Hospital Admissions (Control group)

H2: Among patients who had a hospitalization, the mean number of days admitted to the hospital is greater in patients who receive Beers Criteria medications compared to patients who do not receive Beers Criteria medications.

H0: μ Hospital Days (Beers Criteria group) = μ Hospital Days (Control group)

Ha: μ Hospital Days (Beers Criteria group) ≥ μ Hospital Days (Control group)

Aim 2

To determine the total healthcare costs for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria.

Hypothesis

H1: Total healthcare costs are greater in patients who receive Beers Criteria medications compared to patients who do not receive Beers Criteria medications.

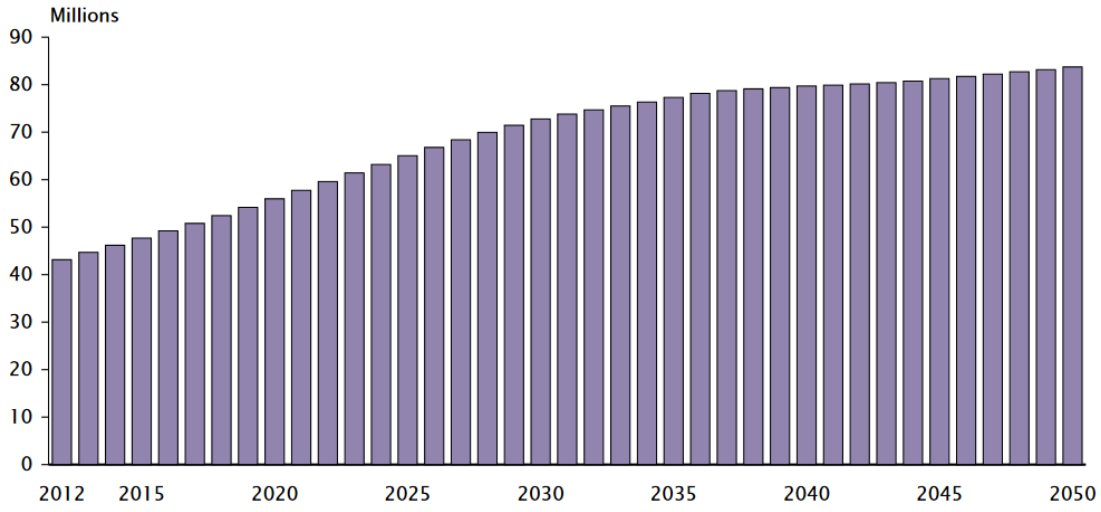
H0: μ Healthcare Cost (Beers Criteria group) = μ Healthcare Cost (Control group)

Ha: μ Healthcare Cost (Beers Criteria group) ≥ μ Healthcare Cost (Control group)

II. REVIEW OF THE LITERATURE

In 1972, the U.S. life expectancy at age 65 was 15 years, compared to a life expectancy of 19 years in 2010 (Ortman, Velkoff, & Hogan, 2014). Americans are living longer, and, as a result, the elderly population continues to increase dramatically. As depicted in Figure 2.1, there will be over 83 million Americans over the age of 65 by the year 2050, nearly double the size of the population in 2012 (Ortman et al., 2014). More than 20% of the total U.S. population will be represented by adults over the age of 65 by 2050. For comparison, in 1970 the elderly population represented less than 10% of the total U.S. population (Ortman et al., 2014).

Figure 2.1: Population Aged 65 and Older for the United States: 2012 to 2050 (Ortman et al., 2014)



The growing elderly population is a burden to the U.S. healthcare system and a public health concern. The cost of providing health care for one person over the age of 65

is nearly five times greater than the cost of providing care to someone under the age of 65 (Centers for Disease Control and Prevention, 2013). As the aging population continues to grow, healthcare costs are expected to increase as much as 25% by the year 2030 (Centers for Disease Control and Prevention, 2013).

Factors that contribute to the high cost of healthcare in the elderly population include deterioration of health as people age and increased use of medications to treat a growing number of health problems. Older adults are often prescribed medications that are not medically necessary, thus making consequences of polypharmacy a major concern. Older people have more health problems, take more medications than younger people, and, as a result, are seven times more likely to experience negative health outcomes that require an emergency room visit and/or hospitalization (Budnitz, Lovegrove, Shehab, & Richards, 2011). ADEs in particular are a common cause of hospital admission. One in six elderly hospital admissions is attributed to an ADE, and one in three adults over the age of 75 experience at least one ADE every year (Pretorius, Gataric, Swedlund, & Miller, 2013).

There are classes of medications that are especially inappropriate for use in adults aged 65 and older. The American Geriatric Society created a medication evaluation tool, referred to as Beers Criteria, that contains lists of PIMs in which the risks outweigh potential benefits for adults over the age of 65 (American Geriatrics Society, 2012). The criteria are used to evaluate the appropriateness of medications and are intended to serve as a guideline in geriatric care. Experts suggest there is a relationship between ADEs, poor patient outcomes, and medications listed in Beers Criteria (American Geriatrics Society, 2012).

Considering that the life expectancy of this population is expected to increase, prescription drug coverage through Medicare has improved, and more medications are available on the U.S. market each year, it is expected that the rate of medication use in the elderly population will continue to rise in the years ahead (Page et al., 2010). It was estimated that over $7 billion in annual incremental healthcare expenditures in 2001 were related to inappropriate medication use in community dwelling individuals over the age of 65 (Fu et al., 2007), and novel strategies are needed to minimize the burden the elderly population has on the healthcare system.

In the following sections, the consequences of polypharmacy in the elderly and the medication evaluation tools available to minimize PIM use in the aging population are discussed. The most commonly used medication evaluation tool currently used in practice is Beers Criteria. What started as a tool specifically for nursing home residents, Beers Criteria has been revised several times since its creation in 1991, increasing from 23 PIMs to over 50 medications and medication classes that can be potentially detrimental to the health of elderly patients using these medications. A history of Beers Criteria is provided which highlights the primary changes in medications included on or removed from Beers Criteria since its creation. The limitations of Beers Criteria are also discussed.

Also included in this section is a review of previous research that has included Beers Criteria. The studies selected for this review included Beers Criteria as the primary, or one of the primary, medication evaluation tools of elderly adults. Beers Criteria has been used in previous studies primarily to describe the prevalence of PIM use in the elderly. Previous research has also evaluated health outcomes associated with PIMs included in Beers Criteria. Although Beers Criteria was developed in the U.S., interestingly, Beers

Criteria has also been incorporated in a number of studies outside of the U.S. Included in this review are international studies of Beers Criteria that were conducted in Europe, Africa, Asia, Australia, and South America. Technology-based interventions to minimize PIM use in the elderly are beginning to incorporate Beers Criteria, and previous studies of these interventions are highlighted in this section. Reviews of the few studies that have used Beers Criteria to quantify the impact of PIM use on healthcare costs are also discussed in this section. To conclude this review of the literature, an overview of propensity score matching (PSM) and a review of how this technique has been used in previous studies of Beers Criteria is provided. Measures of baseline health conditions that will be used in PSM in this dissertation are also addressed in this chapter.

2.1 Polypharmacy

As they age, older adults experience a greater number of health problems, and these conditions usually require treatment with multiple medications (Hajjar, Cafiero, & Hanlon, 2007). The use of multiple medications concurrently by the same patient to treat one or more health conditions is referred to as polypharmacy. Polypharmacy also represents "the use of more medications than are medically necessary" (Maher et al., 2013) and has been associated with PIM prescribing (Cahir et al., 2010). Polypharmacy is a concern for community-dwelling individuals as well as patients in ambulatory care settings, those that are hospitalized, and patients residing in nursing homes (Maher et al., 2013). Approximately half of hospitalized patients, ambulatory care patients, and nursing home residents receive at least one drug that is deemed unnecessary (Tjia, Velten, Parsons, Valluri, & Briesacher, 2013).

Although the elderly population represents only 15% of the total population, this group is the largest consumer of medications (Page et al., 2010). Results from the National Health and Nutrition Examination Survey indicate that 90% of adults over the age of 65 take at least one prescription medication (Kantor, Rehm, Haas, Chan, & Giovannucci, 2015). National trends in prescription drug use among all adults are on the rise. Fifty one percent of U.S. adults reported using at least one prescription medication in the 1999-2000 survey, while 59% of US adults reported using at least one prescription in the 2011-2012 survey (Kantor et al., 2015). A comparison of survey results from 1999-2000 and 2011-2012 indicate that rates of polypharmacy (represented by the use of five of more medications) in older adults has increased over time as well. In the 2011-2012 survey 39% of adults over the age of 65 were taking five or more medications, compared to 24% in the 1999-2000 survey (Kantor et al., 2015).

There are a number of negative health consequences of polypharmacy, including drug-drug interactions, medication non-adherence, decline in functional status, and ADEs. The use of multiple medications puts the elderly at an increased risk for interactions between drugs (Hajjar, Cafiero, & Hanlon, 2007). In a study of community-dwelling older adults living in six different countries, nearly 50% of the participants experienced at least one significant drug-drug interaction (Bjorkman et al., 2002). The risk for drug-drug interactions increases with the number of medications consumed, and these interactions cause unnecessary adverse events and preventable hospitalizations (Maher et al., 2013).

Medication non-adherence is associated with poor clinical outcomes and has significant clinical and economic implications. Poorly treated health conditions require additional medical treatment and often hospitalization, which in turn negatively impact the

patient's quality of life (Hughes, 2004). An estimated 10% of hospitalizations and nearly 25% of LTC facility admissions are attributed to medication compliance issues, and roughly 125,000 deaths occur each year as a result of non-adherence (Peterson, Takiya, & Finley, 2003). Non-adherence is also economically burdensome. The direct and indirect costs of medication non-adherence is estimated to be anywhere from $100 to nearly $290 billion each year (Viswanathan et al., 2012).

Functional status is frequently used to measure overall well-being within the older adults. Polypharmacy can threaten functional status, and any limitations to functional status can negatively impact the use of healthcare resources, quality of life, independence, and risk of mortality (Peron, Gray, & Hanlon, 2011). Additionally, poor functional status is a predictor of LTC facility admissions (Hilmer & Gnjidic, 2008). Previous studies have demonstrated how polypharmacy can negatively impact functional status. A study of elderly adults found that as the number of prescriptions consumed increased, the patient's ability to perform basic and instrumental activities of daily living declined (Magaziner, Cadigan, Fedder, Hebel, 1989). A study of community-dwelling, disabled women demonstrated that participants receiving polypharmacy (more than five medications in this study) experienced increased difficulty performing instrumental activities of daily living (Crentsil, Ricks, Xue, & Fried, 2010). Another study evaluated the relationship between PIMs included on 2003 Beers Criteria and functional status among the very old (older than 80 years), and results indicated a correlation between PIM use and impaired functioning (Landi et al., 2007).

Another consequence of polypharmacy is an increased risk of experiencing an ADE. ADEs are defined as harm caused by a medication or use of an inappropriate

medication (Nebeker, Barach, & Samore, 2004). Adverse events that are common in adults over the age of 65 include mental decline, delirium, falls, fractures, and car accidents (American Geriatrics Society, 2012). Falls are especially detrimental to this population as they are attributed to increased morbidity and mortality (Maher et al., 2013). Results from a study of elderly ED admissions indicates that the risk of experiencing an ADE is significantly higher as the number of medications consumed by this population increases. Patients that consumed two medications had nearly a 15% increased risk of experiencing an ADE, and that risk increased to almost a 40% likelihood of having an ADE when using five medications. Those using seven or more medications had over an 80% risk of experiencing an ADE requiring an ED visit (Goldberg, Mabee, Chan, & Wong, 1996). An 11-year study using outpatient and ED visit data from the National Center for Health Statistics estimates that over 4 million older adults experience an ADE requiring medical attention annually (Bourgeois, Shannon, Valim, & Mandl, 2010). A meta-analysis of 39 prospective studies conducted in the U.S. revealed that over 2 million hospitalized patients experienced an ADE and over 100,000 patients died as a result of an ADE in one year alone (Lazarou, Pomeranz, & Corey, 1998). Based on these calculations, ADEs could be as high as the fourth leading cause of death in the U.S. (Center for Drug Evaluation and Research, 2016).

Consequences of polypharmacy and inappropriate medication use directly affect elderly patients, however, caregivers, hospitals, and LTC facilities are indirectly affected by these consequences as well. Caregivers must face the burden of caring for loved ones that are directly impacted by the consequences of polypharmacy. They often are faced with

insurmountable hospital and/or LTC expenses to ensure their loved ones receive the level of care required to treat ADEs and functional consequences of polypharmacy.

Hospitals and LTC facilities face an increased burden of caring for patients that experience unnecessary drug events associated with using too many medications or using inappropriate medications that increase the risk for adverse events. These events are a common cause of hospital admission. The elderly population represents over 35% of annual hospital admissions (Page et al., 2010), and one in six hospital admissions of older adults can be attributed to an ADE (Beijer & De Blaey, 2002). These events are not only costly to initially address in these institutions, but there is also a risk of increased hospital readmission rates as a result of negative drug outcomes (Sehgal et al., 2013). Polypharmacy is associated with an increase in outpatient and hospital visits, and it is responsible for nearly a 30% increase in medical expenses (Maher et al., 2013). ADEs can also have long-term consequences that impair a patient's functioning in such a way that they require institutionalization in LTC facilities for treatment or prevention of future negative drug outcomes. Not only do consequences of polypharmacy and ADEs immediately impact healthcare costs, but readmissions and the need for long-standing treatment continue to drive up costs in the long-term as well.

2.2 Medication Evaluation Tools

Geriatric clinicians can minimize consequences of polypharmacy by using appropriate medication evaluation tools to help guide clinical decision making when prescribing medications to elderly patients. ADEs and other consequences of polypharmacy associated with PIM use can be minimized if clinicians perform frequent medication reviews and adhere to prescribing guidelines (Ryan et al., 2009). While there

is not one globally accepted medication evaluation tool, several explicit (criterion-based) and implicit (judgment-based) criteria have been developed to help guide medication decisions and ensure clinicians are adhering to quality prescribing practices (Levy, Marcus, & Christen, 2010). Beers and colleagues (1991) were the pioneers of explicit medication criteria, not only within the U.S. but internationally as well. Explicit criteria are more efficient to use and allow for consistency when performing medication reviews, compared to implicit criteria which tend to require more time to use given the clinical interpretation that is required (Levy et al., 2010). Beers Criteria was the first objective tool to benchmark the use of inappropriate medications within the elderly population (Levy et al., 2010). Following the initial development of Beers Criteria in 1991, several medication evaluation tools have emerged.

2.2.1 Medication Appropriateness Index

The Medication Appropriateness Index (MAI) was developed by Hanlon and colleagues (1992) during the same time period that colleagues were developing the 1991 version of Beers Criteria. The goal of this implicit tool is to identify several elements of prescribing practices that are relevant to a variety of medications and clinical settings (Hanlon et al., 1992). The team conducted an initial literature review to identify articles that included medication evaluation measures or scales. Those studies that specifically addressed drug-related problems were evaluated by a pharmacists and geriatrician. Using the literature and their own clinical judgment these individuals "independently identified key elements of desirable medication use" (Hanlon et al., 1992, p. 1046) to create the MAI.

The MAI, as shown in Appendix A, is a set of 10 questions that addresses drug indication, medication effectiveness, dosing, correct and practical directions, drug-drug

interactions, drug-disease interactions, duplication with other drugs, duration, and cost (Hanlon et al., 1992). This tool differs from Beers Criteria and other explicit criteria discussed in sections 2.2.2 and 2.2.3 in that specific medications deemed inappropriate are not specifically listed on the MAI. As is the case with implicit criteria, the MAI requires clinical judgment to answer the 10 medication-related questions represented in the tool. Hanlon and colleagues (1992) standardized the rating process by including definitions of each criteria and detailed instructions to guide clinicians on how to answer each of the 10 questions. Clinicians rate each item as appropriate, marginally appropriate, or inappropriate medication use (Hanlon et al., 1992). The MAI has also been used to identify and define inappropriate drug use in patients receiving at least one medication rated as inappropriate on three of the 10 MAI criteria: indication, efficacy, and therapeutic duplication (Hajjar et al., 2005).

Hanlon and colleagues (1992) evaluated the reliability of the MAI in a randomly selected sample of 10 elderly patients regularly using five or more medications and receiving care at a Veterans Affairs Medical Center. Medication use and medical history was obtained from each patient chart. A pharmacist and a geriatrician applied the MAI and evaluated each patient's medication use at baseline and again two to four months later (Hanlon et al., 1992). To evaluate generalizability of the MAI, a second chart review of 10 randomly selected sample of patients regularly using five or more medications was conducted by a separate pharmacist and geriatrician. Inter-rater and intra-rater reliability was achieved, and the authors present the MAI as a valid and reliable tool (Hanlon et al., 1992).

Despite the reliability and validity of the MAI, this evaluation tool is not without its limitations. The MAI requires considerable clinician time to complete compared to other medication evaluation tools. The tool takes on average about 10 minutes for a clinician to complete an evaluation for each individual drug (Samsa et al., 1994). While the MAI addresses many elements of prescribing appropriateness, it does not take into account consequences of polypharmacy. The tool does not offer guidance to help clinicians prioritize specific drugs that should be avoided or changed, and the MAI is not a useful tool to help clinicians evaluate those specific medications that are attributable to unnecessary ADEs (Hanlon & Schmader, 2013).

2.2.2 Improved Prescribing in the Elderly Tool

The Improved Prescribing in the Elderly Tool (IPET) was developed in Canada by Naugler and colleagues (2000) to identify inappropriate prescribing in adults over the age of 65. This tool was developed using criteria previously established by McLeod et al. (1997). In the McLeod study, a 32-member panel comprised of pharmacologists, geriatricians, family practitioners, and pharmacists from academic medical centers across Canada rated the clinical significance (not significant to highly significant) of 71 prescribing practices in the elderly population. The panel also offered alternative treatments for each prescribing practice. A final list of 38 inappropriate prescribing practices were agreed upon by the panel and were categorized into three groups: medications contraindicated for the elderly (based on the 1991 version of Beers Criteria), medications with drug-drug interactions, and medications that can cause drug-disease interactions (McLeod, Huang, Tamblyn, & Gayton, 1997).

Naugler and colleagues (2000) used McLeod et al.'s (1997) list of 38 inappropriate prescribing practices as the basis for the IPET. The goal of the study conducted by Naugler and colleagues was to apply the McLeod et al. (1997) guidelines to inpatient hospital records to develop a brief and valid screening tool to enable clinicians to screen for PIMs in the elderly (Naugler, Brymer, Stolle, & Arcese, 2000). Records of 361 consecutive inpatient discharges of elderly patients over the age of 70 that occurred in 1997 were reviewed. Medications and medical conditions that were included in the McLeod et al. (1997) guidelines that were identified in the charts were recorded. Inappropriate prescriptions were identified in 12.5% of the inpatient charts (45 of the 361 charts included at least one PIM) (Naugler et al., 2000). The IPET, represented in Appendix B, consists of 14 questions based on the specific PIMs detected in the review. To confirm the validity and reliability of the tool, the IPET was applied to a new set of 100 consecutive discharge charts from the same hospital that occurred over a six-month period in 1998 (Naugler et al., 2000).

Compared to Beers Criteria, the IPET is not as widely used in clinical practice or research (Ryan et al., 2009). It also has not had the international success as Beers Criteria. The primary criticism of the IPET is its narrow scope and inclusion of obsolete criteria (Levy et al., 2010). The IPET includes a select number of medications. There are only three medication classes found on both Beers Criteria and the IPET (long-acting benzodiazepines, nonsteroidal anti-inflammatory drugs [NSAIDs] in peptic ulcer disease, and the use of b-blockers in Chronic Obstructive Pulmonary Disease) (Barry, O'Keefe, O'Connor, & O'Mahony, 2006). Many commonly used classes of medications that are attributed to specific problems in the elderly population are excluded. The limited number

of medications represented in the IPET does make it an easier tool for the user (Barry et al., 2006), but there are concerns about the validity of the tool given the number of well recognized PIMs that are omitted from the list. Previous research conducted by Barry et al. (2006) compared Beers Criteria and the IPET. In this study, Barry and colleagues measured the frequency of PIM prescribing among 350 elderly patients hospitalized in Ireland and compared the efficacy of 2003 Beers Criteria and the IPET in detecting PIM prescribing in this population. Beers Criteria identified 34% of patients were prescribed at least one PIM compared to 22% of patients that were prescribed at least one PIM as identified by the IPET (Barry et al., 2006). Results from this study indicate that Beers Criteria has greater sensitivity than the IPET mainly due to the fact that Beers Criteria includes a vastly greater list of medications, the majority of which are not represented in the IPET (Barry et al., 2006).

2.2.3 STOPP and START Criteria

Earlier versions of Beers Criteria have been criticized for their applicability in Europe, primarily because some drugs included in Beers Criteria were not approved in most European countries (Dalleur, Boland, & Spinewine, 2012). As a result, an 18-member panel comprised of geriatricians, pharmacists, pharmacologists, and primary care clinicians from academic centers in Ireland and the United Kingdom developed the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria. Initially published in 2008, the STOPP/START criteria have been well-received internationally and have been used to evaluate medication use in community-dwelling, hospitalized, and institutionalized elderly patients in countries across the world (Hill-Taylor et al., 2013). The criteria were developed

after careful consideration of Beers Criteria (1991, 1997, and 2003 versions), the MAI, and the IPET. The goal in developing STOPP/START criteria was to create a comprehensive list of PIMs that were (a) valid, (b) based on consensus from an expert panel, (c) based on current clinical practice (at the time of development), and (d) easy and time-efficient for clinicians (Gallagher, Ryan, Byrne, Kennedy, & O'Mahony, 2008). Another characteristic that distinguished STOPP/START criteria from previously developed medication evaluation tools was the inclusion of medications associated with drug-drug and drug-disease interactions as well as drugs unlikely to be prescribed despite clear evidence that the drug is likely to benefit the elderly patient (Gallagher et al., 2008).

A two round Delphi validation process was used to evaluate 68 STOPP criteria and 22 START criteria. Consensus was established on all 22 START criteria and 65 of the 68 STOPP criteria (Gallagher et al., 2008). The final list of agreed upon STOPP criteria, shown in Appendix C, and START criteria, shown in Appendix D, were organized in a way to allow for clinicians to screen medication regimens easily in busy practices. The 65 PIMs included on STOPP are organized into 10 categories based on physiological systems, and a specific explanation as to why each individual PIM may be inappropriate in the elderly is also included. The 22 PIMs included on START are organized by physiological systems into 4 categories (Gallagher et al., 2008).

The STOPP/START criteria were recently updated in 2014 (O'Mahony et al., 2015). A 19-member panel consisting of geriatric experts from 13 European countries executed a two-round Delphi validation process to generate the current version. The current list includes 80 STOPP criteria and 34 START criteria organized by physiological systems.

Fifteen medications previously included in STOPP/START were removed from the second version (O'Mahony et al., 2015).

It is important to note the similarities and differences in the specific medications included on STOPP and Beers Criteria. Similar recommendations between the two lists include avoiding "benzodiazepines in individuals with history of falls or fractures, calcium channel blockers in individuals with chronic constipation, and long-duration sulfonylureas" (Dalleur, Boland, & Spinewine, 2012, p. 2188). Considering the two medication evaluation tools were developed in separate countries, and it is not surprising that there is variability in the specific PIMs included in the individual tools given the differences in medications available in each country. There are 33 PIMs included on STOPP are not represented in 2003 Beers Criteria. There are 27 medications represented in 2003 Beers Criteria that were rarely used in European healthcare settings at the time STOPP was developed (Gallagher et al., 2008), however, 14 of those medications were removed in recent revisions to Beers Criteria (American Geriatrics Society, 2012; American Geriatrics Society, 2015). A comparison of 2012 Beers Criteria to STOPP revealed that the two lists share only a minority of the criteria. About 55% of medications addressed through STOPP are not included in 2012 Beers Criteria (Dalleur, Boland, & Spinewine, 2012). The 2012 Beers Criteria includes delirium and dementia, which are prevalent medical concerns in the elderly population, among the health conditions of concern included in the list (American Geriatrics Society, 2012). Alternatively, STOPP addresses the use of warfarin and opiates which are often associated with ADEs in the elderly (Budnitz, Lovegrove, Shehab, & Richards, 2011). Warfarin and opioids have since been added to the 2015 version of Beers Criteria (American Geriatrics Society, 2015).

Additionally, the 2012 Beers Criteria also addresses risks of using anticholinergics in a more explicit way compared to STOPP (Dalleur, Boland, & Spinewine, 2012).

Recent studies have identified Beers Criteria to be more successful in identifying PIM use in the elderly compared to STOPP/START. Using three years of managed care administrative claims data, Brown et al. (2016) compared 2003 Beers Criteria, 2012 Beers Criteria, and STOPP criteria to determine the prevalence of PIM prescribing among 174,275 commercially insured patients in the U.S. The 2003 version of Beers Criteria identified PIM use in 32% of patients, 2012 Beers Criteria identified PIM use in 34% of patients, and STOPP criteria identified PIM use in 27% of the cohort (Brown et al., 2016). Fadare and colleagues (2015) used 2012 Beers Criteria and STOPP criteria to estimate the incidence of PIM use among 358 elderly Nigerian outpatients. Beers Criteria identified 30% of the patients were prescribed at least one PIM, and STOPP criteria identified 15% of the study participants were using at least one PIM (Fadare et al., 2015). Oliveira et al. (2015) applied the 2012 Beers Criteria and STOPP criteria to 142 patients included in the study to identify the prevalence of PIM use among the elderly in primary care settings in Brazil. The prevalence of PIM use in this group was over 51% according to Beers Criteria, compared to 33% of PIMs used according to the STOPP criteria (Oliveira et al., 2015). A cross-sectional study of community-dwelling elderly patients residing in Spain was designed to evaluate the prevalence of PIM use. 2003 Beers Criteria, 2012 Beers Criteria, and STOPP Criteria were compared. Although 2003 Beers Criteria did not perform as well in detecting PIM use in this population compared to STOPP criteria, 2012 Beers Criteria was successful in identifying the largest number of PIMs prescribed to this population. The 2012 version of Beers Criteria was able to detect 44% of participants using PIMs compared

to 35% identified with the STOPP criteria (Blanco-Reina, Ariza-Zafra, Ocaña-Riola, & León-Ortiz, 2014). Grace and colleagues (2014) used the 2012 Beers Criteria and STOPP criteria to evaluate the prevalence of PIM use among 165 Irish elderly nursing home residents that were admitted to the ED. There were 242 different medications prescribed in this cohort, and 91 of those medications were defined as a PIM according to 2012 Beers Criteria or STOPP. Beers Criteria had greater success in identifying PIM use. Over 89% of patients were using PIMs according to Beers Criteria compared to 84% of patients were using PIMs according to STOPP (Grace et al., 2014). Results from these studies indicate that despite the international use of STOPP/START, Beers Criteria remains a reliable and valid tool to minimize PIM use in the elderly.

It is unlikely that a universally accepted medication evaluation tool will become available in the years ahead. The majority of research evaluating PIM use in the elderly has used Beers Criteria over any other evaluation tool. Intervention studies aimed to improve the quality of geriatric prescribing practices have also used Beers Criteria more frequently than any other medication evaluation tool (Levy et al., 2010). Clinicians must consider several factors when selecting a tool among the available medication evaluation criteria, including ease of use, accuracy of the tool, drug availability, and clinician preference (Levy et al., 2010). Although a variety of medication evaluation tools are available, Beers Criteria remains the most commonly used tool among healthcare providers treating the elderly population (Griebling et al., 2016).

2.3 History of Beers Criteria

Dr. Mark Beers and a group of 13 geriatric clinicians created the first Beers Criteria in 1991 (Appendix E) (Beers et al., 1991). The panel completed a literature review of the appropriateness of medication use in the elderly and a review of published medication prescribing guidelines used in the elderly in general or for nursing home residents specifically. A survey was developed based on the guidelines identified and completed by the 13-member panel. A two-round, modified Delphi technique was used to process the responses of each individual panel member to establish a group consensus on the guidelines derived from the literature. The original list was comprised of 30 medications, including commonly prescribed antidepressants, antipsychotics, and sedative-hypnotics, and was intended to serve as a tool to assist clinicians in identifying those medications that should be avoided specifically in nursing home patients regardless of clinical diagnosis, dose, and frequency of use. At that time, nursing home patients were specifically targeted because patients residing in nursing homes were particularly at risk for suffering from medication-related negative outcomes (Beers et al., 1991).

Beers Criteria was modified and republished in 1997 to expand the applicability of prescribing patterns to include non-institutionalized elderly individuals (Appendix F) (Beers, 1997). This expansion identified specific medications that should be avoided all together in this population, medication dose or frequency that should not be exceeded, and medications that should be avoided in elderly patients with specific co-morbidities. Following a similar modified Delphi process, a six-member panel of geriatric experts established consensus on 28 medications or classes to avoid all together in the elderly

population and 35 medications or classes considered to be potentially inappropriate when taking medical condition into consideration (Beers, 1997).

A 12-member panel employed the modified Delphi method to develop the 2003 Beers Criteria revision (Appendix G) (Fick et al., 2003). Fifteen medications included in the 1997 Beers Criteria were removed during the 2003 revision. The panel identified 48 medications or classes to avoid regardless of medical condition, and they identified medications considered inappropriate for use with 20 specific medical conditions. Another notable addition to the 2003 version is the use of a high or low rating that was assigned to each medication to reflect the level of severity of ADEs for each medication included on the list (Fick et al., 2003).

An 11-member panel, led by the American Geriatric Society, followed the Institute of Medicine standards to conduct a systematic review of over 2,000 high-quality research studies of medications prescribed for older adults to generate the 2012 update (Appendix H) (American Geriatrics Society, 2012). The 2012 list includes 53 PIMs or classes in which the increased risks of experiencing an ADE outweigh potential benefits for adults over the age of 65. One notable change to the criteria was the addition of a third category, compared to the two categories in which medications were classified in previous versions of Beers Criteria. The 53 medications or classes are classified as (a) medications to avoid all together in this population, (b) medications to avoid in adults with certain medical conditions, and (c) medications to be used with caution in the elderly population (American Geriatrics Society, 2012).

The most current version of Beers Criteria was published in 2015 (Appendix I) (American Geriatrics Society, 2015). Thirteen panelists reviewed close to 7,000 clinical

trials and research studies that were published since the last Beers Criteria update in 2012. Changes are not as extensive as previous revisions, and medications are still classified under one of the three categories. New to this list are medications that should be avoided or have their dose adjusted in patients with poor kidney function and medications that may be inappropriate when prescribed at the same time (American Geriatrics Society, 2015)**.**

A combined graphical representation of all five versions of Beers Criteria is presented in Appendices J, K, and L. These figures provide a comparison of medications that have been added or removed through the various revisions to Beers Criteria. Appendix J includes all PIMs included on all five versions that were classified as those medications to avoid in older adults. Appendix K includes PIMs to avoid in older adults due to drug–disease or drug–syndrome interactions that may exacerbate the disease. This separate classification was added in the 1997 revision, thus medications represented in 1991 Beers Criteria do not apply to this category. Lastly, Appendix L represents the new category of PIMs be used with caution that was added in 2012 and updated in 2015.

2.4 Medication Classes Included in Beers Criteria

Beers Criteria is an explicit medication evaluation tool comprised of three separate categories of inappropriate medications: (a) PIMs that should be avoided all together in older adults, (b) PIMs to avoid in older adults due to drug–disease or drug–syndrome interactions that may exacerbate the disease, and (c) PIMs to be used with caution in older adults (American Geriatrics Society, 2012; American Geriatrics Society, 2015). Beers Criteria is intended to be applied to all adults over the age of 65 with the exception of those adults receiving palliative and hospice care. Individuals receiving palliative and hospice care were excluded from the criteria given that risk-to-benefit of medication use and end-

of-life clinical decision making is vastly different compared to individuals not receiving palliative and hospice care. Controlling symptoms through end-of-life care is usually more imperative than avoiding PIMs (American Geriatrics Society, 2012; American Geriatrics Society, 2015).

The PIMs included in Beers Criteria that should be avoided all together in older adults include Anticholinergics, Antithrombotics, Anti-infective medications, cardiovascular medications, pain medications, and medications targeting the central nervous system, endocrine system, and gastrointestinal system (American Geriatrics Society, 2015). These medications should be avoided all together and safer medications or non-medication treatments are preferable to these PIMs (American Geriatrics Society, 2012).

Anticholinergics represented in Beers Criteria include first-generation antihistamines (Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Dimenhydrinate, oral Diphenhydramine, Doxylamine, Hydroxyzine, Meclizine, Promethazine, and Triprolidine), Antiparkinsonian agents (oral Benztropine and Trihexyphenidyl), and Antispasmodics (Atropine, Belladonna alkaloids, Clidinium-Chlordiazepoxide, Dicyclomine, Hyoscyamine, Propantheline, and Scopolamin) (American Geriatrics Society, 2015). First-generation antihistamines included in Beers Criteria are associated with a risk of "confusion, dry mouth, constipation, and other anticholinergic effects or toxicity" (American Geriatrics Society, 2015, p. 2231). Those Antiparkinsonian agents included Beers Criteria should be avoided and medications that are more effective in the treatment of Parkinson's disease should be used (American Geriatrics Society, 2015).

Antispasmodics included in Beers Criteria are considered to be highly anticholinergic and the effectiveness of these specific PIMs is unknown (American Geriatrics Society, 2015).

Antithrombotics represented in Beers Criteria include oral short-acting Dipyridamole and Ticlopidine. Dipyridamole "may cause orthostatic hypotension" (American Geriatrics Society, 2015, p. 2231). Dipyridamole and Ticlopidine should be avoided in favor of safer alternatives that are available (American Geriatrics Society, 2015). Nitrofurantoin, the only anti-infective included in Beers Criteria, is associated with "pulmonary toxicity, hepatoxicity, and peripheral neuropathy" (American Geriatrics Society, 2015, p. 2231). These conditions are exacerbated with long-term use, and, given that safer anti-infective medications are available, Nitrofurantoin should be avoided "in individuals with creatinine clearance <30 mL/min or for long-term suppression of bacteria" (American Geriatrics Society, 2015, p. 2231).

Cardiovascular medications represented in Beers Criteria include peripheral alpha-1 blockers (Doxazosin, Prazosin, and Terazosin), central alpha blockers (Clonidine, Guanabenz, Guanfacine, Methyldopa, and Reserpine [>0.1 mg/d]), Disopyramide, Dronedarone, Digoxin, immediate release Nifedipine, and Amiodarone. Peripheral alpha-1 blockers and central alpha blockers included in Beers Criteria are not recommended for regular treatment of hypertension and are associated with an increased risk of orthostatic hypotension. Additionally, central alpha blocker PIMs are also associated with a higher risk of negative effects on the central nervous system, and they may also cause bradycardia. These Peripheral alpha-1 blockers and central alpha blockers should not be used as an antihypertensive (American Geriatrics Society, 2015). Disopyramide may increase heart failure in older adults (American Geriatrics Society, 2015). Individuals with permanent

atrial fibrillation experience worse outcomes when prescribed Dronedarone (American Geriatrics Society, 2015). Digoxin is associated with increased mortality and should be avoided as a first-line treatment of atrial fibrillation and heart failure (American Geriatrics Society, 2015). Immediate release Nifedipine is associated with an increased risk for hypotension and precipitating myocardial ischemia (American Geriatrics Society, 2015). Amiodarone has a greater toxicity compared to other antiarrhythmics when used as first-line treatment of atrial fibrillation (American Geriatrics Society, 2015).

Pain medications represented in Beers Criteria include Meperidine, oral non-cyclooxygenase-selective NSAIDs (Aspirin >325 mg/d, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Ibuprofen, Ketoprofen, Meclofenamate, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin, Indomethacin, and Ketorolac), Pentazocine, Skeletal muscle relaxants (Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, and Orphenadrine), and Desmopressin (American Geriatrics Society, 2015). Meperidine is associated with an increased risk of neurotoxicity and delirium, and safer opioid alternatives should be used (American Geriatrics Society, 2015). Pentazocine may cause central nervous system ADEs including confusion and hallucinations, and safer opioid analgesics should be used (American Geriatrics Society, 2015). Oral non-cyclooxygenase-selective NSAIDs included in Beers Criteria may cause gastrointestinal bleeding, peptic ulcer disease, upper gastrointestinal ulcers, gross bleeding, perforation, or acute kidney injury (American Geriatrics Society, 2015). Skeletal muscle relaxants included in Beers Criteria tend to be poorly tolerated by this population are associated with an increased risk of anticholinergic ADEs, sedation, and fractures (American Geriatrics Society, 2015). Desmopressin use is associated with an

increased risk of hyponatremia, and should not be used for the treatment of nocturia or nocturnal polyuria (American Geriatrics Society, 2015).

PIMs targeting the central nervous system represented in Beers Criteria include Antidepressants alone or in combination (Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin >6 mg/d, Imipramine, Nortriptyline, Paroxetine, Protriptyline, and Trimipramine), first and second generation antipsychotics, Barbiturates (Amobarbital, Butabarbital, Butalbital, Mephobarbital, Pentobarbital, Phenobarbital, and Secobarbital), Short- and intermediate-acting Benzodiazepines (Alprazolam, Estazolam, Lorazepam, Oxazepam, Temazepam, and Triazolam), Long-acting Benzodiazepines (Clorazepate, Chlordiazepoxide [alone or in combination with amitriptyline or clidinium], Clonazepam, Diazepam, Flurazepam, and Quazepam), Meprobamate, Nonbenzodiazepine - benzodiazepine receptor agonist hypnotics (Eszopiclone, Zolpidem, and Zaleplon), Ergoloid mesylates, and Isoxsuprine (American Geriatrics Society, 2015). Due to a lack of efficacy, use of ergoloid mesylates and Isoxsuprine should be avoided in older adults (American Geriatrics Society, 2015). Antidepressants included in Beers Criteria are considered to be "highly anticholinergic, sedating, and cause orthostatic hypotension" (American Geriatrics Society, 2015, p. 2233). Older adults using first and second generation antipsychotics have an increased risk of stroke and cognitive decline, and individuals with dementia have can experience increased mortality. These medications should be avoided in the older adult population except to treat schizophrenia and bipolar disorder or for short-term use during chemotherapy (American Geriatrics Society, 2015). Barbiturates included in Beers Criteria are associated with greater likelihood of physical dependence and overdose (American Geriatrics Society, 2015). Benzodiazepine use is

associated with an increased risk of "cognitive impairment, delirium, falls, fractures, and motor vehicle crashes" (American Geriatrics Society, 2015, p. 2233). Benzodiazepine-receptor agonists are associated with similar ADEs. Benzodiazepine use is also associated with a higher rate or hospitalization and emergency department visits and should be avoided in this population (American Geriatrics Society, 2015). Meprobamate is highly sedative and should be avoided due to the increased likelihood of physical dependence (American Geriatrics Society, 2015).

PIMs targeting the endocrine system represented in Beers Criteria include Androgens (Methyltestosterone and Testosterone), Desiccated Thyroid, Estrogens with or without progestins, growth hormone, sliding scale insulin, Megestrol, and long-duration sulfonylureas (Chlorpropamide and Glyburide) (American Geriatrics Society, 2015). Androgens and Desiccated Thyroid are associated with cardiac-related ADEs. Androgens are especially problematic for men with prostate cancer. Androgens may be used to treat clinical symptoms of hypogonadism, but otherwise should be avoided (American Geriatrics Society, 2015). Estrogens with or without progestins have the potential to cause breast and endometrial cancer and are also associated with negative cardiac and cognitive outcomes *(*American Geriatrics Society, 2015). Growth hormone use is associated with "edema, arthralgia, carpal tunnel syndrome, gynecomastia, and impaired fasting glucose [and should be avoided] except as hormone replacement after pituitary gland removal" (American Geriatrics Society, 2015, p. 2234). Use of sliding scale insulin and long-duration sulfonylureas is associated with an increased risk of hypoglycemia (American Geriatrics Society, 2015). Megestrol is associated with increased risk of thrombotic events and death (American Geriatrics Society, 2015).

PIMs targeting the gastrointestinal system represented in Beers Criteria include Metoclopramide, orally received mineral oil, and proton-pump inhibitors (American Geriatrics Society, 2015). Metoclopramide "can cause extrapyramidal effects, including tardive dyskinesia" (American Geriatrics Society, 2015, p. 2235) and should be avoided except for treatment of gastroparesis (American Geriatrics Society, 2015). Oral mineral oil used daily can cause aspiration and should be avoided in favor of safer gastrointestinal medications (American Geriatrics Society, 2015). Proton-pump inhibitors are associated with an increased risk of Clostridium difficile and fractures (American Geriatrics Society, 2015).

In addition to those medications that should be avoided all-together in older adults, Beers Criteria also provides recommendations of medications that should be avoided in older adults with specific diseases or syndromes. This classification of PIMs is categorized according to cardiovascular events (heart failure and syncope), central nervous system conditions (chronic seizures or epilepsy, delirium, dementia or cognitive impairment, history of falls or fractures, insomnia, and Parkinson's disease), gastrointestinal conditions (history of gastric or duodenal ulcers), and kidney and urinary tract conditions (chronic kidney disease, urinary incontinence in women, and lower urinary tract symptoms in men) (American Geriatrics Society, 2015).

Individuals with heart failure should avoid NSAIDs and COX-2 inhibitors, Diltiazem, Verapamil, Thiazolidinediones (pioglitazone and rosiglitazone), Cilostazol, and Dronedarone. These medications have the potential to "promote fluid retention and exacerbate heart failure" (American Geriatrics Society, 2015, p. 2237). Individuals with syncope should avoid Acetylcholinesterase inhibitors, peripheral alpha-1 blockers,

Doxazosin, Prazosin, Terazosin, Tertiary tricyclic antidepressants (TCAs), Chlorpromazine, Thioridazine, and Olanzapine. These medications are associated with an increased risk of orthostatic hypotension and bradycardia (American Geriatrics Society, 2015).

Due to the potential to lower the seizure threshold, individuals with chronic seizures or epilepsy should avoid using Bupropion, Chlorpromazine, Clozapine, Maprotiline, Olanzapine, Thioridazine, Thiothixene, and Tramadol (American Geriatrics Society, 2015). Individuals with a high risk of experiencing delirium should avoid using anticholinergics, antipsychotics, Benzodiazepines, Chlorpromazine, Corticosteroids, H2-receptor antagonists (Cimetidine, Famotidine, Nizatidine, Ranitidine, and Meperidine), and sedative hypnotics. These medications can induce or worsen delirium. Individuals with dementia or cognitive impairment should avoid anticholinergics, Benzodiazepines, H2-receptor antagonists, Nonbenzodiazepine/benzodiazepine receptor agonist hypnotics (Eszopiclone, Zolpidem, and Zaleplon), and antipsychotics (chronic and as-needed use) due to adverse events to the central nervous system. Antipsychotics in particular are also associated with a greater risk of stroke and mortality in individuals with dementia (American Geriatrics Society, 2015). The use of anticonvulsants (except for seizures and mood disorders), antipsychotics, Benzodiazepines, Nonbenzodiazepine/benzodiazepine receptor agonist hypnotics (Eszopiclone, Zaleplon, and Zolpidem), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and opioids (except for pain management due to recent fracture or joint replacement) is not recommended in individuals with a history of falls or fractures. These medications are associated with a higher risk of ataxia, impaired psychomotor function, syncope, and may cause additional falls (American

Geriatrics Society, 2015). Individuals with insomnia should avoid the use of oral decongestants (Pseudoephedrine and Phenylephrine), Stimulants (Amphetamine, Armodafinil, Methylphenidate, and Modafinil), and Theobromines (Theophylline and Caffeine) (American Geriatrics Society, 2015). Due to the potential to worsen symptoms of Parkinson's disease, individuals with Parkinson's should avoid all antipsychotics (except aripiprazole, quetiapine, and clozapine) and Antiemetics (Metoclopramide, Prochlorperazine, and Promethazine) (American Geriatrics Society, 2015).

Non-COX-2 selective NSAIDs and doses of aspirin greater than >325 mg per day "may exacerbate existing ulcers or cause new or additional ulcers" (American Geriatrics Society, 2015, p. 2239) and should be avoided in individuals with a history of gastric or duodenal ulcers. Non-COX and COX-selective, oral and parenteral NSAIDs "may increase risk of acute kidney injury and further decline of renal function" (American Geriatrics Society, 2015, p. 2239) and should be avoided in individuals with stage 4 chronic kidney disease. Women with urinary incontinence should avoid estrogen oral and transdermal (excludes intravaginal estrogen), and peripheral alpha-1 blockers (Doxazosin, Prazosin, and Terazosin) to prevent the risk of aggravating existing incontinence (American Geriatrics Society, 2015). Men with lower urinary tract symptoms should avoid strongly anticholinergic drugs, except antimuscarinics for urinary incontinence. These medications "may decrease urinary flow and cause urinary retention" (American Geriatrics Society, 2015, p. 2239).

Lastly, Beers Criteria also provides recommendations of medications to use with caution in older adults. Aspirin should be used with caution in adults over the age of 80 years for the prevention of cardiac events due to a lack of evidence of the risk-to-benefit

ratio of aspirin use in adults over the age of 80 (American Geriatrics Society, 2015). Dabigatran, an anticoagulant medication, is associated with an increased risk of gastrointestinal bleeding compared to other anticoagulants. This medication should be used with caution in adults over the age of 75 and in adults with a creatinine clearance of <30 mL/minute (American Geriatrics Society, 2015). Prasugrel, a blood thinner, is associated with an increased risk of bleeding and should be used with caution in adults over the age of 75 (American Geriatrics Society, 2015). Vasodilators should be used with caution in all older adults as they "may exacerbate episodes of syncope in individuals with history of syncope" (American Geriatrics Society, 2015, p. 2240). Beers Criteria also recommends using caution in all older adults before prescribing the following medications: Antipsychotics, Diuretics, Carbamazepine, Carboplatin, Cyclophosphamide, Cisplatin, Mirtazapine, Oxcarbazepine, serotonin–norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and Vincristine (American Geriatrics Society, 2015).

2.5 Limitations of Beers Criteria

Beers Criteria is not without its limitations. As highlighted in section 2.3, Beers Criteria was developed using an evidence-based approach. An extensive review of the existing body of literature related to polypharmacy and ADEs specific to the elderly population was used to guide the development of each version of Beers Criteria (American Geriatrics Society, 2012). Unfortunately, vulnerable populations are significantly underrepresented in clinical trials (Herrera et al., 2010). This is especially true for the elderly population (Herrera et al., 2010), even though they remain the largest consumers of medication (American Geriatrics Society, 2012). Evidence shows that despite the fact that

the elderly population suffers from the majority of the disease burden in the U.S., less than 35% of the elderly are represented in clinical trials (Herrera et al., 2010). Although inclusion of the elderly in clinical trials is problematic due to a variety of issues (comorbidities, lack of insurance, economic concerns, etc.), there are consequences for not appropriately including this population in research. Not appropriately representing the elderly population "may limit generalizability, provide insufficient data about positive or negative effects of treatment among septic populations, and hinder much-needed access to new treatments" (Herrera et al., 2010, p. 105). As a result, using an evidence-based approach to develop Beers Criteria "may underestimate some drug-related problems or lead to weaker evidence grading" (American Geriatrics Society, 2012, p. 628).

It is important to note that the panel used very specific search criteria to identify the studies that were used in the decision-making process that ultimately impacted the published criteria. As is the case in any systematic review with specific search criteria, potentially valuable studies were likely excluded. Data sources used to identify relevant citations were limited to Medline, The Cochrane Library, International Pharmaceutical abstracts, and select references lists from peer-reviewed publications (American Geriatrics Society, 2012). This search did not include studies published in languages other than English. Additionally, potentially valuable results published outside of these data sources such as white papers, technical reports, and Grey Literature sources, were not included in the development of Beers Criteria (American Geriatrics Society, 2015).

Another limitation of Beers Criteria is that it does not take into account the individual patient's medication preferences and lifestyle attributes. While Beers Criteria is intended to guide clinical decision-making in regards to medication prescribing in the

elderly at the population level, the criteria does not account for all elderly individuals and special populations, (American Geriatrics Society, 2015). For example, in individuals receiving palliative and hospice care, it may be more important to control the patient's symptoms (which may require the use of PIMs listed in Beers Criteria) rather than simply avoiding the use of PIMs all together (American Geriatrics Society, 2012). The risks and benefits of PIMs listed in Beers Criteria may differ when used within special populations compared to the risks and benefits of PIMs used in the general population of older adults.

Clinicians also misinterpret the criteria, and many mistakenly believe that the list of PIMs in Beers Criteria is universally inappropriate (Steinman et al., 2015). Although Beers Criteria provides a well-developed and extensive list of medications to avoid, it does not include a list of alternative medications in the criteria (American Geriatrics Society, 2015). This is likely due in part to the complexity of individual patient health conditions and other medications used to treat a variety of health problems. These complexities require individualized clinician judgment to appropriately determine which alternative medications would be appropriate for each individual patient based on their health status. It should be noted that the criteria were not intended to completely remove clinical judgment in regards to the needs of the individual patient (Molony, 2003).

Despite its limitations, Beers Criteria remains the most widely used medication evaluation tool in geriatric care in acute care facilities, outpatient or ambulatory care facilities, and locations where the elderly are institutionalized. The criteria are widely used by practicing clinicians, pharmacists, researchers, regulators, and policymakers. Use of the criteria has expanded beyond geriatric clinical care and is also used in education, research, and in quality improvement initiatives (American Geriatrics Society, 2015). For example,

the National Committee for Quality Assurance has included performance measures based in Beers Criteria for managed care organizations to evaluate PIM use in the elderly within the Healthcare Effectiveness Data and Information Set (HEDIS) (Stockl, Le, Zhang, & Harada, 2010). HEDIS is not only used by almost all of the U.S. national healthcare plans, but it is also considered the gold standard in health care performance measurement ("HEDIS & Quality Measurement", 2017). Beers Criteria is a valuable quality measure and reputable tool used to educate healthcare providers, reduce unnecessary PIM use, and ultimately improve the level of care elderly patients receive (American Geriatrics Society, 2012). "Beers Criteria have done more than any other tool in the past decade to improve the awareness of and clinical outcomes for older adults with polypharmacy and for the most vulnerable older adults at risk of adverse drug events" (Griebling et al., 2016).

2.6 Using Beers Criteria to Describe the Prevalence of PIM Use

The vast majority of research using Beers Criteria has sought to understand the prevalence of PIM use in the elderly population. This literature review will highlight the significant findings from these prevalence studies by focusing first on studies that incorporated Beers Criteria as the only medication evaluation tool, and then by outlining ways in which Beers Criteria has been used with other screening tools. This review will be chronological in regards to the version of Beers Criteria used in the studies (beginning with studies of early versions of Beers Criteria). Studies conducted in the U.S. as well as research conducted outside the U.S are also presented.

2.6.1 Prevalence of PIMs Using Beers Criteria (U.S. studies)

Eleven studies have used various versions of Beers Criteria to understand the prevalence of PIM use in the U.S. In these studies, Beers Criteria was the only medication

evaluation tool used to describe PIM use. Of those studies, one study used the initial version of Beers Criteria developed in 1991 (Aparasu & Sitzman, 1999), six studies used 1997 Beers Criteria (Aparasu & Mort, 2004; Fick et al., 2001; Gallagher, 2001; Perri et al., 2005; Piecoro, Browning, Prince, Ranz, & Scutchfield, 2000; Zhan et al., 2001), two studies used 2003 Beers Criteria (Fick, Mion, Beers, & Waller, 2008; Stevenson et al., 2014), and two studies used 2012 Beers Criteria (Davidoff et al., 2015; Jirón et al., 2016).

Aparasu and Sitzman (1999) conducted a nation-wide study of data files from the National Hospital Ambulatory Medical Care Survey (NHAMCS) from the 1994 calendar year to calculate the prevalence of PIM use in the elderly in outpatient settings. Although the research team used the 1991 Beers Criteria, it is important to note that they did not include all PIMs on the 1991 Beers Criteria in their study. Instead, Aparasu and Sitzman (1999) included 20 medications or classes listed in Beers Criteria as those medications that should be generally avoided in the elderly population. Ten medications or classes that Beers and colleagues (Beers et al., 1991) classified as inappropriate based on dose amount or therapy time were excluded from this study. Nearly 10.9 million outpatient visits occurred in the U.S. in 1994 according to data included in NHAMCS. Aparasu and Sitzman (1999) calculated the number of outpatient visits that involved one of the 20 PIMs selected for the study. Results from this study indicate that 1 in 20 prescriptions provided to the elderly included a PIM. Five of the 20 medications included in the study were responsible for over 85% of the outpatient visits involving PIMs, and psychotropic and analgesic agents were the most commonly prescribed PIM (Aparasu & Sitzman, 1999).

Aparasu and Mort (2004), Fick and colleagues (2001), and Zhan and colleagues (2001) each conducted a nation-wide study of prevalence of PIM use and used 1997 Beers

Criteria to identify or define PIMs. Using the 1996 Medical Expenditure Panel Survey, Aparasu and Mort (2004) focused specifically on the use of Beers Criteria psychotropic medications in community-dwelling older adults. Results from this study indicate that over two million older adults received a PIM psychotropic medication included in Beers Criteria in 1996 (Aparasu & Mort, 2004). Fick et al. (2001) conducted a retrospective review of administrative claims data to examine prescribing of PIMs in a Medicare managed care setting. PIMs were identified using 1997 Beers Criteria, but not all medications on the 1997 list were included. Fick et al. (2001) included 37 PIMs that should be avoided in the elderly regardless of dose or diagnosis (Beers, 1997). Of the 2,336 adults over the age 65 that were included in the database, 24% received a prescription for at least one PIM (Fick et al., 2001). Similarly, Zhan et al. (2001) conducted a retrospective cohort study using a nationally representative sample of community-dwelling adults to calculate the prevalence of PIM use. As was the case in Fick et al. (2001), the 1997 Beers Criteria was used to define PIMs, but only a subset of 33 medications included on 1997 Beers Criteria were included in the study (Zhan et al., 2001). Using the 1996 Medical Expenditure Panel Survey, 2,455 individuals were included in the study, and results indicate that "more than 1 in 5 of the community-dwelling elderly in the U.S. used at least 1 of the 33 drugs" (Zhan et al., 2001, p. 2826) included on the 1997 Beers Criteria.

Piecoro, Browning, Prince, Ranz, and Scutchfield (2000) conducted a cross-sectional retrospective review of Medicaid Pharmacy claims of 64,832 older adults who received at least one prescription to evaluate the prevalence of PIM use in community-dwelling and nursing home residents of Kentucky. Piecoro and colleagues (2000) used 1997 Beers Criteria to identify at least one PIM used in 27% of patients. Additionally,

prevalence of PIM use was higher in nursing home residents compared to community-dwelling older adults (Piecoro et al., 2000). Gallagher (2001) studied a sample of 146 patients residing in New York that were diagnosed with congestive heart failure. Medication use was analyzed, and the 1997 version of Beers Criteria was applied to identify PIM use. There was a total of 1,161 medications prescribed to this group. Almost 10% of the sample was prescribed a PIM. Additionally, almost 45% were prescribed the wrong combination of medications (Gallagher, 2001). Perri et al. (2005) also included 1997 Beers Criteria in their evaluation of PIM use in a study that specifically focused on Georgia nursing home residents. In their cohort design, Perri and colleagues (2005) included 1,117 medical records of elderly patients residing in 15 nursing homes. Using 1997 Beers Criteria as a guide to define PIMs, a team of pharmacists performed retrospective medication reviews of each record. Unlike previous studies, Perri et al. (2005) used all medications listed on 1997 Beers Criteria to identify PIM use. Results from this study indicate that over 46% of Georgia nursing home residents were prescribed at least one PIM in Beers Criteria (Perri et al., 2005). Additionally, Perri and colleagues (2005) also determined that polypharmacy increased the likelihood of receiving a PIM.

Stevenson and colleagues (2014) also used nursing home residents in a retrospective cohort study to examine the use of high-risk PIMs before and after hospitalization. The 2003 version of Beers Criteria was used to identify high-risk medications. Not all medications on 2003 Beers Criteria were used in the study, but Stevenson and colleagues (2014) focused specifically on those medications on 2003 Beers Criteria categorized with a high severity rating independent of medical condition or diagnosis (Fick et al., 2003). Several national datasets were used to conduct the analysis,

including demographic characteristics from the Medicare Beneficiary Summary, inpatient claims obtained from Medicare Provider and Analysis Review, and pharmacy claims obtained from Omnicare (Stevenson et al., 2014). The study included 52,559 nursing home residents over the age of 65 hospitalized and discharged to the same nursing home in 2008. Stevenson et al. (2014) examined the use of high-risk medications 30 days before hospitalization and 30 days after return to the nursing home. Over 20% of nursing home residents that were hospitalized used at least one high-risk PIM before hospitalization. Interestingly, of that group, less than half were using a high-risk PIM immediately following discharge. However, 60% had returned to using a high-risk PIM at the end of the 30 days post-discharge (Stevenson et al., 2014). Results from this study indicate that nursing homes can impact the frequency of PIM use.

Also using 2003 Beers Criteria, Fick, Mion, Beers, and Waller (2008) conducted a nation-wide retrospective cohort study using administrative claims data to evaluate the prevalence of PIM use in 17,971 community-dwelling older adults. Not all medications included on 2003 Beers Criteria were used. Fick and colleagues (2008) included those medications and classes that should be generally avoided in the elderly (Fick et al., 2003) to define PIM use, and medications categorized on 2003 Beers Criteria as those to avoid while considering diagnosis or condition were excluded from this study. Results from this study indicate that over 40% filled a prescription for one PIM and almost 14% filled a prescription for two or more PIMs (Fick et al., 2008).

Davidoff et al. (2015) and Jirón et al. (2016) each conducted a retrospective cohort study that included a national sample of Medicare beneficiaries aged 65 and older and used the 2012 Beers Criteria to identify the prevalence of PIM use in this group. Davidoff and

colleagues (2015) identified a sample of 18,475 community dwelling older adults using at least one prescription medication according to the 2006-2010 Medical Expenditure Panel Survey. Not all medications included on 2012 Beers Criteria were used in the study. Davidoff and colleagues (2015) specifically included 36 medication classes classified on 2012 Beers Criteria as medications to avoid in older adults (American Geriatrics Society, 2012). Analysis of the prevalence of PIM use from this study identified over 42% of the sample filled a prescription for at least one PIM included on 2012 Beers Criteria. Nonsteroidal anti-inflammatory drugs had the highest prevalence of use in this population (Davidoff et al., 2015).

Jirón et al. (2016) included 38,250 individuals and 1,308,116 observations derived from Medicare fee-for-service claims data in their analysis of prevalence of PIM use. Those medications included on 2012 Beers Criteria classified as medications to avoid and medications to be used with caution in older adults (American Geriatrics Society, 2012) were used to define PIMs. Insulin dosed on a sliding scale and all medication classes categorized on 2012 Beers Criteria as those to avoid in older adults with certain diseases and conditions (American Geriatrics Society, 2012) were excluded in this analysis. PIM use for a one month period in 2012 was identified in over 34% of the sample, indicating that one in three elderly adults use a PIM each month. PIM use over a calendar year period in 2012 was identified in over 56% of the sample, indicating that one out of every two older adults is exposed to a PIM each year (Jirón et al., 2016). Polypharmacy (use of five or more medications in this study) was identified in almost 40% of the population, and nearly 10% used 10 or more medications. Results from this study, as well as the previous studies

mentioned above, indicate that the prevalence of PIM use in the U.S. remains a clinical concern.

2.6.2 Prevalence of PIMs Using Beers Criteria (Non-U.S. studies)

Sixteen studies using Beers Criteria as the only medication evaluation tool have been conducted outside of the U.S. to describe prevalence of PIM use in other parts of the world. There were no studies identified that used the 1991 initial version of Beers Criteria to describe PIM prevalence outside of the U.S. Of the 16 international studies of PIM prevalence, two studies used both the 1997 and 2003 versions of Beers Criteria (Martins, Soares, Mil, & Cabrita, 2006; Van Der Hooft et al., 2005), six studies used the 2003 version of Beers Criteria (Gallagher, Barry, Ryan, Hartigan, & Omahony, 2007; Kondo et al., 2014; Lai et al., 2009; Lin, Peng, Chen, Lin, Hwang, 2011; Niwata, Yamada, & Ikegami, 2006; Ruggiero et al., 2010), one study used both the 2003 and 2012 versions of Beers Criteria (Tsao et al., 2016), and six studies used the 2012 version of Beers Criteria (Ble et al., 2015; Danisha et al., 2015; Dörks, Herget-Rosenthal, Schmiemann, Hoffmann, 2016; Nam, Han, Kim, Bae, & Lee, 2016; Narayan & Nishtala, 2015; Reich, Rosemann, Rapold, Blozik, & Senn, 2014).

Martins, Soares, Mil, and Cabrita (2006) conducted an observational cross-sectional study to identify PIM use in 213 elderly outpatients residing in Lisbon, Portugal. Twelve community pharmacies were selected to identify patients that presented with a prescription for two or more medications. Select medications from the 1997 and 2003 versions of Beers Criteria were used to define PIMs. There were 1,543 total medications reported, and the sample was prescribed an average of 7 medications. The maximum number of medications observed in a patient was 17 (Martins et al., 2006). Using 1997

Beers Criteria, a PIM was identified in almost 28% of the patients. The 2003 Beers Criteria was more robust in identifying PIM use. Almost 39% of the patients were prescribed at least one PIM according to 2003 Beers Criteria (Martins et al., 2006).

Van Der Hooft and colleagues (2005) also used the 1997 and 2003 versions of Beers Criteria to examine the prevalence of PIM use in the Netherlands from 1997 through 2001. Medications included on either version of Beers Criteria that were not marketed in the Netherlands were excluded. This population-based cohort study included ambulatory adults aged 65 years and older. Results identified 20% of patients were using at least one PIM each year (Van Der Hooft et al., 2005).

The 2003 version of Beers Criteria has been used most frequently to define PIM use in other countries. Gallagher, Barry, Ryan, Hartigan, and Omahony (2007) conducted a prospective, observational study to determine the prevalence of PIM use within community-dwelling older adults that were hospitalized. The study population included 597 consecutive acute care admissions, and over 95% of the sample was taking at least one medication. Beers Criteria were used to identify 32% of patients who used at least one PIM prior to hospitalization. Polypharmacy (use of 5 or more medications in this study) was also attributed to a greater likelihood of using PIMs included on 2003 Beers Criteria (Gallagher et al., 2007).

Two studies conducted in Japan used 2003 Beers Criteria. Kondo et al. (2014) focused specifically on PIM use in patients receiving hemodialysis. Using a cross-section design, data of 1,367 hemodialysis patients over the age of 65 was analyzed. Beers Criteria were modified to account for PIMs available in Japan and was used to identify PIMs in the cohort. The frequency of PIM use in this population was 57%. Similar to previous studies,

the greater the number of mediations used, the greater the likelihood of PIM use. For example, in patients consuming greater than 10 medications, 75% were classified as inappropriate (Kondo et al., 2014). Niwata, Yamada, and Ikegami (2006) employed a retrospective, cross-sectional study of PIM use in 17 LTC facilities. Beers Criteria was used to identify PIMs, and medications included on 2003 Beers Criteria that were not available in Japan or medications in which long-term use was unable to be tracked were excluded. Prescription data was analyzed for 1,669 LTC residents aged 65 and older. Over 21% of patients received at least one PIM (Niwata et al., 2006).

Two studies conducted in Taiwan used 2003 Beers Criteria. Lai et al. (2009) evaluated the prevalence of PIM prescribing in ambulatory care settings. Beers Criteria was modified to exclude medications not available or medications classified as controlled substances in Taiwan, and the remaining medications included on 2003 Beers Criteria were used to identify PIMs. Patients aged 65 years and older and covered by the national health insurance program were included. Of the 176,661,994 ambulatory care visits involving a medication prescription that occurred from 2001 to 2004, almost 20% of the visits represented a prescription of a PIM included on 2003 Beers Criteria (Lai et al., 2009). Lin, Peng, Chen, Lin, and Hwang (2011) conducted a retrospective analysis of 327 patients over the age of 65 receiving care in an outpatient community health center in rural Taiwan. Using a modified version of 2003 Beers Criteria to identify PIMs, 105 PIMs were identified in the study sample, and almost 28% of the patients were prescribed at least one PIM (Lin et al., 2011).

Ruggiero et al. (2010) employed a prospective study to analyze PIM use in 31 Italian LTC facilities. A total of 1,716 residents aged 65 years and older receiving long-

term medication treatment (continuous use of a medication at least 3 months before baseline) were evaluated at baseline, 6 month, and 12 month time periods (Ruggiero et al., 2010). The 2003 version of Beers Criteria was used to identify PIMs. The average number of medications consumed per patient was over 5, and almost 50% of the cohort received at least one PIM. Nearly 20% received two or more PIMs (Ruggiero et al., 2010).

Using both the 2003 and 2012 Beers Criteria, Tsao and colleagues (2016) describe the prevalence of PIM use in frail elderly patients receiving home care in Taiwan. Using a retrospective study design, 145 patients over the age of 60 receiving prescription medications for chronic diseases for longer than four weeks were included in analysis (Tsao et al., 2016). The 2003 and 2012 versions of Beers Criteria were used separately to identify PIMs. Medications listed on 2012 Beers Criteria that should be used with caution (American Geriatrics Society, 2012) were excluded from analysis. Of the 145 patients analyzed, 81 patients (just under 60%) received PIMs according to 2003 Beers Criteria, compared to 97 patients (almost 70%) that received PIMs based on 2012 Beers Criteria.

The 2012 Beers Criteria has been used in six prevalence studies (Ble et al., 2015; Danisha et al., 2015; Dörks, Herget-Rosenthal, Schmiemann, Hoffmann, 2016; Nam, Han, Kim, Bae, & Lee, 2016; Narayan & Nishtala, 2015; Reich, Rosemann, Rapold, Blozik, & Senn, 2014) in Germany, India, Korea, New Zealand, Switzerland, and the United Kingdom. Dörks, Herget-Rosenthal, Schmiemann, and Hoffmann (2016) focused on one medication class represented in Beers Criteria. The goal of this multi-center cross-sectional study was to examine the prevalence of NSAID use specifically in German nursing home patients with severe renal failure (Dörks et al., 2016). A total of 685 patients were included in the study, of which 106 patients had severe renal failure. Roughly 20% of the total study

population and 20% of the severe renal failure group were treated with at least on NSAID included on 2012 Beers Criteria (Dörks et al., 2016). Danisha and colleagues (2015) conducted a prospective observational prevalence study in a 350-bed inpatient hospital in India. All patients over the age of 60 that were hospitalized were included in the study (n=200), and 1,690 prescriptions were analyzed. The 2012 version of Beers Criteria was applied to define PIMs. Over 50% of the 200 patients were prescribed at least one PIM (Danisha et al., 2015).

Four population level studies of PIM prevalence were conducted using 2012 Beers Criteria (Ble et al., 2015; Nam, Han, Kim, Bae, & Lee, 2016; Narayan & Nishtala, 2015; Reich, Rosemann, Rapold, Blozik, & Senn, 2014). Ble and colleagues (2015) adapted 2012 Beers Criteria for the United Kingdom in their prevalence study. The study was limited to an analysis of 34 drugs or classes to avoid in older adults. Three cross-section samples of primary care medical records from 2003-2004, 2007-2008, and 2011-2012 were analyzed to understand the prevalence of PIM use and prescribing patterns over time (Ble et al., 2015). A sample of 13,900 primary care patients aged 65 years and older was included for analysis. The total number of medications and PIMs deemed high risk were calculated for each year for each patient included in the study. Results from this study demonstrate that the number of medications used increased over time. Nearly 40% of patients were exposed to a PIM deemed to be high-risk, and over 17% of those patients were classified as long-term consumers of PIMs. Increase in polypharmacy was also detected, and the number of patients using 10 or more medications increased to 24% by 2011-2012 (Ble et al., 2015).

Narayan and Nishtala (2015) performed a cross-sectional analysis pharmaceutical claims data to examine the prevalence of PIM use in older adults living in New Zealand.

A total of 537,387 community-dwelling and residential care individuals were included in the analysis. Those medications from 2012 Beers Criteria available in New Zealand were used to identify PIMs. PIM use was identified in over 40% of the individuals. Nearly 80% of those were prescribed at least one PIM, and over 20% were prescribed two or more PIMs. Reich, Rosemann, Rapold, Blozik, and Senn (2014) used five years of insurance claims data to describe prevalence of PIM use in community-dwelling managed care patients living in Switzerland. The 2012 version of Beers Criteria was used to identify PIMs. Over 22% of managed care patients were prescribed at least one PIM (Reich et al., 2014).

A retrospective cross-sectional population based study was conducted in Korea to study the prevalence of PIM use in elderly outpatients (Nam, Han, Kim, Bae, & Lee, 2016). Select classes of medications represented in 2012 Beers Criteria were used to identify PIMs. Some medication classes were excluded, and those medications not available in Korea were also excluded. Using outpatient prescription claims data for three years (2009-2011), Nam et al. (2016) included 523,811 adults aged 65 years or older that filled at least one prescription during the study period. A total of 45,727,527 prescriptions were analyzed. Over 80% of the patients included were prescribed at least one PIM included in Beers Criteria (Nam et al., 2016).

2.6.3 Prevalence of PIMs Using Beers Criteria and other evaluation tools (U.S. studies)

While Beers Criteria remains the most frequently used medication evaluation tool for the elderly in clinical practice (Griebling et al., 2016), few studies have been conducted that have used Beers Criteria and at least one additional medication evaluation process to

describe the prevalence of PIM use in the U.S. Two studies used the 1997 version of Beers Criteria along with another tool. One study was conducted on a national level (Goulding, 2004), and one study was conducted at the state level (Cannon, Choi, & Zuniga, 2006). Two additional state-level studies were conducted in VA settings in Iowa using the 2003 version of Beers Criteria along with the MAI (Lund, Carnahan, Egge, Chrischilles, & Kaboli, 2010; Steinman et al., 2006).

Goulding (2004) examined trends in the prevalence of PIM use in patients receiving care in ambulatory care settings. Data from two national datasets were used, including the National Ambulatory Medical Care Survey, which provides data from physician office settings, and the National Hospital Ambulatory Medical Care Survey, which provides data from hospital outpatient and emergency departments (Goulding, 2004). Only those medications included on 1997 Beers Criteria that were classified as medications that should generally be avoided regardless of medical condition or medication dosage (Beers, 1997) were included in the study. In addition to using Beers Criteria to identify PIMs, Goulding (2004) also used a drug classification developed by Dr. Chunliu Zhan in 2001 (Zhan et al., 2001). The 1997 Beers Criteria provides a list of PIMs and classifies the medications based on high or low severity (Beers, 1997). Dr. Zhan further categorized the medications included on 1997 Beers Criteria into specific groups, and Goulding focused specifically on those medications classified as always avoid" or "rarely appropriate" (Goulding, 2004). In 1995 and 2000 Goulding (2004) identified that nearly 8% of ambulatory care visits included a prescription for at least one PIM included on 1997 Beers Criteria. Additionally, of those PIMs prescribed, nearly 4% of the PIMs were classified by Zhan (Zhan et al., 2001) as never or rarely appropriate (Goulding, 2004).

In a retrospective chart review of older adults receiving home healthcare in Texas, Cannon, Choi, and Zuniga (2006) analyzed medication use of 786 patients to determine prevalence of PIM use in home health settings. In addition to using the 1997 Beers Criteria to identify PIMs, Cannon and colleagues (2006) also used criteria from the Multidisciplinary Medication Management Project developed by the American Medical Directors Association and the American Society of Consultant Pharmacists. This criterion was developed to improve prescribing in LTC settings, and Cannon and colleagues (2006) used the criteria to identify those medications with a dangerous drug interaction. Over 30% of the patients included in the study were prescribed at least one PIM, and of those medications 10% were considered to have a dangerous drug interaction. Polypharmacy was also identified in this study, with 8 medications on average that were used in home health patients and nearly 40% of patients receiving polypharmacy (Cannon et al., 2006).

Lund and colleagues (2010) and Steinman et al. (2006) studied patients over the age of 65 receiving care in VA facilities in Iowa. Both studies included 2003 Beers Criteria and the MAI. In a sample of 236 patients, Lund and colleagues (2010) identified issues of PIM use and polypharmacy. According to the MAI, patients received over 10 medications on average. Almost half of the sample was prescribed at least one medication included on 2003 Beers Criteria (Lund et al., 2010). Steinman et al. (2006) conducted a cross-sectional study in which outpatient veterans over the age of 65 using five or more medications were included in the study (n=196). Steinman and colleagues (2006) used 2003 Beers Criteria to identify PIMs. The MAI was used to determine whether the medications were duplicate therapies, ineffective, or not indicated for use in this population (Steinman et al., 2006). The researchers also used the Assessment of Underutilization of Medications to determine

whether medications were underused (Steinman et al., 2006). Results from this study indicate that patients were prescribed an average of 8 medications. PIMs included on 2003 Beers Criteria were prescribed to 65% of the sample, of which 57% were prescribed a duplicate, ineffective, or not indicated medication according to MAI (Steinman et al., 2006). Using both 2003 Beers Criteria and the Assessment of Underutilization of Medications, both inappropriate and underuse of medications was identified in 64% of patients (Steinman et al., 2006).

2.6.4 Prevalence of PIMs Using Beers Criteria and other evaluation tools (Non-U.S. studies)

Fourteen studies have used Beers Criteria and at least one additional medication evaluation process to describe the prevalence of PIM use outside of the U.S. Most of the international research of the prevalence of PIM use has used Beers Criteria and STOPP/START (Blanco-Reina, Ariza-Zafra, Ocaña-Riola, & León-Ortiz, 2014; Dalleur et al., 2015; Fadare et al., 2015; Gallagher & O'Mahony, 2008; Grace et al., 2014; Hudhra et al., 2014; Nicieza-Garcia, Salgueiro-Vazquez, Jimeno-Demuth, & Manso, 2016; Oliveira et al., 2015; Rongen et al., 2016; Ubeda et al., 2012; Yang et al., 2015). One study used Beers Criteria and the IPET (Barry, O'Keefe, O'Connor, & O'Mahony, 2006), one study used Beers Criteria, IPET, and STOPP/START (Di Giorgio, Provenzani, & Polidori, 2016), and one study (Chang et al., 2015) used Beers Criteria and a Taiwan-specific evaluation process to evaluate prevalence of PIM use. Those studies which used Beers Criteria and the IPET (Barry, O'Keefe, O'Connor, & O'Mahony, 2006) or Beers Criteria and STOPP/START (Blanco-Reina, Ariza-Zafra, Ocaña-Riola, & León-Ortiz, 2014;

Fadare et al., 2015; Grace et al., 2014; Oliveira et al., 2015) that have been discussed previously in section 2.2 are not included in this section.

Chang et al. (2015) conducted a national cross-section study of PIM use in ambulatory care settings in Taiwan. The 2012 Beers Criteria was used along with a list of PIMs specifically generated for Taiwan to identify PIMs in 1,164,701 patients over the age of 65 that visited an ambulatory care center in 2009 (Chang et al., 2015). Beers Criteria was successful in identifying over 86% of patients that received at least on PIM compared to 73% of patients using PIM according to the Taiwan list of PIMs (Chang et al., 2015). Di Giorgio, Provenzani, and Polidori (2016) compared 2012 Beers Criteria, STOPP/START, and the IPET to describe PIM use in before and during hospitalization in a sample of Italian older adults. After analyzing 1,027 hospitalizations, STOPP/START identified 21% of patients with PIMs at admission and 27% who received a PIM during hospitalization compared to 28% of PIM users at admission and 25% during hospitalization according to the IPET (Di Giorgio et al., 2016). Beers Criteria was the most successful medical evaluation tool to identify PIM use in this population. Results indicate that 24% of patients used a PIM at admission and 49% were prescribed a PIM during hospitalization (Di Giorgio et al., 2016).

An additional seven studies (Dalleur et al., 2015; Fadare et al., 2015; Gallagher & O'Mahony, 2008; Grace et al., 2014; Hudhra et al., 2014; Nicieza-Garcia, Salgueiro-Vazquez, Jimeno-Demuth, & Manso, 2016; Rongen et al., 2016; Ubeda et al., 2012; Yang et al., 2015) identified in the literature that were not previously discussed in section 2.2.2 used Beers Criteria and STOPP/START to evaluate PIM use prevalence in the elderly. Gallagher and O'Mahony (2008) and Ubeda and colleagues (2012) each used 2003 Beers

Criteria and STOPP/START. Gallagher and O'Mahony (2008) conducted a prospective study of acute care admissions in a teaching hospital in Ireland. A total of 715 consecutive admissions were analyzed for PIM use. PIM use in the population was as high as 35% according to STOPP/START and 25% using 2003 Beers Criteria (Gallagher and O'Mahony, 2008). Ubeda and colleagues (2012) conducted a cross-sectional retrospective study of 81 institutionalized patients residing in a region of Spain. Medication and clinical records were reviewed, and STOPP/START and 2003 Beers Criteria were used to identify as many as 48% of nursing home patients received a PIM (Ubeda et al., 2012).

Dalleur et al. (2015), Hudhra et al. (2014), Nicieza-Garcia, Salgueiro-Vazquez, Jimeno-Demuth, and Manso (2016), Rongen et al. (2016), and Yang et al. (2015) each used the 2012 version of Beers Criteria and STOPP/START to evaluate prevalence of PIM use. Dalleur and colleagues (2015) included 567 Belgian primary care patients over the age of 80 in their cross-sectional analysis. Beers Criteria was successful in identifying PIM use in 32% of the sample according (Dalleur et al., 2015). Using a cross-sectional design, Hudhra and colleagues (2014) analyzed prescriptions in 624 patients over the age of 65 discharged from a hospital in Spain. Almost 23% of the patients were prescribed at least one PIM included on 2012 Beers Criteria at discharge, and roughly 14% of patients were prescribed PIMs at discharge that are included on both 2012 Beers Criteria and 2008 STOPP criteria (Hudhra et al., 2014). Nicieza-Garcia, Salgueiro-Vazquez, Jimeno-Demuth, and Manso (2016) focused specifically on PIM prevalence in community-dwelling older patients receiving polypharmacy (10 or more medications used daily in this study) in Spain. Over 63% of patients receiving polypharmacy were also using at least one PIM included on 2012 Beers Criteria (Nicieza-Garcia et al., 2016). Rongen and colleagues (2016) conducted a

cross-sectional study evaluating PIM use in 164 psychiatric hospital patients in the Netherlands. A total of 1,269 medications were evaluated, and almost 50% of patients were using a PIM include on 2012 Beers Criteria (Rongen et al., 2016). Yang and colleagues (2015) studied PIM use in 141 disabled patients with chronic disease aged 65 years and older from Taiwan. STOPP criteria and 2012 Beers Criteria each identified at least one PIM in almost 67% of the sample (Yang et al., 2015).

Beers Criteria is commonly used to evaluate PIM use in the elderly in clinical and residential settings, and there are other medication evaluation tools available to clinicians to appropriately evaluate medication use in the elderly. However, PIM use in older adults has been prevalent for several decades and is likely to continue in the years ahead. The prevalence of PIMs is not limited to just a few select healthcare settings. Rather PIM use has been detected in all healthcare settings, including acute care, ambulatory care, primary care, psychiatric facilities, VA centers, long term care, and home care settings. Use of PIMs included in Beers Criteria remains a widespread health concern for the elderly population. Not only is the prevalence of PIM use in older adults a national health concern in the U.S., but research indicates that PIM use is a global problem as well.

2.7 Using Beers Criteria to Measure Health Outcomes

Although it is important to understand the frequency of PIM use in various healthcare settings, it is just as important to consider the consequences those medications can have on the health and well-being of patients. While previous research of Beers Criteria has focused primarily on prevalence of PIM use, some studies have examined the negative health outcomes associated with PIM use in the U.S. and globally. The studies included in

this review will highlight the significant and negative outcomes that are associated with using PIMs included in Beers Criteria based on research conducted in the U.S., Australia, Japan, Sweden, and Taiwan. The primary health outcomes represented in research of Beers Criteria include hospitalizations, ED visits, institutionalization in LTC facilities, ADEs, and impact on quality of life.

2.7.1 Hospitalizations, ED Visits, & Institutionalization

Nine studies included in this review measured the impact PIMs included in Beers Criteria has on hospitalizations, ED visits, or LTC admission (Brown, Hutchison, Li, Painter, & Martin, 2016; Budnitz, Shehab, Kegler, & Richards, 2007; Chin et al., 1999; Fillenbaum et al., 2004; Klarin, Wimo, & Fastbom, 2006; Lau, Kasper, Potter, Lyles, & Bennett, 2005; Price, Holman, Sanfilippo, & Emery, 2014; Price, Holman, Sanfilippo, & Emery, 2015; Zuckerman et al., 2006). Using the 1991 and 1997 Beers Criteria and data from the 1996 Medical Expenditure Panel Survey Nursing Home Component, Lau, Kasper, Potter, Lyles, and Bennett (2005) studied the relationship between PIM use and hospitalization within a sample of 3,372 patients over the age of 65 that stayed in a nursing home for three consecutive months or longer. Results from this study indicate that patients receiving a PIM included in Beers Criteria had over 1.2 greater odds of being hospitalized the following month compared to patients that were not using a PIM (Lau et al., 2005). Patients using PIMs for two consecutive months had close to a 30% greater risk for hospitalization compared to patients taking non-PIMs (Lau et. al, 2005). Additionally, patients using Beers Criteria PIMs had a 28% greater risk of death compared to patients not using PIMs (Lau et al., 2005).

Chin and colleagues (1999) conducted a prospective cohort study that included 898 patients that were admitted to a Chicago ED in 1995 and 1996. Medications that patients received in the ED and at discharge were collected, and patients were surveyed during their ED visit and at two weeks and three months post-discharge (Chin et al., 1999). The team used 1997 Beers Criteria to identify PIMs. Health outcomes, specifically ED revisits and hospitalizations, were calculated. Within three months of discharge from the ED, almost 20% of patients returned to the ED and almost 20% were hospitalized. Additionally, 10% of the patients included in the study experienced a death (Chin et al., 1999). Of the patients that experienced an ED revisit, hospitalization, or death, over 20% previously used a PIM (Chin et al., 1999).

Klarin, Wimo, and Fastbom (2006) employed a population-based, longitudinal study to analyze the relationship between PIMs and hospitalization within a cohort of 785 community-dwelling residents of rural Sweden over the age of 75. Hospitalization and mortality data was collected for three years, and 1997 Beers Criteria was used to identify PIM use (Klarin et al., 2006). Results from this study demonstrate that PIM use was present in almost 20% of the cohort, and PIM use was associated with an increased-risk for hospitalization (Klarin et al., 2006). Fillenbaum et al. (2004) also used 1997 Beers Criteria in their analysis of PIM related hospitalizations. Community-dwelling patients included in the study that used a PIM in Beers Criteria had a 20% greater risk of hospitalization. Budnitz and colleagues (2007) conducted a nationally representative study using public health surveillance data to estimate the frequency and risk of an ED visit for patients over the age of 65 using select PIMs included on 2003 Beers Criteria. Budnitz et al. (2007)

analyzed 177,504 ED visits of which almost 4% of the ED visits were attributed to a Beers Criteria PIM generated ADE.

Two studies included in this review (Price, Holman, Sanfilippo, & Emery, 2014; Price, Holman, Sanfilippo, & Emery, 2015) included an analysis of hospitalizations due to PIM use in Australia. Price et al. (2014) conducted an analysis of pharmaceutical claims for 251,305 older adults using medications classified as high risk. Eight specific high-risk PIMs represented in 2003 Beers Criteria were included in the study. Results from this study indicate that all included medications (amiodarone, diazepam, digoxin, ferrous sulphate, indomethacin, naproxen, oxazepam, and temazepam) were associated with increased risk of hospitalization (Price et al., 2014). Indomethacin and naproxen (both are NSAIDs and included on 2003 Beers Criteria) were attributed to the greatest risk for hospitalization. Price and colleagues (2015) also studied rates of hospitalization in patients receiving PIMs on 2003 Beers Criteria. Patients in this study also received varying levels of primary care. A total of 245,436 Australians over the age of 65 with at least one pharmaceutical claim of a PIM included on 2003 Beers Criteria were analyzed (Price et al., 2015). Results from this study indicate that regardless of the level of primary care received, using PIMs included in Beers Criteria increased the risk of hospitalization as much as 36% (Price et al., 2015).

Brown and colleagues (2016) conducted a retrospective cohort study analyzing managed care administrative data for 174,275 commercially insured adults over the age of 65. Both 2003 and 2012 Beers Criteria were used in the study, as well as STOPP criteria to determine the relationship between PIMs and hospitalizations and ED visits. Over 41% of the cohort used a PIM. Results from this study indicate that using PIMs was associated

with anywhere from two to three times greater risk for hospitalization and ED visits (Brown et al., 2016).

Zuckerman and colleagues (2006) conducted a retrospective cohort study using three years of data from the MarketScan Medicare Supplemental and Coordination of Benefits database to examine the relationship between PIM use and admission into LTC facilities. Patients were included if they were over the age of 65 and had not previously had a nursing home admission for one year prior to the study (Zuckerman et al., 2006). Subjects were followed until they were admitted to a nursing home, lost to follow-up, or the two-year study period ended. A total of 487,383 subjects were included in the study, and 22,042 were admitted to a nursing home (Zuckerman et al., 2006). Medication use was also analyzed, and PIMs were identified using 2003 Beers Criteria. Results from this study indicate that patients receiving a PIM in Beers Criteria had a 31% increased risk of being admitted to a nursing home compared to patients that used non-PIMs (Zuckerman et al., 2006).

2.7.2 ADEs

Four studies (Brown, Hutchison, Li, Painter, & Martin, 2016; Chang et al., 2005; Kanaan et al., 2013; Onda et al., 2015) included in this review specifically analyzed ADEs attributed to use of PIMs included in Beers Criteria. Previously discussed above, Brown and colleagues (2016) also included risk of experiencing an ADE due to PIM use as one of the primary outcomes of interest. As was the case with hospitalizations and ED visits in this study, PIM use was also associated with an increased risk of experiencing an ADE (Brown et al., 2016).

Chang et al. (2005) employed a prospective cohort study in Taiwan to evaluate if PIMs included on 1997 Beers Criteria were associated with ADEs in an outpatient setting. The study included 882 patients over the age of 65 that were prescribed at least one medication at an outpatient visit (Chang et al., 2005). Participants were surveyed one week following the outpatient visit, and information collected during the survey included ADEs that occurred within one week of receiving the prescription. All reported ADEs were independently evaluated. Of the 882 participants, phone surveys were completed for 550 patients. Almost 12% of the respondents were using a PIM, and a total of 126 patients experienced an ADE within one week of the outpatient visit (Chang et al., 2005). In this study, Beer Criteria PIM use was associated with a higher risk of experiencing an ADE. Additionally, medication non-compliance and polypharmacy were also associated with a higher risk of ADEs (Chang et al., 2005).

Using a nation-wide survey completed by pharmacists in Japan, Ondo et al. (2015) identified PIM-related ADEs present in older adults receiving home health care. The 2003 version of Beers Criteria, modified for medications available in Japan, was used to classify medications as PIMs. Survey data for 4,243 patients was analyzed. Almost 3,000 total PIMs were prescribed, and almost 50% of those surveyed received a PIM prescription. PIMs were responsible for 182 ADEs (Ondo et al., 2015). Ondo and colleagues (2015) identified five PIMs included in Beers Criteria that were responsible for the majority of ADEs, and short-acting benzodiazepines were responsible for almost 41% of ADEs. The most common ADEs attributed to benzodiazepine use included lightheadedness, sleepiness, and drowsiness (Ondo et al., 2015).

Kanaan and colleagues (2013) conducted a review of 1,000 consecutive ambulatory care discharge records from Massachusetts. The goal was to identify ADEs that occur within 45 days post-discharge (Kanaan et al., 2013). Patients included in the study were over the age of 65 and discharged to the community. Medications responsible for the ADEs were recorded, and 2012 Beers Criteria was used to identify PIMs. From the 1,000 records, 330 drug-related events occurred within the 45 day period post-discharge and 242 were categorized as an ADE (Kanaan et al., 2013). Of the 242 ADEs identified, "35% were considered to be preventable, 32% of which were serious and 5% life threatening" (Kanaan et al., 2013, p. 1896). Within the class of preventable ADEs, over 50% were occurred as a result of medication prescribing errors (i.e. wrong medication or wrong dose prescribed) (Kanaan et al., 2013). Results from this study indicate that Beers Criteria PIMs were responsible or almost 17% of the ADEs (Kanaan et al., 2013).

2.7.3 Quality of Life

Two studies (Fu, Liu, & Christensen, 2004; Franic & Jiang, 2006) included in this review investigated the relationship between Beers Criteria PIMs and the impact on quality of life or health status. Fu, Liu, and Christensen (2004) conducted a national study of the impact PIM use has on health outcomes, specifically on self-perceived health status. The Medicare Expenditure Panel Survey served as the data source in the study, and 2,305 patients were selected to be representative of the U.S. population of adults over the age of 65. Information collected in this data source included an individual patient's rating of their own health status (very good, good, fair, or poor) compared to others their age (Fu et al., 2004). Not all medications included in Beers Criteria were used in the study. Twenty-three medications included on 1997 Beers Criteria were used to define PIM use in the population.

Within the sample, 306 patients were classified as PIM users. Results from the survey data indicate that PIM use is significantly more likely to negatively impact a patient's perception of their health status compared to patients that use medications classified as appropriate (Fu et al., 2004).

Franic and Jiang (2006) also used the Medicare Expenditure Panel Survey in their longitudinal retrospective cohort study of the relationship between select PIMs included on 2003 Beers Criteria and health-related quality of life. Two common and widely used measures, the Short Form-12 and EuroQol's EQ-5D, were used to measure health related quality of life (Franic & Jiang, 2006). Participants were divided into case and control groups. There were 74 patients that received PIMs were included in the case group, and 370 patients that had appropriate medication use served as controls. The case group received more medications in general compared to the control group, with over 77% of cases received anywhere from five to 20 medications (Franic & Jiang, 2006). The number of prescriptions patients used is important to highlight as results from this study indicate that the number of prescriptions is a predictor for impact on health related quality of life. Results from this study also indicate that PIM use was associated with worse scores on the measures of health-related quality of life (Franic & Jiang, 2006).

As PIM use remains prevalent throughout the U.S. and other parts of the world, evidence suggests that Beers Criteria medications are linked to negative health outcomes, and it is expected that poor outcomes will continue as Beers Criteria medications continue to be prescribed in the future. Based on results from previous research, PIM use has serious implications on the health and well-being of older adults. PIM users face a greater risk of

hospitalization and institutionalization than those elderly patients using appropriate medications. Mortality rates are also impacted by PIM use, and elderly patients face a greater risk of death when prescribed PIMs. Patients are also more likely to experience a PIM-related ADE. ADEs attributed to PIMs in Beers Criteria negatively impact a patient's quality of life and are associated with a decline in functional status and diminished ability to perform activities of daily living.

2.8 Using Beers Criteria in Technology-Based Studies

As the use of technology assisted programs and electronic medical records becomes more prevalent, it is important to highlight how Beers Criteria has previously been integrated into technology-based intervention studies aimed to modify clinician behavior as it relates to medication management in elderly patients. A recently published study conducted in Canada developed a new technology system to evaluate clinical decision making within electronic medical records and the impact it has on improving medication prescribing in the elderly (Alagiakrishnan et al., 2016). Colleagues in Boston, Massachusetts conducted a prospective before-and-after study to evaluate whether PIM prescriptions could be reduced through a computerized order entry warning (CPOE) system (Mattison, Afonso, Ngo, & Mukamal, 2010). Terrell and colleagues (2009) and Raebel and colleagues (2007) each utilized a randomized, controlled trial using computer-assisted support to reduce PIM prescribing in the elderly.

Recognizing the impact polypharmacy and inappropriate medication use has in the elderly, Alagiakrishnan and colleagues (2016) aimed to demonstrate that incorporating medication alerts into an electronic medical record can improve medication safety. Additionally, the research team evaluated how this alert technology would best be used by

clinicians without disrupting their clinical workflow. An interesting component of this study was the use of both qualitative and quantitative methods (an approach not commonly used in previous studies of Beers Criteria). The intervention used was the Seniors Medication Alert and Review Technology, referred to as SMART. The 2012 version of Beers Criteria was integrated in the SMART application. Several types of events were collected including if clinicians accepted the SMART guidance, if they rejected the guidance and their reason for rejecting, and if they selected a recommendation or evidence link in the SMART system for review (Alagiakrishnan et al., 2016). One notable result of this study was the improvement in adhering to Beers Criteria recommendations through the SMART system. Clinicians were somewhat familiar with Beers Criteria, but were not adept in applying Beers Criteria recommendations in their clinical care routine. The medication alerts and the use of SMART encouraged clinicians to pay close attention to the drugs patients were already on and to give careful consideration before prescribing additional medications. Embedding Beers Criteria recommendations directly into the technology saved time in that clinicians did not have to stop to look up the recommendations during their clinical routine (Alagiakrishnan et al., 2016).

Mattison and colleagues (2010) incorporated medication-specific alerts into a non-commercialized CPOE system developed in-house within an academic medical center in Boston. Three medication classes included on 2003 Beers Criteria were used in the study. All medications were prescribed through the CPOE system, and the system was used with all hospitalized patients over the age of 65. The primary purpose of the CPOE system was to alert clinicians when PIMs were ordered and to recommend changing the PIM dose or recommend an alternative medication. The study team calculated the number of orders of

medications represented in the three select medication classes that were prescribed to patients admitted within a six-month period before the CPOE system was in place. The newly implemented system was tested for roughly five months, after which all medication orders were recorded for a three-year period. Before-and-after analyses were conducted, and the mean rate of PIM prescribing decreased from 11.56 to 9.94 orders per day (Mattison et al., 2010). Results also indicated an immediate reduction in the rate of PIM orders upon CPOE implementation, and the decrease in PIM orders was sustained over time. Additionally, adherence to the medication warnings was monitored, and clinicians showed no signs of being fatigued by repeated alerts and warnings. Results from this study indicate that CPOE systems can be a useful tool to positively impact clinician prescribing patterns. Incorporating alerts and alternative medication recommendations in such systems has the potential to decrease the number of PIMs ordered for elderly hospitalized patients (Mattison et al., 2010).

Raebel and colleagues (2007) conducted a prospective intervention trial that included all ambulatory care patients over the age of 65 represented in the Kaiser Permanente Colorado health maintenance organization. All 59,680 elderly health plan members were randomized to either an intervention or usual care group, and patients and providers (clinicians and pharmacists) were blinded to the group assignments. Patients randomized to the usual care group were prescribed medications according to usual clinical practice. Eleven PIMs, of which nine are represented in 2003 Beers Criteria, were selected prior to the study by a group of physicians and pharmacists specializing in geriatric care to be included as medications of interest in the intervention group. A medication warning system was used to alert a pharmacist when a patient in the intervention group was

prescribed one of the 11 PIMs. Upon receiving the medication alert, pharmacists communicated the medication warning to the provider by phone. Pharmacists did not receive these warnings for patients in the usual care group (Raebel et al., 2007). A total of 1,187 patients were dispensed at least one of the 11 PIMs included in the study. Medication alerts and pharmacist intervention impacted PIM use. Of the patients randomized to the usual care group, 2.2% were dispensed a PIM compared to 1.8% of patients randomized to the intervention group (Raebel et al., 2007). Raebel and colleagues (2007) also demonstrate the importance of collaboration between healthcare providers that work specifically with the elderly population, which is something that cannot be imposed through computerized systems. In this study, pharmacists were alerted when a PIM was prescribed, but minimizing PIM dispensing required the pharmacists and physicians to collaborate to discuss safer medication alternatives (Raebel et al., 2007).

A more recent randomized trial (Terrell et al., 2009) was implemented to evaluate the use of a computerized decision support system to reduce PIM use in elderly adults discharged from the ED. Sixty-three physicians from an academic hospital in Indiana were randomized to an intervention or a usual care control group. Nine medications represented in 2003 Beers Criteria were selected by an expert panel to be included in the intervention. The panel also selected safer alternative medications for each of the nine PIMs. Computerized decision support was only available to the physicians in the intervention group. When the ED physician attempted to prescribe one of the select nine PIMs at patient discharge, the computer system alerted the physician. The physician could choose to order one of the pre-determined safer alternative medications or ignore the alert and recommendations all together (Terrell et al., 2009). The intervention lasted for

approximately 18 months. At least one of the select PIMs was prescribed during 3.9% of the visits managed by the usual care physicians, compared to 2.6% of the visits managed by a physician in the intervention group. When comparing the number of PIMs to all medications prescribed by physicians, the proportion of prescribed PIMs decreased from 5.4% to 3.4% (Terrell et al., 2009).

2.9 Using Beers Criteria to Quantify Impact of PIM Use on Healthcare Costs

Few studies included in this literature review used Beers Criteria medications in their evaluation of economic outcomes related to PIM use. Very limited information is available linking the use of PIMs included in Beers Criteria to the overall impact on healthcare costs on a national level. The limited research that is available includes information derived from what is now an outdated version of Beers Criteria. Only two studies were identified that represented a primary goal of quantifying the economic impact that PIM ADEs have on healthcare costs (Fu et al., 2007; Stockl et al., 2010).

Fu and colleagues (2007) were the first to include healthcare cost analyses in a study of PIMs included on the 2003 version of Beers Criteria. This retrospective cohort study aimed to describe how PIM use is related to healthcare expenditures and to quantify the incremental healthcare expenditures related to PIM use (Fu et al., 2007). Fu and colleagues (2007) used the 2000–2001 Medical Expenditure Panel Survey, a nationally representative survey of the U.S. non-institutionalized population that captures healthcare utilization, expenditures, payment source, and insurance coverage. The sample included patients over the age of 65 at the start of 2000 that were continuously enrolled in all five rounds of the Medical Expenditure Panel Survey. Rounds one and two were used as a washout period, and patients receiving any PIMs included on 2003 Beers Criteria in rounds

one and two were excluded. This ensured that all patients included in the analysis began without PIM exposure. Patients that received at least one PIM in rounds three and/or four were classified as the exposed group, and patients not receiving a PIM in rounds three and four were classified as the unexposed group. To ensure all healthcare expenditures associated with PIM use were captured in the analysis, patients receiving a PIM in round 5 were also excluded (Fu et al., 2007).

Stockl and colleagues (2010) also conducted a retrospective cohort study of the risk of experiencing select ADEs while on a limited number of PIMs and the costs associated with those specific PIMs. Pharmacy and medical claims data from a managed care organization were analyzed. Using the 2003 version of Beers Criteria, 23 anticholinergics and sedative hypnotics classified with a high ADE severity rating and 4 adverse event categories were included in the study (Stockl et al., 2010). Patients over the age of 65 receiving one of the 23 PIMs comprised the exposed group, and patients not receiving one of the 23 PIMs were classified as controls (Stockl et al., 2010).

Although national healthcare expenditure figures associated with Beers Criteria PIM use are limited, these two studies suggest that PIM use is associated with higher healthcare costs. Fu et al. (2007) reported that average costs for patients in the group exposed to Beers Criteria PIMs were over $6,800 compared to costs of nearly $5,000 for the unexposed group. Similarly, Stockl et al. (2010) reported higher costs in their PIM groups as well. In the anticholinergic group, the adjusted total healthcare costs for the exposed group was $18,400 compared to just over $15,000 in the group exposed to anticholinergic PIMs in Beers Criteria. Those exposed to sedative hypnotics had nearly

$27,500 in total healthcare costs compared to $22,500 total costs for non-exposed (Stockl et al., 2010).

2.10 Propensity Score Matching

While randomized controlled trials continue to serve as the gold standard to analyze interventions (Spieth et al., 2016), there is growing interest in using observational, or nonrandomized, data to estimate treatment effect. Researchers have no control over treatment assignment in observational data (D'Agostino & Rubin, 2000), and since randomization is not possible in observational studies, careful design and statistical techniques are needed to appropriately manage these data (Stuart, 2010). First developed by Rosenbaum and Rubin (1983), PSM is a statistical approach used to create baseline matched comparison groups where they do not otherwise exist in observational data. Treated patients are often significantly different than untreated patients in observational studies due to variation in baseline characteristics (Austin, 2011). The large differences that may exist in treatment and control groups in observational studies can lead to bias in the interpretation of treatment effect (D'Agostino & Rubin, 2000). As is the case for any study of observational data, the risk of selection bias and the threats to internal validity are much higher compared to randomized controlled trials. Although randomization is not possible in observational studies, PSM techniques are used to analyze observational data in a way that mimics some of the characteristics of a randomized controlled trial by creating two balanced samples, one that received treatment and a sample that did not receive treatment, that are comparable on all observed differences (Austin, 2011). If these methods are used successfully to closely model selection into one group or the other they may be referred to as quasi-experimental design.

The term matching in PSM refers to the process of balancing the distribution of observed baseline covariates in the treatment and control groups (Stuart, 2010), and the propensity score represents the likelihood of receiving treatment based on the covariates (D'Agostino & Rubin, 2000). The PSM procedure includes multiple steps.

The first step is to select the covariates that are hypothesized to be related to the treatment and sometimes the outcome, although there remains some controversy here. Once covariates have been selected based on clinical knowledge, a multivariable logistic regression is performed to model selection into one comparison group or the other conditional on all of the covariates (Garrido et al., 2014; Stuart, 2010). The logistic regression results in one probability per person of selecting into the treatment group, this is the propensity score. Including a variable that is not associated with the treatment will have little impact on the propensity score. However, not including a variable that is associated with treatment is much more detrimental in terms of bias (Stuart, 2010). The second step is to use a mathematical algorithm to one person who received treatment to a similar person who did not based on similarity of propensity score. These algorithms are available in most statistical software packages today. Next it is important to confirm the propensity score is balanced across the treatment and control groups, i.e. that it was a good match.

There is not a single ideal matching algorithm or technique. Instead, the ideal matching technique is the one that best balances the groups at baseline to reduce selection bias (Garrido et al., 2014). Researchers should choose whether to match controls with or without replacement (i.e. whether a control should be matched to more than one treated individual) (Austin, 2011). Matching controls with replacement is useful when there are

few similar controls to match and compare to individuals in the treatment group (Stuart, 2010), however this has some ramification with regard to non-independence between subjects which may have to be accounted for in the final analysis. In greedy matching, or nearest neighbor matching, a treated individual is selected at random and matched the control with the propensity score that is closest to the randomly selected treated individual (Austin, 2011). Greedy matching performs best when there is no competition for controls (Stuart, 2010). Researchers can also choose to employ nearest neighbor matching within a pre-specified caliper, or required maximum distance allowed between the treated propensity score and the control. Another technique, optimal matching, ensures that the total overall difference between the propensity score of the matched pairs is minimized (Austin, 2011). Greedy matching is ideal to generate well matched treatment and control groups, and optimal matching is ideal to generate well matched pairs within the treated and control groups (Stuart, 2010).

After matching is complete, the quality of the matched samples should be evaluated to ensure the covariates are balanced appropriately across the treatment and comparison groups. Matching techniques may need to be modified and the propensity score may need to be redefined in order to create new treatment and comparison groups that achieve balance after matching (Garrido et al., 2014; Stuart, 2010). Once treatment and comparison groups with adequate balance are finalized, the researcher can continue to the outcomes analysis (Stuart, 2010). Adequate balance is often indicated as being achieved when the standardized differences in means or proportions in each variable used in the propensity score model is less than 0.2 (Stuart, 2010).

The primary advantage of PSM is that baseline characteristics are similar between comparison groups. This ensures that observed differences, or covariates, are similar between groups (Austin, 2011) and this, alone, has been shown to reduce selection bias by at least 90% (Rubin). However, weakness remains as PSM cannot account for unobserved factors that may impact treatment assignment and outcome and hidden bias may still exist after matching (Garrido et al., 2014). Another challenge of PSM is that the propensity score must be estimated. Errors in propensity score modeling can also result in bias of the estimated treatment effect (Imai & Ratkovic, 2014). Despite its limitations, PSM offers advantages to health services researchers in that observational data can be used to understand how the treatment effects multiple outcomes (i.e. cost and health outcomes) (Garrido et al., 2014).

2.10.1 Beers Criteria Research using Propensity Score Matching

Fu and colleagues (2007) and Stockl and colleagues (2010) are the only studies identified in this literature review that included Beers Criteria and PSM techniques. In their analysis examining differences in total healthcare expenditures, Fu and colleagues (2007) identified 115 patients classified as being exposed (received at least one PIM on 2003 Beers Criteria during the washout period) and 605 patients classified as being unexposed (did not receive a PIM on 2003 Beers Criteria during the washout period). PSM (simple matching with caliper) was used to match exposed and unexposed patients. To ensure balance of baseline characteristics observed in the sample of patients, and to minimize sample selection bias, several covariates were included in the matching: age, race, gender, insurance type, total number of prescriptions in 2001, baseline health conditions measured by Charlson comorbidity index and SF-12 physical condition summary, and healthcare

expenditures for 2000 (expenditures associated with emergency room visits, inpatient visits, outpatient visits, office-based visits, homecare, and prescription drug use) (Fu et al., 2007). The sample was balanced across each group, with 103 included in the exposed group matched to 103 in the unexposed group. Based on analysis of these matched groups with similar demographic and baseline characteristics, Fu and colleagues (2007) estimated that the incremental healthcare expenditures associated with PIM use in the elderly in 2001 was over $7 billion.

Using medical and pharmacy claims from a U.S. managed care organization, Stockl and colleagues (2010) classified patients to an exposed group if they received one of 23 selected medications represented in 2003 Beers Criteria included in the analysis. Patients not receiving one of the 23 medications of interest served as controls. The 23 medications were categorized to one of four medication groups that patients could be matched to: Anticholinergics, Narcotics, Trimethobenzamide Hydrochloride, and Sedative Hypnotics (Stockl et al., 2010). Patients in the exposed and control groups were matched on a one-to-one basis using PSM. The sample was balanced across each group, and an equal number of exposed patients and controls were included in the Anticholinergics, Narcotics, Trimethobenzamide Hydrochloride, and Sedative Hypnotic groups. Covariates used in the matching included demographics, health plan type, Charlson Comorbidity Index, number of Beers Criteria medications other than index medication during 180 day pre-period, sum of days supply for non-Beers Criteria anticholinergics during 180 day pre-period, pre-period claims for specific medications with potential to cause cognitive impairment, days supply for opioid agonists or partial agonists other than index medication during pre-period, pre-period claims for specific medications with potential to cause extrapyramidal

effects, pre-period claims for specific medications with potential to cause sedation, pre-period claims for specific hypotensive medications with potential to increase risk of fall or fracture, and pre-period claims for specific conditions that may increase the risk of fall or fracture (Stockl et al., 2010). Results from this study indicate that patients using medications from the four Beers Criteria categories included in this study had higher medical expenses at baseline compared to controls (Stockl et al., 2010).

Studies of Beers Criteria employing PSM are limited, and the few studies that have been conducted utilized, what are now, outdated versions of Beers Criteria and or a limited set of Beers Criteria. A current economic analysis is needed to determine the increased health care costs associated with using PIMs included in a more current version of Beers Criteria.

2.11 Summary

People over the age of 65 are living longer, and, as a result, require more medications to manage an increasing number of health problems as they age. Polypharmacy, the use of multiple medications concurrently by the same patient to treat one or more health conditions, is prevalent and problematic in this population. The use of too many medications, and especially those medications classified as potentially inappropriate in Beers Criteria, is associated with an increased risk for drug interactions, medication non-adherence, decline in functional status, and ADEs. These events often require an ED visit, hospitalization, or institutionalization, which in turn drives up healthcare costs. ADEs are especially detrimental to the healthcare system and are responsible for billions of dollars in healthcare spending. One strategy that will address increasing healthcare costs prevalent in older adults is to reduce unnecessary ADEs,

especially those events associated with potentially inappropriate medications included in Beers Criteria.

Several medication evaluation tools are used throughout the world; however, Beers Criteria remains the most frequently used tool in geriatric care. Previous studies of medications included in Beers Criteria indicate that PIM use occurs frequently in outpatient care, primary care, acute care, psychiatric centers, LTC settings, and home health care. Many commonly used medications may not be appropriate for this population, placing older adults at greater risk for negative health outcomes and a decline in quality of life. PIM use negatively impacts healthcare utilization and is associated with a higher frequency of outpatient visits, hospitalizations, and ED visits compared to patients not using PIMs. These unnecessary visits ultimately impact healthcare expenditures and are taxing for individual patients and their families, healthcare settings, third party payers, and federal health programs.

Evaluating the relationship between PIM use, healthcare utilization, and healthcare spending is clearly an underrepresented area in the literature, and was one of the primary aims of this dissertation. No published studies were found that included a current, nationwide cost analysis of PIM use in the elderly. Studies that have incorporated a recent version (2012 or 2015) of Beers Criteria have failed to offer information related to cost or spending as a result of healthcare utilization associated with using medications included in Beers Criteria. Given the modifications to Beers Criteria over the years, it is difficult to determine whether the analyses of Fu and colleagues (2007) and Stockl and colleagues (2010) remain relevant to current medication use. Our goal was to analyze utilization and costs in the framework of the current healthcare environment while using PSM to control

for selection bias. We also elected to use a more recent version of Beers Criteria that allowed us to examine those medications that have been added to Beers Criteria since the 2003 version used by Fu et al. (2007) and Stockl et al. (2010). Additionally, to our knowledge, no one has compared healthcare utilization and cost of using medications included in Beers Criteria compared to alternative medications not included in Beers Criteria.

The primary aim of this dissertation was to demonstrate the impact that using PIMs included in Beers Criteria has on healthcare resource utilization and spending by including medications that are relevant to today's prescribing practices. We also sought to reveal how healthcare costs associated with using Beers Criteria medications differ from using alternative, and arguably safer, medications not included in Beers Criteria. Given the number of health conditions and medications used within the elderly population, a well-managed medication regimen is imperative to minimize unnecessary hospitalizations and decrease healthcare costs.

III. METHODOLOGICAL BACKGROUND

Americans are living longer, and, as a result, the elderly population continues to increase dramatically. More than 20% of the total U.S. population will be represented by adults over the age of 65 in the coming decades (Ortman et al., 2014). The growing elderly population is a burden to the U.S. healthcare system, and as the aging population continues to grow, healthcare costs are expected to increase as much as 25% by the year 2030 (Centers for Disease Control and Prevention, 2013). One factor responsible for the high cost of healthcare in the elderly population is an increased use of medications to treat a growing number of health problems. The rate of medication use in the elderly population will continue to rise in the coming years (Page et al., 2010). Older adults are often prescribed medications that are not medically necessary, and, as a result, are seven times more likely to experience a negative health outcome attributed to medication use that require an emergency room visit and/or hospitalization (Budnitz et al., 2011). It was estimated that over $7 billion in annual incremental healthcare expenditures in 2001 were related to inappropriate medication use in community dwelling individuals over the age of 65 (Fu et al., 2007). Medications included in Beers Criteria may be especially inappropriate for use in adults aged 65 and older. Novel strategies are needed to reduce PIM use in order to minimize the burden the elderly population has on the healthcare system.

We conducted a retrospective cohort study to quantify healthcare resource utilization and healthcare costs attributable to using PIMs included in 2012 Beers Criteria. Community-dwelling Medicare patients with private supplementary insurance were

included in the study, and healthcare utilization and costs were analyzed using 2013 Truven Health Marketscan® Commercial Claims and Encounters Database (Truven Health Analytics, 2017). We compared hospital admissions, days spent in the hospital, and total healthcare costs generated from inpatient and outpatient visits and prescription medication use for patients that received medications in Beers Criteria compared to a well-matched group of patients that received medications not included in Beers Criteria.

Aim 1

To examine the healthcare resource utilization for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria.

Hypotheses

H1: The odds of hospital admission in a group of patients who receive Beers Criteria medications is greater than the odds of hospital admission in a group of patients who do not receive Beers Criteria medications.

H0: OR Hospital Admissions (Beers Criteria group) = OR Hospital Admissions (Control group)

Ha: OR Hospital Admissions (Beers Criteria group) ≥ OR Hospital Admissions (Control group)

H2: Among patients who had a hospitalization, the mean number of days admitted to the hospital is greater in patients who receive Beers Criteria medications compared to patients who do not receive Beers Criteria medications.

H0: μ Hospital Days (Beers Criteria group) = μ Hospital Days (Control group)

Ha: μ Hospital Days (Beers Criteria group) ≥ μ Hospital Days (Control group)

Aim 2

To determine the total healthcare costs for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria.

Hypothesis

H1: Total healthcare costs are greater in patients who receive Beers Criteria medications compared to patients who do not receive Beers Criteria medications.

H0: μ Healthcare Cost (Beers Criteria group) = μ Healthcare Cost (Control group)

Ha: μ Healthcare Cost (Beers Criteria group) ≥ μ Healthcare Cost (Control group)

3.1 Study Design

The health services research aims in this retrospective cohort study required a specialized set of methodological approaches. A summary of the study design is depicted in Figures 3.1 and 3.2. Data was purchased from Truven Analytics, a company that maintains healthcare utilization and cost records linked at the patient level. One year (2013) of health insurance billing data was analyzed using the Marketscan® insurance database containing files for paid claims generated by over 40 million continuously insured individuals covered by commercial insurance and Medicaid and Medicare supplemental benefits. Data for community-dwelling patients aged 65 and over were included in this study. A preliminary review of the 2013 Marketscan® sample indicated a minimum of 4.1 million covered lives 65 or older were represented in the database.

Patients were divided into either a treatment group (patients that received Beers Criteria medications) or control/comparison group (patients that received non-Beers Criteria medications). In order to appropriately assign patients to these groups, all patients

were observed for a three-month baseline period from January 1, 2013 through March 31, 2013. PIM use was identified using the list of 2012 Beers Criteria medications represented in Table 3.1 since this was the most recently updated Beers Criteria prior to the data collection year.

A total of 138 medications from eight therapeutic areas in 2012 Beers Criteria were included in the study. We obtained each individual National Drug Code (NDC) number represented in the 2013 version of Red Book for each of the 138 included Beers Criteria medications. Red Book includes prescription drug product and pricing information (Kokoski, 2009). An NDC is a unique, three-segment number comprised of 10 digits assigned by the U.S. Food and Drug Administration that identifies the manufacturer, strength, dosage form (i.e. capsule, tablet, liquid), formulation of the drug, and the commercial package size (U.S. Food and Drug Administration, 2017). We excluded mineral oil as there are no NDC codes available since this is not a prescription medication. Phenothiazines were also excluded from our prescription data as this medication is used so infrequently that NDC codes are limited. A total of 73,644 individual NDC codes were used to identify Beers Criteria medications in Marketscan®. Individuals that received at least one Beers Criteria medication during the baseline period were categorized into the treatment group, and patients that did not receive a medication included in Beers Criteria in the baseline period were assigned to the control group.

During the baseline period, inpatient records were used to construct the Charlson Score (outlined further in section 3.5) (Quan et al., 2011), and patients were classified as 1 for having a hospital admission or 0 for not having a hospital admission during baseline. Outpatient visits were used to construct a score for Elixhauser Comorbidity indicator

conditions (outlined further in section 3.5) (Elixhauser et al., 1998) observed at baseline. A frailty index (outlined further in section 3.5) was used to classify patients at baseline into three groups: robust, pre-frail, or frail (Faurot et al., 2015; Rockwood, Andrew, & Mitnitski, 2007). This process was applied to both the treatment and control groups.

To ensure that patient characteristics were similar during the baseline period, PSM techniques (outlined further in section 3.5) were used to match patients treated with Beers Criteria medications and controls that did not receive Beers Criteria medications. Patients were matched on age, gender, geographic region, hospital admission, member days, frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators. All patients that received a Beers Criteria medication in the baseline period, designated as the treated group, were matched in a 1:1 fashion to controls that did not receive a Beers Criteria medication in the baseline period.

The primary outcomes for this study were 1) having at least one hospital admission; 2) of those that were hospitalized, the total number of hospital admissions and the total numbers of days spent in the hospital; and 3) total costs derived from inpatient visit, outpatient visit, and prescription drug costs. After PSM matching was completed, and the treatment and control groups were determined to meet PSM balance standards of less than or equal to 0.2 standardized differences for each matched covariate, inpatient and outpatient encounters and prescription drug use was analyzed post-baseline for 275 days (April 1 through December 31, 2013). A detailed description of the Marketscan® database, including advantages and limitations to using this database, and the statistical analyses used to address the aims of this study are included in this chapter.

Figure 3.1: Treatment & Control Group Design

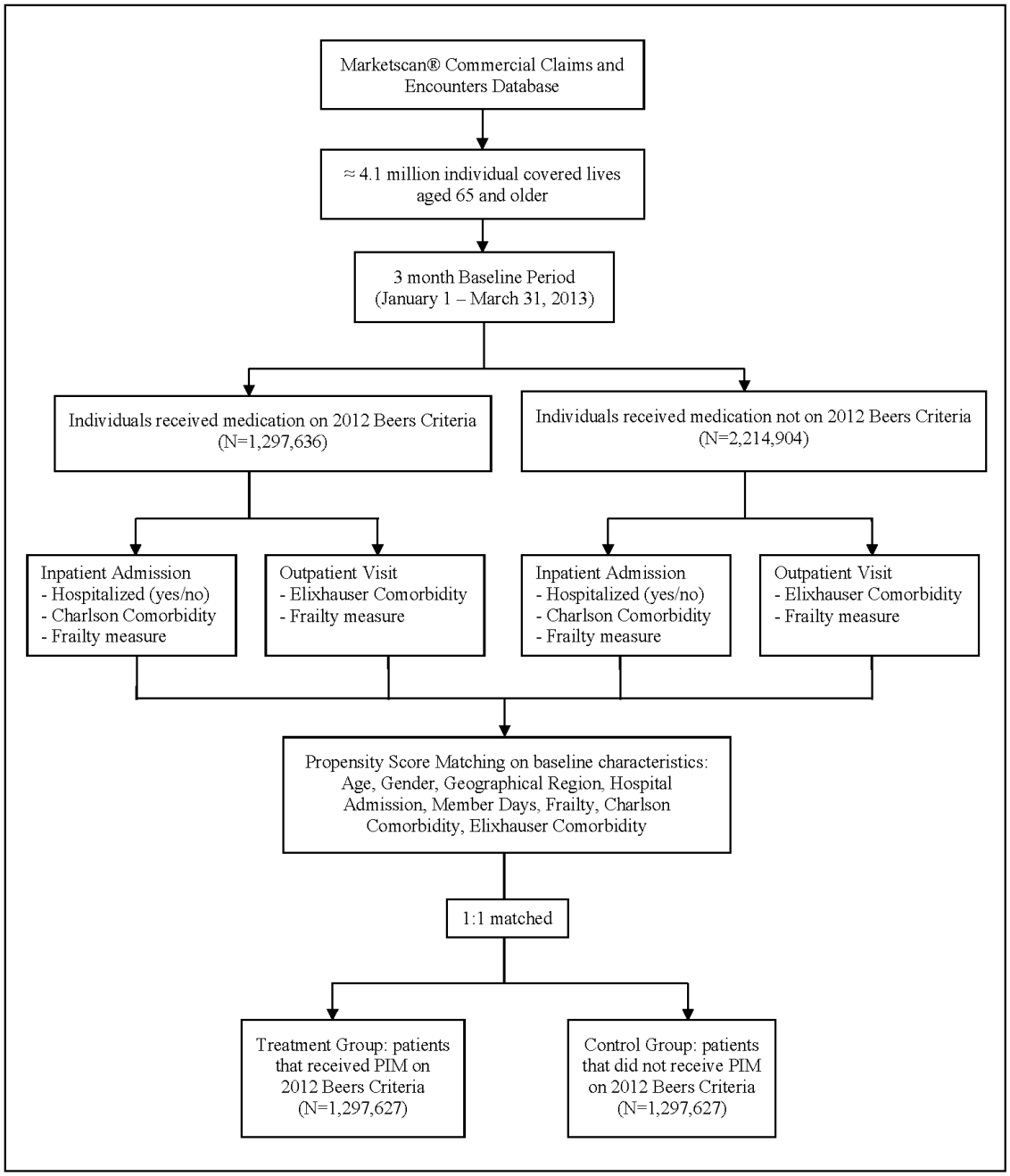


Figure 3.2: Analysis of Primary Outcome Measures

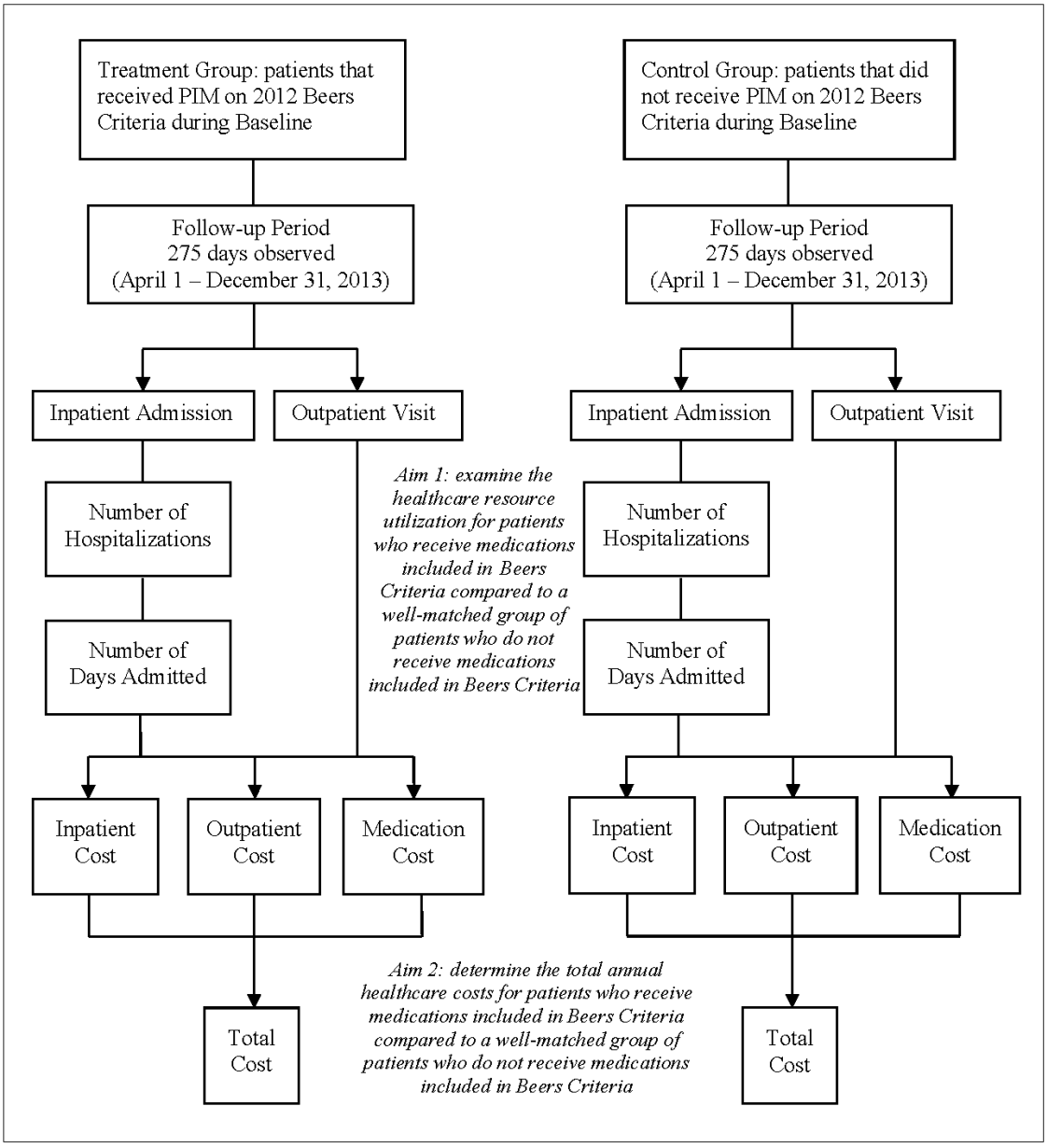


Table 3.1: 2012 Beers Criteria Medications Used in Study

Beers Medications & Classes
Anticholinergics 1st Generation Antihistamines *Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Diphenhydramine, Doxylamine, Hydroxyzine, Promethazine, Triprolidine* Antiparkinson Agents *Benztropine, Trihexyphenidyl* Antispasmodics *Belladonna alkaloids, Clidinium-Chlordiazepoxide, Dicyclomine, Hyoscyamine, Propantheline, Scopolamine*
Antithrombotics Antithrombotic *Dipyridamole, Ticlopidine*
Anti-infective Anti-infective *Nitrofurantoin*
Cardiovascular Alpha$_1$ Blocker *Doxazosin, Prazosin, Terazosin* Alpha Agonist, Central *Clonidine, Guanabenz, Guanfacine, Methyldopa, Reserpine* Antiarrhythmic *Amiodarone, Digoxin, Disopyramide, Dofetilide, Dronedarone, Flecainide, Ibutilide, Procainamide, Propafenone, Quinidine, Sotalol* Antihypertensive *Nifedipine* Diuretic *Spironolactone*

Central Nervous System
Tertiary TCA
Amitriptyline, Chlordiazepoxide-amitriptyline, Clomipramine, Doxepin, Imipramine, Perphenazine-amitriptyline, Trimipramine

1st Generation Antipsychotic
Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Molindone, Perphenazine, Pimozide, Promazine, Thioridazine, Thiothixene, Trifluoperazine, Triflupromazine

2nd Generation Antipsychotic
Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone

Anxiolytic
Meprobamate

Barbiturates
Amobarbital, Butabarbital, Butalbital, Mephobarbital, Pentobarbital, Phenobarbital, Secobarbital

Benzodiazepines Short Acting
Alprazolam, Estazolam, Lorazepam, Oxazepam, Temazepam, Triazolam

Benzodiazepines Long Acting
Chlordiazepoxide, Chlordiazepoxide-amitriptyline, Clidinium-chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Flurazepam, Quazepam

Ergoloid
Ergoloid mesylates

Nonbarbiturate Sedative
Chloral hydrate

Nonbenzodiazepine hypnotics
Eszopiclone, Zaleplon, Zolpidem

Vasodilator
Isoxsuprine

Endocrine
Hormones
Desiccated thyroid, Estrogens, Growth Hormone, Insulin, Megestrol, Methyltestosterone, Testosterone

Sulfonylurea
Chlorpropamide, Glyburide

Gastrointestinal Antiemetic *Trimethobenzamide* Gut Motility Stimulator *Metoclopramide*
Pain Narcotic *Meperidine, Pentazocine* NonCOX NSAIDs *Aspirin, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Ibuprofen, Ketoprofen, Meclofenamate, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin* NSAIDs *Indomethacin, Ketorolac* Skeletal Muscle Relaxants *Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine*

3.2 Study Population

Community-dwelling Medicare patients aged 65 and older with private supplementary insurance represented in the Truven Health Marketscan® Commercial Claims and Encounters Database for the year 2013 were the target population to examine the aims of this study. Marketscan® does not capture data for poor or dually insured individuals, and this study did not include poor or dually insured individual patients in the study population. We selected 2013 data because this is the most current data available through Marketscan® that can capture prescription drug use based on a recent version of Beers Criteria. Unfortunately, a full year of data was not available at the time of this project to use 2015 Beers Criteria. As a result, we used 2012 Beers Criteria to identify PIM use in

the study population. We selected patients aged 65 and older to align with the Beers Criteria age of interest given that the criteria are intended for the care of individuals specifically aged 65 and older. The 2013 Marketscan® database contains a minimum of 4.1 million covered lives that are 65 or older.

3.2.1 Medicare Coverage in the Elderly

Established in 1966, Medicare is a single-payer, national health insurance program funded by payroll taxes, beneficiary premiums, and general revenue and provides coverage for beneficiaries over the age of 65, the disabled, and end-state rental disease patients. The program is comprised for four parts, each covering specific healthcare services. Medicare Part A is hospital insurance to cover expenses generated from hospital admissions, LTC, home care, and hospice care. Part B provides coverage for outpatient services and medical supplies. Part C represents the Medicare Advantage Plan offered by private companies. Medicare Part D provides prescription drug coverage. In 2015, Medicare provided coverage to over 45 million elderly Americans (Altman & Frist, 2015). Medicare has been attributed to improved access to care in the elderly, a reduction in healthcare disparities, and has positively impacted life expectancy since its creation (Altman & Frist, 2015).

As adults age, they are more likely to experience an increase in chronic conditions and a decline in functional status. Nearly half of Medicare beneficiaries have at least four chronic conditions, over 30% experience some level of functional cognitive, and/or mental impairment, and over 25% of beneficiaries perceive their health to be fair or poor (Altman & Frist, 2015). Chronic conditions and poor functional status result in an increased likelihood of requiring an ED visit or hospitalization, and these conditions are also attributed to increased Medicare spending on inpatient services, LTC, and home health

(Neuman, Cubanski, Huang, & Damico, 2015). Medicare spending exceeded $585 billion in 2013 (Altman & Frist, 2015). In 2011, nearly 25% of Medicare beneficiaries were over the age of 80, and this group was responsible for roughly 33% of total Medicare spending (Neuman et al., 2015). Approximately 32% of the Medicare population aged 70 to 79, and these beneficiaries are responsible for 30% of Medicare spending (Neuman et al., 2015). The 65 to 69 age group was responsible for 15% of total Medicare spending (Neuman et al., 2015). The largest share of Medicare spending in beneficiaries over the age of 65 was on inpatient care, and inpatient service expenses increased more than 2.5 times in 66 to 89-year-old beneficiaries (Neuman et al., 2015). As the U.S. elderly population continues to grow in the years ahead, the number of Medicare beneficiaries and the total Medicare spending will increase as well. This phenomenon will not only strain the Medicare system, but other payers as well (Neuman et al., 2015).

3.3 Administrative Claims Data

Every patient encounter within the healthcare system (i.e. hospitalizations, outpatient office visits, use of prescription medications) generates healthcare administrative data (Cadarette & Wong, 2015). This data is available for large populations and includes information related to individual health services that are used (Riley, 2009). Administrative claims databases were originally created for administrative or billing purposes and, more specifically, to manage payments for services rendered by healthcare providers in managed care organizations or nationally funded health programs (Suissa & Garbe, 2007). Health insurance claims and encounter data from Medicare, Medicaid, and the Veterans' Health Administration are a common source of administrative claims data in the U.S. (Riley, 2009). "Medicare has the broadest population-based administrative data

system in the health arena, covering about 97% of the elderly" (Riley, 2009, p.51). Claims data from private insurance payers are also available and frequently used, and managed care plans, state hospital discharge datasets, and hospital data are used to describe healthcare utilization and costs on an individual level (Riley, 2009). Additionally, drug dispensing data is also available in claims databases to describe medication use. Although dispensing data reflect specific medications that were dispensed as opposed to actual prescriptions written, drug dispensing data can also be used to infer prescribing patterns (Cadarette & Wong, 2015).

Administrative claims data are frequently used in research to study utilization, benefits, negative outcomes, and costs of health care delivery (Cadarette & Wong, 2015). Cost-analyses are especially common given that administrative claims records often include the billed charges or the amount that was actually paid for a given service (Riley, 2009). Economic research of health conditions and diseases often requires patient-level data represented in administrative claims data to capture healthcare services used, the costs associated with specific services, and healthcare costs generated over time (Riley, 2009). Patient-level data files can be linked by a unique patient identifier and use of healthcare services and the costs associated with those services can often be tracked longitudinally (Suissa & Garbe, 2007).

3.3.1 Marketscan®

Truven Health Analytics created the Marketscan® warehouse to address a growing need for quality data for privately insured individuals in the U.S. This warehouse is comprised of nine fully integrated claims databases containing the largest collection of employer-based patient data in the U.S. These databases include over 28 billion patient

records for 22 million covered lives and reflect healthcare utilization and costs for all aspects of care (Hansen & Chang, 2011).

The Marketscan® Commercial Claims and Encounters Database, one of nine Marketscan® databases, is a nationally representative administrative claims database that consists of de-identified, standardized medical and pharmaceutical claims data. In addition to providing data for all claims generated by commercially insured individuals annually, the Marketscan® insurance database also includes a number of key data elements, including demographic information, type of admission and date, diagnosis codes, diagnosis-related group, financial information such as total and net payments, and drug information including national drug code. A unique enrollee identifier is assigned to each individual in Marketscan®, and these member identification codes allow researchers to follow patients longitudinally over time (Truven Health, 2016).

3.3.2 Advantages and Limitations of Marketscan®

There are numerous advantages to using administrative databases, including Marketscan® data, commonly used in research to examine health related questions. Administrative data, also known as billing data or archival data, are commonly used in research to examine health related questions. Retrospective billing data are readily available and less costly to obtain (Suissa & Garbe, 2007). Patients represented in administrative databases can be followed over long, continuous periods of time offering advantages for retrospective studies. Administrative databases are advantageous for their large sample sizes that enable health services researchers to generalize results to a larger population providing stronger external validity than is generally seen in smaller randomized study designs (Suissa & Garbe, 2007). These databases also include vulnerable

subgroups, such as the elderly population represented in this study. Marketscan® has the largest convenience sample available in proprietary databases. Marketscan® captures the full continuum of care in all settings, including hospital visits that were important to this study. The data contains individual-level healthcare claims and hospital discharge information from large employers, managed care organizations, hospitals, Medicare, and Medicaid (Hansen & Chang, 2011).

Marketscan® offers the advantage of high-quality coding, and a diagnosis is coded on 99% of all claims. Other coding advantages of Marketscan® include procedure coding on claims and payment and charge information (Hansen & Chang, 2011). However, one weakness of administrative databases is the variation of coding practices and the possibility that potential errors may occur in diagnosis coding. Coding is used specifically for billing purposes, and information represented in these databases is not collected for research purposes (Suissa & Garbe, 2007). Coding practices may threaten the internal validity of this study; however, many coding weaknesses were equally present in both the treatment and control groups resulting in a marginal effect estimate not biased by most coding variation. Considering that we had to rely on coding information and billing data which may not be completely accurate, we may have unintentionally excluded patients that should be included in the sample based on these errors and coding limitations. Additionally, some individuals were excluded from the sample population given that medium and small employers are not represented in Marketscan® data (Hansen & Chang, 2011). Marketscan® databases are based on a large sample, but this is sample is not random. There may be hidden biases in the data.

Retrospective research based on these data must be done with care and with the awareness that issues might arise given the unalterable challenges of administrative data. We addressed these weaknesses through statistical techniques such as propensity score matching (outlined in further detail below). These techniques allowed us to create a well-matched control group in order to examine differences between the Beers Criteria and non-Beers Criteria groups. Any data-related bias is expected to be equally distributed across both groups, ensuring that the non-random sample represented in Marketscan® remains the ideal source of data for this study.

Important to note is the inclusion of detailed prescription drug information in Marketscan® data, and this was of particular interest in this study. The database includes complete information on drug use patterns and outpatient prescriptions (Hansen & Chang, 2011). This database offers a distinct advantage over other databases for research on medication use. Other administrative databases do not include prescription drug information or these databases only track individual drug prescription trends or prescription fills. Marketscan® data combine clinical visits and prescription drug data to allow for analyses necessary to understand the impact of medication use on healthcare utilization and healthcare costs (Hansen & Chang, 2011).

This particular database was especially valuable to address the aims of this study. Marketscan® data allowed us to study healthcare resource utilization (Aim 1) and measure total healthcare costs in a well-matched group of Medicare patients that received either Beers Criteria or non-Beers Criteria medications (Aim 2). The use of Marketscan® data to answer these health services and cost-related questions about PIM use is essential, especially in situations where prospectively collected data are not feasible.

3.4 Study Variables

Claims data from the Marketscan® Commercial Claims and Encounters Database were analyzed and data elements representing demographic information, inpatient and outpatient medical information, financial information, and prescription drug use were included in this study. Table 3.2 outlines the specific variables used in the PSM design phase of this dissertation, and Table 3.3 outlines the data elements that were used for final outcomes analysis. Patient data on age, gender, geographical region of residence, number of days insured (member days), and a binary variable of any hospital admission during baseline was used to define demographic characteristics that were used for dataset construction and for PSM. Patient race was not used because this variable is not available in Marketscan®. Inpatient and outpatient records were used to construct baseline health measure variables used in PSM. Prescription drug variables included a binary variable for having received any medication included in Beers Criteria, NDC number, and generic product ID. Healthcare utilization variables used for data analysis included hospital admission, number of hospital admissions for those that had a hospital admission, and number of days hospitalized for those that had a hospital admission. The sum of inpatient visit costs, outpatient visit costs, and prescription drug costs as well as total costs were used in final analysis. A comprehensive list of all variables included in the final dataset is included in Appendix M.

Table 3.2: Variables used in PSM

Demographic Information	Age Gender Geographic Region
Healthcare Coverage	Member Days
Hospital Admissions	Hospital Admission (yes/no)
Baseline Health Measures	Frailty Score (robust, pre-frail, frail) Charlson Comorbidity Score Elixhauser Comorbidity Indicators Asthma Cardiac dysrhythmias Chronic obstructive pulmonary disease Chronic renal failure Conduction disorders of the heart Congestive Heart Failure Cystic fibrosis Diabetes with chronic complications Diabetes without chronic complications Diverticulosis and diverticulitis Epilepsy Heart valve disorders Hepatitis HIV infection Hypertension Multiple sclerosis Otitis media Parkinson's Disease Peri-; endo-; and myocarditis Pulmonary heart disease Rheumatoid arthritis Schizophrenia Senile Sickle cell anemia Systemic lupus erythematosus Vertigo

Table 3.3: Variables used for dataset construction and final analysis

Demographic Information	Patient ID Age Gender Geographic Region Member Days
Healthcare Utilization Information	Hospital admission (yes/no) Number of hospital admissions Number of days hospitalized
Drug Information	Received any beers medication (yes/no) National Drug Code Generic product ID
Financial Information	Sum of inpatient visit costs Sum of outpatient visit costs Sum of prescription drug costs Total costs

3.5 Propensity Score Matching

PSM techniques are used to analyze observational data in a way that mimics some of the characteristics of a randomized controlled trial (Austin, 2011). For the purposes of this study, PSM was used to create a control group where a control did not otherwise exist to design a quasi-randomized study structure (Rosenbaum & Rubin, 1983). These techniques ensured that we created a well-matched control group to examine differences between the Beers Criteria (treatment) and non-Beers Criteria (control) groups. We used this technique to equally distribute any measured bias, or hidden bias correlated with any PSM variables, across both groups, ensuring that the non-random sample represented in the Marketscan® observational databases behaved more like a randomized design with selection bias control.

PSM allowed us to attribute excess poor outcomes in the study groups, on an averaged population level, to the causative factor of use of Beers Criteria or non-Beers Criteria medications because average baseline characteristics between the groups were the

same. If this were a randomized study, we would take a large cohort of screened patients that needed a medication for a particular condition and randomize them to receive either a Beers Criteria or a non-Beers Criteria medication. The resulting poor outcomes in the Beers Criteria group, for example, should be able to be attributed to being on the Beers Criteria medication (or vice versa), allowing us to determine the negative outcomes that may be attributed to Beers Criteria or non-Beers Criteria medications. PSM controlled for most sources of selection bias, allowing us to make causal inferences where there was non-random assignment (Heckman, Ichimura, Smith, & Todd, 1996). PSM reduces or eliminates the effects of confounding by indication when using observational data (Austin, 2011).

In the first step of the propensity score matching process, we performed a logistic regression analysis to estimate the propensity of being allocated to the Beers Criteria group. Known available variables, including age, gender, geographic region, hospital admission, member days, and baseline health measures (frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators), that were related to the likelihood of receiving Beers Criteria medications were included as covariates in the logistic regression model in order to create similar treatment and control groups (Brookhart et al., 2006). Controlling for these patient characteristics ensured that the differences we observed in the groups were not due to baseline imbalance across these populations. In a set of subjects, all of whom have the same propensity score, the distribution of observed baseline covariates was the same between the Beers Criteria and non-Beers Criteria individuals.

We used 1:1 greedy matching in our propensity model in which a treated individual was selected at random and matched to a control individual with the propensity score

closest to the randomly selected treated individual (Austin, 2011). This process was repeated until all Beers Criteria patients were matched to a control patient or until a control patient could not be found to match to a treated patient. Greedy matching is ideal to generate well matched treatment and control groups (Stuart, 2010). The propensity model was considered final when appropriate balance between groups of all the covariates included in the propensity score logistic regression model was indicated by standardized differences less than 0.2 (Stuart, 2010). This method eliminates over 90% of those differences that are inherent in the analysis of observational data and minimizes the chance for selection bias (Austin & Mamdani, 2006; Austin, 2009).

3.5.1 Baseline Health Conditions Used in Propensity Score Matching

One key step in PSM was to ensure observed baseline characteristics were balanced between the treatment and control groups. If this were a randomized trial, we would assume that the characteristics observed in the group that received Beers Criteria medications would be balanced with those characteristics observed in the control group (patients that did not receive Beers Criteria medications). In our study, by comparing matched treatment and control groups with the same observable characteristics we were able to mimic the characteristics of a randomized controlled trial.

It is well recognized that patients with multiple chronic conditions have an increased risk of having poor health outcomes and experiencing medical events that ultimately impact healthcare utilization and cost (Sambamoorthi, Tan, & Deb, 2015). Often time patients with multiple chronic conditions are also categorized as frail (Weiss, 2011). For the purposes of this dissertation, baseline health conditions were a key covariate to include in PSM. We used the Charlson Comorbidity Index, Elixhauser Comorbidity

Indicators, and a frailty measure to account for baseline health conditions in both the treated and control groups in PSM matching.

The Charlson Comorbidity Index was developed by Charlson, Pompei, Ales, and MacKenzie (1987) to evaluate and classify those comorbid conditions that impact the risk of death within patients participating in longitudinal studies. A review of 559 hospital medical records identified 17 comorbidity variables that were associated with death within one year. A weighted score was applied to each of the 17 conditions. This weighted index considers the presence and number of comorbid conditions and the severity of those conditions (Charlson et al., 1987). A Charlson score is derived by identifying specific comorbid conditions included in the index, scoring each condition using pre-determined points, and accounting for additional points associated with the patient's age group (Charlson et al., 1987). What was originally created for use with medical records, the Charlson Comorbidity Index has been applied to administrative data generated from hospital discharges. Deyo and colleagues (1992), Romano et al. (1993), and D'Hoore and colleagues (1996) independently adapted the index for use in research using International Classification of Diseases (ICD) diagnosis and procedure codes, specifically ICD-9 and ICD-9-CM. Quan and colleagues (2011) also developed ICD-10 coding algorithms that to apply the Charlson Comorbidity Index to administrative data. Considering advancements in treatment and management of chronic diseases and improved mortality rates since the initial development of the Charlson Comorbidity Index, Quan and colleagues (2011) updated the work of Charlson et al. (1987) to include a weighted index of 12 comorbidities and a maximum score of 24. A higher score indicates a greater likelihood of death within one year (Quan et al., 2011). The 12 comorbidities included in the Charlson Comorbidity

Score in this study were: AIDS/HIV, any malignancy (including leukemia and lymphoma), chronic pulmonary disease, congestive heart failure, dementia, diabetes with chronic complications, hemiplegia or paraplegia, metastatic solid tumor, mild liver disease, moderate or severe liver disease, renal disease, and rheumatologic disease.

The Elixhauser Comorbidity Index (1998) was developed using administrative data to not only enhance measures of comorbidity represented in administrative databases but to also predict health outcomes. In developing this index, Elixhauser and colleagues (1998) defined comorbidity as a clinical condition present before hospitalization. Although unrelated to the primary reason for hospitalization, the comorbidities included in the index are highly likely to impact mortality and resource use once hospitalized (Elixhauser et al., 1998). Accounting for both acute and chronic conditions, comorbidities were selected for the index based on a review of the literature and the ICD-9-CM coding manual (Elixhauser et al., 1998). Carl van Walraven and colleagues (2009) later translated the binary variables presented in the Elixhauser Comorbidity Index into a single numeric score to be applied to hospital administrative databases to predict inpatient mortality. Similar to the Charlson Comorbidity Index, the Elixhauser Comorbidity Index accounts for comorbidities associated with mortality. However, this index also accounts for comorbidities associated with increased inpatient length of stay and hospital charges (Elixhauser et al., 1998). In this study, we used outpatient records to identify 29 Elixhauser comorbidity indicators, and these indicators were used as a dichotomous variable as being present or not present prior to hospitalization. We excluded three of the 29 Elixhauser Comorbidity Indicators (chronic ulcers of the skin, late stroke, and paralysis) as there were no subjects included in the study that had these conditions. The following 26 conditions were used in PSM: asthma, cardiac

dysrhythmias, chronic obstructive pulmonary disease, chronic renal failure, conduction disorders of the heart, congestive heart failure, cystic fibrosis, diabetes with and without chronic complications, diverticulosis and diverticulitis, epilepsy, heart valve disorders, hepatitis, HIV infection, hypertension, multiple sclerosis, otitis media (middle ear infection), Parkinson's disease, pericarditis, endocarditis, and myocarditis, pulmonary heart disease, rheumatoid arthritis, schizophrenia, senile, sickle cell anemia, systemic lupus erythematosus, and vertigo.

Frailty is associated with negative health outcomes (Faurot et al., 2015) and can serve as a source of confounding bias in pharmacoepidemiologic studies (Kim & Schneeweiss, 2014). Frail patients are already susceptible to a greater risk of negative health outcomes, and clinicians are likely to modify treatment patterns based on the individual condition of the patient. The riskier the condition or intervention is, the more likely a clinician will let frailty impact their judgment regarding the type of treatment that patient receives. In other words, physicians are likely to modify their treatment because they use frailty to bias their judgment (Kim & Schneeweiss, 2014). Frailty is not frequently documented in medical records, and it is unlikely that frailty will be captured in claims data any time in the near future (Faurot et al., 2015). Given that pharmacoepidemiologic and observational studies of administrative claims data must rely on clinical information provided by the treating clinician, it is likely that these studies will be negatively impacted by prognostic factors, such as frailty, that are not captured in the claims data (Kim & Schneeweiss, 2014).

Using a sample of Medicare beneficiaries, Faurot et al. (2015) developed an algorithm in which dependency on activities of daily living may serve as a proxy to

measure frailty in administrative claims data. “Claims that identify ADL [activities of daily living] dependency, used in conjunction with those referring to comorbidity, may serve as proxy for frailty” (Faurot et al., 2015, p. 60). The diagnostic and procedure codes that were associated with dependency on activities of daily living, and therefore predictors of frailty, included use of durable medical equipment (home hospital bed, wheelchair, and home oxygen), podiatry care, and rehabilitation care (Faurot et al., 2015). We chose these predictors and used the frailty score developed by Faurot and colleagues (2015) to separate frailty from our measures of comorbid conditions. For the purposes of this study, patients were categorized as being robust (frailty category 0), pre-frail (frailty category 1), and frail (frailty category 2) (Rockwood, Andrew, & Mitnitski, 2007). Controlling for these frailty predictors in PSM was expected to minimize bias and improve balance between Beers Criteria treated individuals and controls.

3.6 Statistical Analysis

Once PSM techniques were complete, and the matched Beers Criteria treatment group and non-Beers Criteria controls were finalized based on propensity scores, an analytical data set derived from the Marketscan® database was used to conduct analyses for the two aims. Healthcare utilization outcomes of interest included any hospital admission, number of hospital admissions (of those that were admitted), and total days in the hospital (of those that were admitted). We defined cost outcomes of interest from the perspective of an insurer. For the purposes of this study, insurance payments were denoted as costs and measured as the aggregated total in insurance payments captured for each patient during the follow up period in 2013 (post-baseline). Payments by type of resource

used were also examined for inpatient payments, outpatient services, and prescription medications.

Descriptive statistics and crude outcome estimates were compared for the treatment and control groups by using Chi-square tests for categorical variables and two sample Student's t-tests for continuous variables. Mean and standard deviation was calculated to describe age, number of days insured (member days), and Charlson Comorbidity Score before and after PSM, and t-tests were used to test for differences in these variables in the treatment and control groups. Mean and standard deviation was also calculated to describe the number of days those in the treatment group were exposed to each Beers Medication class after PSM. Frequency and percent was calculated to describe gender, geographical region, hospital admission, frailty category, and 26 Elixhauser Comorbidity Indicators before and after PSM, and Chi-square statistics were used to test for differences in these variables in the treatment and control groups.

Unadjusted and adjusted risk of hospital admission, number of admissions (for those that were hospitalized), and number of days spent in the hospital (for those that were hospitalized) during the follow-up period were calculated (Aim 1). Frequency and percent was calculated to describe unadjusted hospital admissions. Of those that had a hospital admission, mean and standard deviation was calculated to describe unadjusted number of admissions and unadjusted number of days hospitalized. We used a logistic regression to predict the risk (adjusted odds ratio) of hospital admission for treated and control patients while controlling for baseline covariates (age, gender, geographic region, hospital admission, member days, frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators). A zero-inflated Poisson model was used to calculate the adjusted

number of hospital admissions for treated and control patients that experienced at least one hospitalization during follow up while controlling for baseline covariates. We used a negative binomial count model to calculate the adjusted number of days spent in the hospital for treated and control patients that experienced at least one hospitalization during follow up.

Inpatient visit costs, outpatient visit costs, prescription medication costs, total unadjusted costs, and total adjusted costs during the follow-up period were analyzed for the treatment and control groups. Means and standard deviations were used to calculate unadjusted inpatient visit, outpatient visit, prescription medication, and total costs. A two sample Student's t-test was used to test for differences in healthcare costs between the treatment and control groups. We used generalized linear modeling, first described by Nelder and Wedderburn (1972), to test the hypothesis that Beers Criteria medications are associated with higher healthcare costs compared to non-Beers Criteria medications (Aim 2). Healthcare cost data are usually right skewed, and as mean costs increases variability increases. Studies using generalized linear modeling for cost analysis have shown good distributional fit when using the gamma response distribution with a log link function (Moran, Solomon, Peisach, & Martin, 2007). To adjust for the expected non-normal distribution of healthcare costs in this study, we used a Gamma distributed generalized linear model with a logarithmic link function to calculate the adjusted total healthcare costs for treated and control patients.

3.7 Summary

This retrospective cohort study used research strategies not previously included in utilization and cost analyses of medication classes represented in 2012 Beers Criteria to

compare healthcare utilization and healthcare costs for patients that received medications included in Beers Criteria compared to patients that received medications not included in Beers Criteria. Prescription drug use and inpatient and outpatient visits were described using medical and pharmaceutical claims data represented in Marketscan® Commercial Claims and Encounters Database. Community-dwelling Medicare patients aged 65 years and older with supplementary commercial health insurance represented in 2013 Marketscan® were included to examine the differences in utilization and cost when medications were prescribed according to Beers Criteria versus when they are not prescribed according to these criteria. Inpatient and outpatient visits and prescription drug records were extracted. Records for services received through March 31, 2013 were separated and used for the construction of baseline measures. Records from April 1st and later were separated and used for constructing the cost and event measures. Patients that received medications that are contraindicated due to Beers Criteria (treatment group) were matched, and compared, to patients that received non-Beers Criteria medications (control group). We examined the healthcare resource utilization for patients who received medications included in Beers Criteria compared to a well-matched group of patients who did not receive medications included in Beers Criteria (Aim 1). The costs of inpatient and outpatient visits and prescription drug use was analyzed and total adjusted costs were compared between the treatment and control groups. (Aim 2). This was the first study to analyze healthcare utilization rates and overall healthcare costs for patients that were prescribed medications that adhere to Beers Criteria guidelines versus patients with the same conditions that were prescribed medications that do not adhere to Beers Criteria guidelines.

IV. RESULTS

4.1 Study Groups

The 2013 Marketscan® database contains 4,146,894 covered lives that are 65 or older and that were potentially eligible for inclusion in this study. Of these patients, we extracted 3,512,540 patients (84.7%) that had at least one prescription medication claim during a three-month baseline period from January 1, 2013 through March 31, 2013. We used National Drug Codes (NDC) represented in the 2013 version of Red Book for each medication included in Beers Criteria to identify 1,297,636 patients (37%) that were prescribed a PIM included in Beers Criteria during baseline. These patients were classified as the treatment group. Alternatively, 2,214,904 patients (63%) received a prescription medication during baseline not represented in Beers Criteria according to the NDC. These patients were classified as the control group.

4.1.1 Demographics and Characteristics Before Matching

The Treatment and Control groups differed significantly with respect to age, gender, geographical region, hospital admission, number of days enrolled in insurance plan (member days), frailty, Charlson Comorbidity Score, and most Elixhauser Comorbidity Indicators (Table 4.1). The treatment cohort had a statistically significant higher average age (74.0 versus 73.4 years, p-value<0.0001), than the control cohort. A greater proportion of patients included in the study were female (53.9%), and more of these females received medications included in Beers Criteria (58.4% female in the treatment group versus 51.2%

female in the control group, p-value<0.0001). The treatment group comprised of a higher proportion of individuals that were admitted to the hospital (3.8% versus 2.0%, p-value<0.0001). On average, the treatment group was also insured longer (355 member days versus 348 member days, p-value<0.0001).

Those that received medications in Beers Criteria had more comorbid conditions and were frail. The mean Charlson comorbidity score for patients treated with Beers Criteria was 0.09 (compared to a mean score of 0.05 in the control group) and ranged from 0-15 at baseline. Of those patients classified as frail, 4.3% received medications included in Beers Criteria compared to 2.4% that did not receive a Beers Criteria medication (p-value<0.0001). In general, the treatment group had a greater proportion of each Elixhauser Comorbidity Indicator included in this study compared to the control group. The greatest differences in comorbid indicators among the treatment and control groups included hypertension (37.0% in the treatment group versus 29.5% in the control group, p-value<0.0001), conduction disorders of the heart (14.1% in the treatment group versus 8.5% in the control group, p-value<0.0001), and cardiac dysrhythmias (12.7% in the treatment group versus 7.6% in the control group, p-value<0.0001).

Table 4.1: Demographics and Characteristics Before Matching of Elderly Patients that Received Prescription Medications During Baseline Period

	Overall N= 3,512,540	**Treatment N= 1,297,636**	**Control N= 2,214,904**	**p-value***
Age [a]	73.6 (±6.8)	74.0 (±6.8)	73.4 (±6.8)	<.0001
Female Gender [b]	1,891,911 (53.9)	757,179 (58.4)	1,134,732 (51.2)	<.0001
Geographical Region [b]				<.0001
Northeast	858,061 (24.4)	291,603 (22.5)	566,458 (25.6)	
North Central	914,256 (26.0)	359,890 (27.7)	554,366 (25.0)	
South	913,578 (26.0)	378,051 (29.1)	535,527 (24.2)	
West	760,253 (21.6)	257,403 (19.8)	502,850 (22.7)	
Unknown	66,392 (1.9)	10,689 (0.8)	55,703 (2.5)	
Hospital Admission [b]	93,115 (2.7)	48,870 (3.8)	44,245 (2.0)	<.0001
Member Days [a]	350.2 (±51.2)	354.7 (±43.5)	347.6 (±55.1)	<.0001
Frailty Score [b]				<.0001
Robust	2,754,407 (78.4)	930,800 (71.7)	1,823,607 (82.3)	
Pre-frail	649,186 (18.5)	311,361 (24.0)	337,825 (15.3)	
Frail	108,947 (3.1)	55,475 (4.3)	53,472 (2.4)	
Charlson Comorbidity Score [a]	0.1 (±0.5)	0.09 (±0.6)	0.05 (±0.4)	<.0001
Elixhauser Comorbidity Indicators [b]				
Asthma	88,923 (2.5)	41,360 (3.2)	47,563 (2.2)	<.0001
Cardiac dysrhythmias	331,772 (9.5)	164,646 (12.7)	167,126 (7.6)	<.0001
Chronic obstructive pulmonary disease	221,536 (6.3)	105,497 (8.1)	116,039 (5.2)	<.0001
Chronic renal failure	121,542 (3.5)	56,523 (4.4)	65,019 (2.9)	<.0001
Conduction disorders of the heart	372,287 (10.6)	183,034 (14.1)	189,253 (8.5)	<.0001
Congestive heart failure	106,323 (3.0)	55,825 (4.3)	50,498 (2.3)	<.0001
Cystic fibrosis	133 (0.0)	64 (0.0)	69 (0.0)	0.008
Diabetes with chronic complications	232,229 (6.6)	107,375 (8.3)	124,854 (5.6)	<.0001

Diabetes without chronic complications	521,671 (14.9)	228,960 (17.6)	292,711 (13.2)	<.0001
Diverticulosis and diverticulitis	65,847 (1.9)	28,475 (2.2)	37,372 (1.7)	<.0001
Epilepsy	20,519 (0.6)	9,491 (0.7)	11,028 (0.5)	<.0001
Heart valve disorders	134,302 (3.8)	59,126 (4.6)	75,176 (3.4)	<.0001
Hepatitis	7,689 (0.2)	3,434 (0.3)	4,255 (0.2)	<.0001
HIV infection	1,448 (0.0)	595 (0.1)	853 (0.0)	0.001
Hypertension	1,134,065 (32.3)	479,773 (37.0)	654,292 (29.5)	<.0001
Multiple sclerosis	5,181 (0.1)	2,556 (0.2)	2,625 (0.1)	<.0001
Otitis media	32,743 (0.9)	14,004 (1.1)	18,739 (0.9)	<.0001
Parkinson's Disease	26,341 (0.8)	12,431 (1.0)	13,910 (0.6)	<.0001
Peri-; endo-; and myocarditis	41,308 (1.2)	21,157 (0.9)	20,151 (0.9)	<.0001
Pulmonary heart disease	29,495 (0.8)	13,587 (1.1)	15,908 (0.7)	<.0001
Rheumatoid arthritis	44,272 (1.3)	21,231 (1.6)	23,041 (1.0)	<.0001
Schizophrenia	2,805 (0.1)	1,905 (0.2)	900 (0.0)	<.0001
Senile	80,738 (2.3)	38,115 (1.9)	42,623 (1.9)	<.0001
Sickle cell anemia	241 (0.0)	85 (0.2)	156 (0.0)	0.59
Systemic lupus erythematosus	12,084 (0.3)	5,905 (0.5)	6,179 (0.3)	<.0001
Vertigo	78,277 (2.2)	36,386 (2.8)	41,891 (1.9)	<.0001

[a] Mean (±SD)
[b] N (%)
* p-values were calculated using two sample t-test

4.1.2 Propensity Score Matching Results

The mean propensity score in both the treated group and control group was 0.40 (minimum score of 0.05 and maximum score of 0.93 in both groups). A total of 39 potentially biasing factors (age, gender, geographic region, hospital admissions, member days, frailty [robust, pre-frail, frail], Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators) were assessed for patients treated with Beers Criteria medications and controls that received medications not in Beers Criteria through PSM. We excluded three of the 29 Elixhauser Comorbidity Indicators (chronic ulcers of the skin, late stroke, and paralysis) from our propensity model as there were no subjects included in the study that had these conditions. In controlling for these factors, we can be sure that baseline

characteristics were similar between comparison groups given that observed differences, or covariates, were similar between groups (Austin, 2011).

A graph of the standardized difference in means is represented in Figure 4.1. As depicted in the graph, we achieved improved balance across all 39 covariates included in the propensity model given that all standardized mean differences for the matched observations are within the recommended limits of -0.25 and 0.25 after matching (represented by the shaded area) (Rubin, 2001). We also reduced selection bias of these known factors by matching on propensity score, which is one of the primary goals of PSM (Stuart, 2010; Rosenbaum & Rubin, 1983). The standardized difference in means and percent reduction in bias for each of the 39 covariates used in the propensity model are also represented in Table 4.2.

Figure 4.1: Standardized Mean Differences

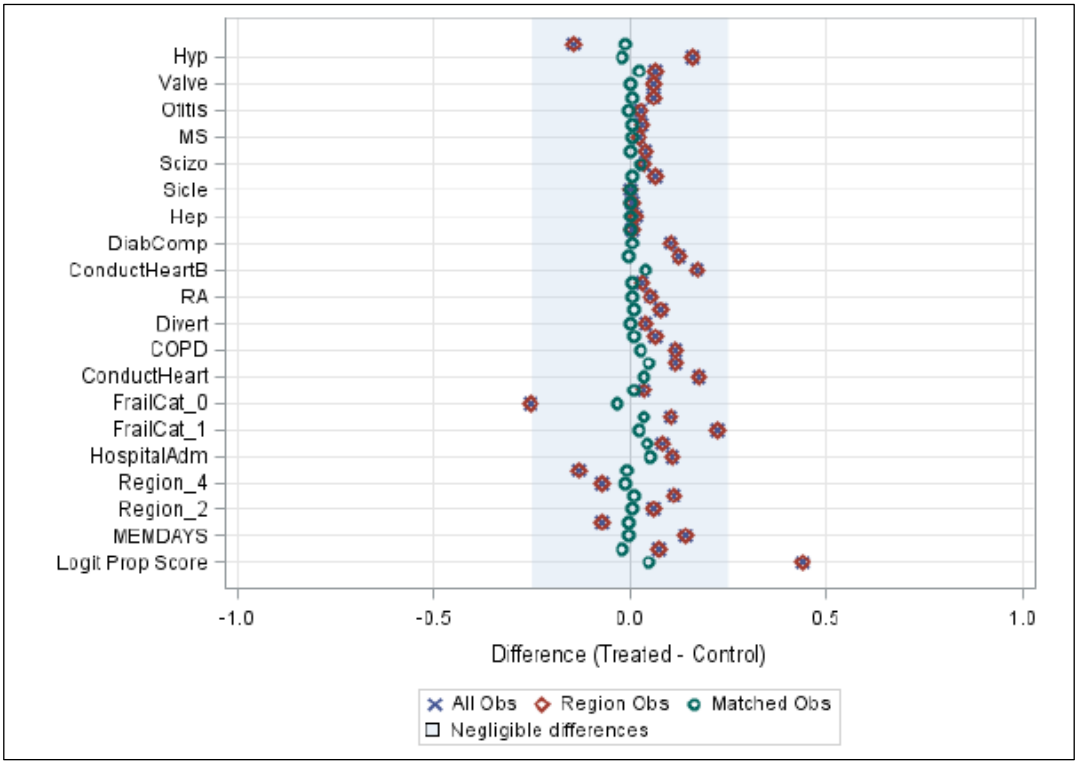


Table 4.2. Demographics, Characteristics, and Reduction in Bias After Matching During Baseline Period

	Total matched N= 2,595,254	**Treatment N= 1,297,627**	**Control N= 1,297,627**	**SD***	**%Reduction in Bias**
Age [a]	74.0 (±6.8)	73.9 (±6.8)	74.1 (±6.9)	-0.02	74.62
Female Gender [b]	1,507,587 (58.1)	757,171 (58.4)	750,416 (57.8)	-0.01	92.69
Geographical Region [b]					
Northeast	585,293 (22.6)	291,603 (22.5)	293,690 (22.6)	-0.00	94.82
North Central	716,286 (27.6)	359,885 (27.7)	356,401 (27.5)	0.01	90.08
South	750,264 (28.9)	378,048 (29.1)	372,216 (28.7)	0.01	90.93
West	520,746 (20.1)	257,402 (19.8)	263,344 (20.3)	-0.01	84.03
Unknown	22,665 (0.9)	10,689 (0.8)	11,976 (0.9)	-0.01	94.14
Hospital Admission [b]	86,951 (3.4)	48,863 (3.8)	38,088 (2.9)	0.05	53.05
Member Days [a]	354.8 (±42.7)	354.7 (±43.5)	354.9 (±41.8)	-0.01	96.34
Frailty Score [b]					
Robust	1,880,420 (72.5)	930,800 (71.7)	949,620 (73.2)	-0.03	86.32
Pre-frail	612,118 (23.6)	311,359 (24.0)	300,759 (23.2)	0.02	90.66
Frail	102,716 (4.0)	55,468 (4.3)	47,248 (3.6)	0.04	65.96
Charlson Comorbidity Score [a]	0.1 (±0.6)	0.09 (±0.6)	0.07 (±0.5)	0.04	50.69
Elixhauser Comorbidity Indicators [b]					
Asthma	80,745 (3.1)	41,358 (3.2)	39,387 (3.0)	0.01	85.39
Cardiac dysrhythmias	314,924 (12.1)	164,637 (12.7)	150,287 (11.6)	0.04	78.50
Chronic obstructive pulmonary disease	203,171 (7.8)	105,489 (8.1)	97,682 (7.5)	0.02	79.19
Chronic renal failure	110,783 (4.3)	56,517 (4.4)	54,266 (4.2)	0.01	87.79
Conduction disorders of the heart	351,845 (13.6)	183,025 (14.1)	168,820 (13.0)	0.03	80.31
Congestive heart failure	100,790 (3.9)	55,820 (4.3)	44,970 (3.5)	0.05	58.65
Cystic fibrosis	122 (0.0)	64 (0.0)	58 (0.0)	0.00	74.55

Diabetes with chronic complications	213,359 (8.2)	107,369 (8.3)	105,990 (8.2)	0.00	95.97
Diabetes without chronic complications	459,253 (17.7)	228,953 (17.6)	230,300 (17.8)	-0.00	97.66
Diverticulosis and diverticulitis	57,205 (2.2)	28,474 (2.2)	28,731 (2.2)	-0.00	96.09
Epilepsy	18,518 (0.7)	9,491 (0.7)	9,027 (0.7)	0.00	84.69
Heart valve disorders	117,893 (4.5)	59,125 (4.6)	58,768 (4.5)	0.00	97.63
Hepatitis	6,771 (0.3)	3,434 (0.3)	3,337 (0.3)	0.00	89.69
HIV infection	1,216 (0.1)	595 (0.1)	621 (0.1)	-0.00	72.71
Hypertension	972,418 (37.5)	479,764 (37.0)	492,654 (38.0)	-0.02	86.63
Multiple sclerosis	4,918 (0.2)	2,555 (0.2)	2,363 (0.2)	0.00	81.14
Otitis media	28,506 (1.1)	14,001 (1.1)	14,505 (1.1)	-0.00	83.34
Parkinson's Disease	24,621 (1.0)	12,431 (1.0)	12,190 (0.9)	0.00	94.37
Peri-; endo-; and myocarditis	39,016 (1.5)	21,154 (1.6)	17,862 (1.4)	0.02	64.80
Pulmonary heart disease	26,232 (1.0)	13,585 (1.1)	12,647 (1.0)	0.01	78.02
Rheumatoid arthritis	41,679 (1.6)	21,231 (1.6)	20,448 (1.6)	0.01	89.87
Schizophrenia	2,776 (0.1)	1,898 (0.2)	878 (0.1)	0.03	25.96
Senile	75,108 (2.9)	38,113 (2.9)	36,995 (2.9)	0.01	91.49
Sickle cell anemia	170 (0.0)	85 (0.0)	85 (0.0)	0.00	100.00
Systemic lupus erythematosus	11,455 (0.4)	5,905 (0.5)	5,550 (0.4)	0.00	84.46
Vertigo	72,004 (2.8)	36,382 (2.8)	35,622 (2.8)	0.00	93.58

[a] Mean (±SD)
[b] N (%)
* Standardized Difference

Matching treated and control patients resulted in an 89.6% total reduction in bias all covariates. Several Elixhauser Comorbidity Indicators demonstrated the greatest amount of reduction in bias compared to all 39 covariates used in matching, including sickle cell anemia (100%), diabetes without chronic complications (97.7%), and heart valve disorders (97.6%). Of the other variables, member days had the greatest amount of reduction bias (96.3%). The least amount of percentage reduction in bias was observed in

Schizophrenia (26.0%), Charlson Comorbidity Score (50.7%), and hospital admission (53.1%).

Each of the 39 matched covariates resulted in statistically equal treatment and control groups on these known potentially biasing factors. As shown in Table 4.2, the standardized mean differences for all covariates were well under the recommended maximum standardized difference value of 0.25 (Rubin, 2001). We reported the standardized mean differences in this study as we expected p-values to be statistically significant due to the large sample size. The largest standardized mean difference after matching was observed in hospital admissions (0.05) and Congestive Heart Failure (0.05).

4.1.3 Demographics and Characteristics After Matching

As shown in Table 4.2, after PSM the total matched sample size was reduced from 3,512,540 to 2,595,254 patients. After using 1:1 matching techniques, the Beers Criteria treated and control groups were each comprised of a sample of 1,297,627 patients included in analysis. The average age of the matched population was 74.0 years. A greater proportion of patients after matching were female (58.1%). On average, the matched population was insured for 354.8 days.

After matching, there were small differences observed in age, sex, hospital admissions, member days, frailty, and Charlson Comorbidity Score between treated individuals and controls (Table 4.2). The smallest differences were observed in age, member days, geographical region, and Charlson Comorbidity Score. The largest differences were observed in sex, hospital admissions, and frailty. The proportion of females that received medications included in Beers Criteria was 58.4% versus 57.8% proportion of controls that did not receive Beers Criteria medications. The treatment group

comprised a slightly higher proportion of individuals that were admitted to the hospital (3.8% versus 2.9%). Of those patients classified as frail, 3.8% received medications included in Beers Criteria compared to 2.9% that did not receive a Beers Criteria medication.

While not all differences in Elixhauser Comorbidity Indicators were completely eliminated after matching, we observed a much better fit with the largest differences detected in hypertension, conduction disorders of the heart, and cardiac dysrhythmias. Prior to matching, there was a 7.5% difference in the proportion of treated individuals with hypertension compared to controls. After matching the difference in the proportion of hypertension between the treatment and control groups was reduced to 1.0%. There was a 5.6% difference in the proportion of treated individuals with conduction disorders of the heart compared to controls before matching, and the proportion difference between groups was reduced to 1.1% after matching. Prior to matching, there was a 5.1% difference in the proportion cardiac dysrhythmias. After matching the difference in the proportion of cardiac dysrhythmias between the treatment and control groups was reduced to 1.1%. The proportion of all other Elixhauser Comorbidity Indicators among the treatment and control groups was under one percent.

4.1.4 Exposure to Beers Criteria Medications After Matching

Table 4.3 represents the average number of days treated individuals were exposed to each Beers Criteria medication class after matching. Of the 29 medication classes included in this study, the greatest exposure to Beers Criteria medications was observed in three cardiovascular drugs: $Alpha_1$ Blockers, Antihypertensive, and Antiarrhythmic. Patients that received $Alpha_1$ Blockers (Doxazosin, Prazosin, or Terazosin) were exposed

to these PIMs on average 288 days. Of patients that received an Antihypertensive in Beers Criteria (Nifedipine), they were exposed on average 285.5 days. Patients that received a Beers Criteria Antiarrhythmic (Amiodarone, Digoxin, Disopyramide, Dofetilide, Dronedarone, Flecainide, Ibutilide, Procainamide, Propafenone, Quinidine, or Sotalol) during the study were exposed to these PIMs on average 278.6 days. The shortest exposure to a Beers Criteria medication was observed in the Antiemetic (used for Gastrointestinal disorders) and Narcotic medication classes. Patients were exposed to an Antiemetic (Trimethobenzamide) for 34.6 days on average, and average exposure to a narcotic (Meperidine, Pentazocine) did not exceed 35.9 days.

Table 4.3: Days Exposed to Beers Medications During Study After Matching

Beers Medications & Classes	**Mean Days Exposed (SD)**
Anticholinergics	
1st Generation Antihistamines *Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Diphenhydramine, Doxylamine, Hydroxyzine, Promethazine, Triprolidine*	57.4 (88.0)
Antiparkinson Agents *Benztropine, Trihexyphenidyl*	209.4 (137.1)
Antispasmodics *Belladonna alkaloids, Clidinium-Chlordiazepoxide, Dicyclomine, Hyoscyamine, Propantheline, Scopolamine*	89.9 (112.3)
Antithrombotics	
Antithrombotic *Dipyridamole, Ticlopidine*	256.2 (122.0)
Anti-infective	
Anti-infective *Nitrofurantoin*	37.5 (78.7)

Cardiovascular	
Alpha$_1$ Blocker *Doxazosin, Prazosin, Terazosin*	288.0 (123.8)
Alpha Agonist, Central *Clonidine, Guanabenz, Guanfacine, Methyldopa, Reserpine*	227.0 (146.6)
Antiarrhythmic *Amiodarone, Digoxin, Disopyramide, Dofetilide, Dronedarone, Flecainide, Ibutilide, Procainamide, Propafenone, Quinidine, Sotalol*	278.6 (148.3)
Antihypertensive *Nifedipine*	285.5 (125.0)
Diuretic *Spironolactone*	235.8 (130.3)
Central Nervous System	
Tertiary TCA *Amitriptyline, Chlordiazepoxide-amitriptyline, Clomipramine, Doxepin, Imipramine, Perphenazine-amitriptyline, Trimipramine*	224.6 (146.1)
1st Generation Antipsychotic *Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Molindone, Perphenazine, Pimozide, Promazine, Thioridazine, Thiothixene, Trifluoperazine, Triflupromazine*	128.8 (145.7)
2nd Generation Antipsychotic *Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone*	233.2 (166.1)
Anxiolytic *Meprobamate*	182.0 (134.0)
Barbiturates *Amobarbital, Butabarbital, Butalbital, Mephobarbital, Pentobarbital, Phenobarbital, Secobarbital*	104.4 (129.3)
Benzodiazepines Short Acting *Alprazolam, Estazolam, Lorazepam, Oxazepam, Temazepam, Triazolam*	139.5 (136.8)

Benzodiazepines Long Acting *Chlordiazepoxide, Chlordiazepoxide-amitriptyline, Clidinium-chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Flurazepam, Quazepam*	127.1 (131.8)
Ergoloid *Ergoloid mesylates*	229.7 (120.8)
Nonbarbiturate Sedative *Chloral hydrate*	38.6 (23.3)
Nonbenzodiazepine hypnotics *Eszopiclone, Zaleplon, Zolpidem*	173.7 (134.0)
Vasodilator *Isoxsuprine*	205.5 (152.4)
Endocrine	
Hormones *Desiccated thyroid, Estrogens, Growth Hormone, Insulin, Megestrol, Methyltestosterone, Testosterone*	240.4 (146.3)
Sulfonylurea *Chlorpropamide, Glyburide*	272.5 (120.9)
Gastrointestinal	
Antiemetic *Trimethobenzamide*	34.6 (63.0)
Gut Motility Stimulator *Metoclopramide*	74.9 (102.2)
Pain	
Narcotic *Meperidine, Pentazocine*	35.9 (78.7)
NonCOX NSAIDs *Aspirin, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Ibuprofen, Ketoprofen, Meclofenamate, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin*	115.0 (125.0)
NSAIDs *Indomethacin, Ketorolac*	40.0 (53.3)

Skeletal Muscle Relaxants *Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine*	67.8 (96.7)

4.2 Aim 1 Results

Aim 1: To examine the healthcare resource utilization for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria.

Hypothesis 1: The odds of hospital admission in a group of patients who receive Beers Criteria medications is greater than the odds of hospital admission in a group of patients who do not receive Beers Criteria medications.

Hypothesis 2: Among patients who had a hospitalization, the mean number of days admitted to the hospital is greater in patients who receive Beers Criteria medications compared to patients who do not receive Beers Criteria medications.

The unadjusted risk for hospitalization was calculated for the treatment and control groups. A total of 213,106 (62.0%) patients treated with Beers Criteria medications had at least one hospital admission during the follow up period compared to a total of 130,489 (38.0%) patients that received medications not in Beers Criteria (p-value <0.0001) (Table 4.4). Of those treated and control patients that were admitted to the hospital, patients that received Beers Criteria medications had more hospital visits on average during follow up compared to those that received medications not in Beers Criteria (1.26 versus 1.20 average number of admissions; p-value <0.0001) (Table 4.4). Additionally, patients that received Beers Criteria medications spent more days in the hospital during follow up compared to control patients (6.63 versus 6.11 average number of days in hospital; p-value <0.0001) (Table 4.4).

Table 4.4: Unadjusted and Adjusted Risk of Hospital Admission, Number of Admissions, and Hospital Days During Follow Up Period

	Unadjusted		Adjusted*	
	Treatment Group	**Control Group**	**Treatment Group**	**Control Group**
Any Admission	213,106 (62.0)[a]	130,489 (38.0)[a]	1.78 (1.76-1.79)[c]	Reference
Number of Admissions	1.26 (±0.68)[b]	1.20 (±0.56)[b]	1.26 (1.26-1.27)[d]	1.19 (1.18-1.20) [d]
Number of Days in Hospital	6.63 (±9.85)[b]	6.11 (±9.40)[b]	6.48 (6.45-6.50) [d]	5.89 (5.86-5.92) [d]

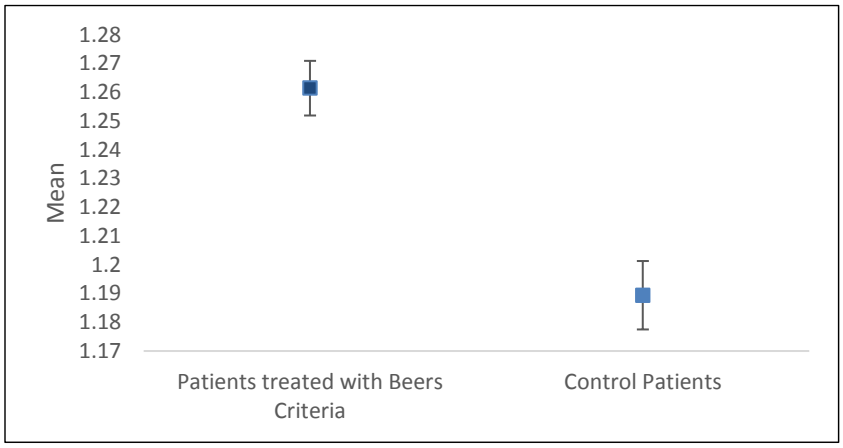
[a] N (%)
[b] Mean (±SD)
[c] Adjusted OR (95% CI)
[d] Mean (95% CI)
* Estimates adjusted for age, gender, geographic region, hospital admissions, member days, frailty, Charlson Comorbidity Score, and Elixhauser Comorbidity Indicators

We used a logistic regression to predict the risk of hospital admission for treated and control patients while controlling for age, gender, geographic region, hospital admission, member days, frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators. The adjusted risk (odds ratio) for hospital admission while using Beers Criteria medications was calculated, and patients using Beers Criteria medications have 77.5% higher odds of a hospital admission compared to patients not using Beers Criteria medications (AOR=1.78; 95% CI 1.76 – 1.79; p-value <0.0001) (Table 4.4).

We used a zero-inflated Poisson model to calculate the adjusted number of hospital admissions for treated and control patients that experienced at least one hospitalization during follow up while controlling for age, gender, geographic region, hospital admission, member days, frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators. Adjusted results did not vary significantly compared to the unadjusted number of hospital admissions. Patients that received Beers Criteria medications that were hospitalized during follow up had 1.26 average number of hospital admissions compared

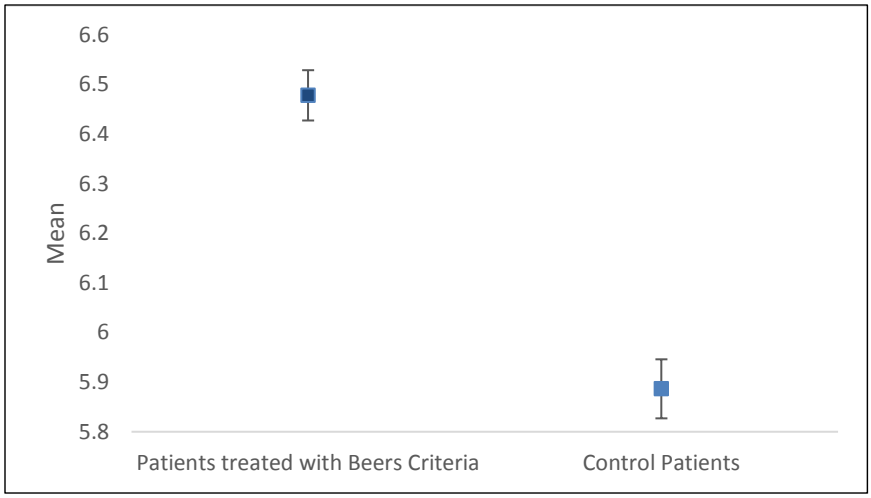
to 1.19 average number of hospital admissions for patients that did not receive Beers Criteria medications that were hospitalized during follow up (p-value <0.0001) (Table 4.4; Figure 4.2).

Figure 4.2: Adjusted Number of Hospital Admissions with 95% Confidence Intervals



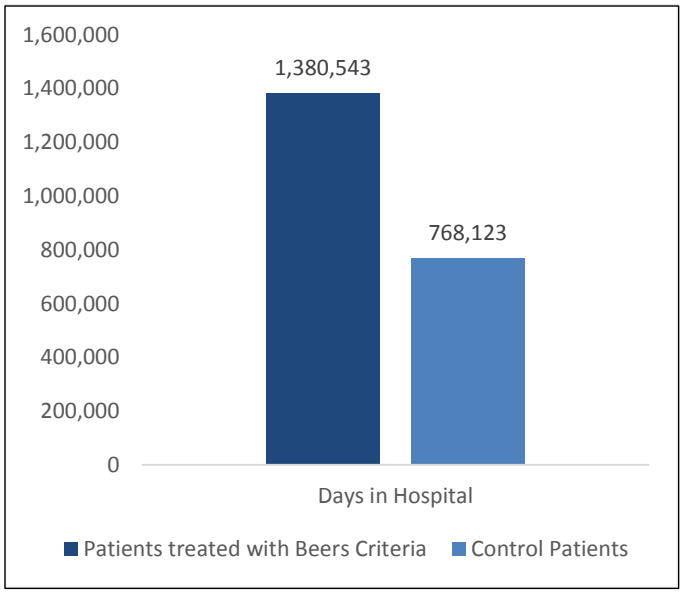
We used a negative binomial count model to calculate the adjusted number of days spent in the hospital for treated and control patients that experienced at least one hospitalization during follow up. Unadjusted and adjusted results varied slightly, but this difference was not statistically significant. After controlling for age, gender, geographic region, hospital admission, member days, frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators, patients that received Beers Criteria medications spent on average 6.48 days in the hospital during follow up compared to control patients who spent on average 5.89 days in the hospital (p-value <0.0001) (Table 4.4; Figure 4.3).

Figure 4.3: Adjusted Number of Days in Hospital with 95% Confidence Intervals



We also calculated the marginal number of days spent in the hospital (Figure 4.4). The sample of patients that received Beers Criteria medications (213,106 patients) were in the hospital a total of 1,380,543 days during follow up. The sample of patients that received medications not in Beers Criteria (130,489 patients) were in the hospital a total of 768,123 days during follow up. The marginal number of days hospitalized, or the number of hospital days that may have been saved not using Beers Criteria medications, was 612,420 days.

Figure 4.4: Adjusted Average Number of Days Spent in Hospital



4.3 Aim 2 Results

Aim 2: To determine the total healthcare costs for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria.

Hypothesis 1: Total healthcare costs are greater in patients who receive Beers Criteria medications compared to patients who do not receive Beers Criteria medications.

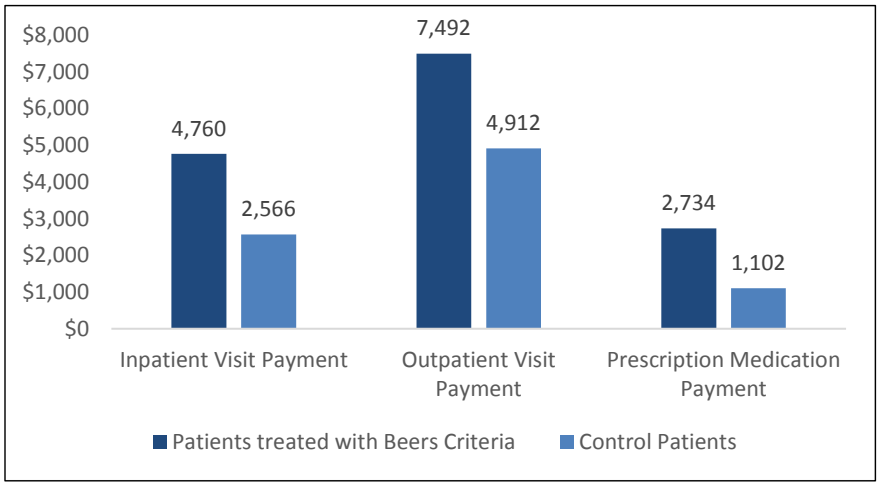
Total inpatient visit costs, outpatient visit costs, and prescription medication costs were calculated to determine the total unadjusted healthcare costs for patients treated with Beers Criteria medications and patients treated with medications not in Beers Criteria (Table 4.5; Figure 4.5). The average total cost of inpatient visits for patients treated with Beers Criteria during the nine month follow up period in 2013 was $4,760 compared to $2,566 average total inpatient cost for patients treated with medications not in Beers Criteria (p-value <0.0001). Average outpatient visit costs during the nine month follow up period in the treated sample was $7,492 and $4,912 in the control group (p-value <0.0001). Average prescription medication costs during the nine month follow up period were also higher for the treatment group. Those treated with Beers Criteria medications were responsible for an average of $2,734 in prescription drug costs compared to $1,102 average prescription drug costs in the control group (p-value <0.0001). Total inpatient, outpatient, and prescription drug costs were higher on average for patients that received Beers Criteria medications during the follow up period.

Table 4.5: Inpatient Visit, Outpatient Visit, Prescription Medication, and Total Study Costs During Follow Up Period*

	Treatment Group	Control Group	p-value^
	Mean (SD)	**Mean (SD)**	
Inpatient Visit Cost	4,760 (23,238)	2,566 (16,055)	<0.0001
Outpatient Visit Cost	7,492 (21,909)	4,912 (23,962)	<0.0001
Prescription Medication Cost	2,734 (5,590)	1,102 (3,633)	<0.0001
Total Unadjusted Study Cost	14,987 (36,033)	8,580 (30,962)	<0.0001
	Adj. Mean (95% CI)	**Adj. Mean (95% CI)**	
Total Adjusted Study Cost+	13,404 (13,373-13,436)	7,310 (7,293-7,327)	<0.0001

* All costs are in 2013 US$; charges have been rounded to the nearest dollar
^ p-values were calculated using two sample t-test
+Estimates adjusted for age, gender, geographic region, hospital admissions, member days, frailty, Charlson Comorbidity Score, and Elixhauser Comorbidity Indicators

Figure 4.5: Unadjusted Inpatient Visit, Outpatient Visit, and Prescription Medication Costs During Follow Up Period

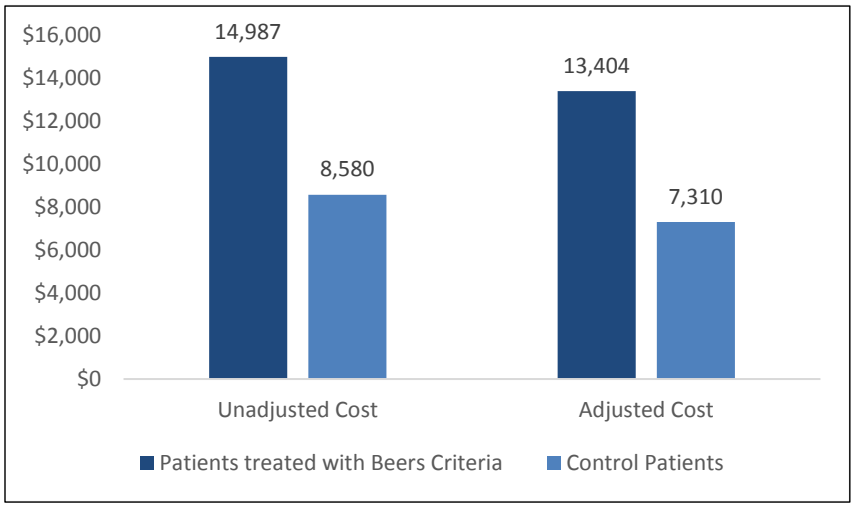


Using the total costs from inpatient and outpatient visits and prescription medications, the average total unadjusted study cost per patient was calculated for both cohorts (Table 4.5; Figure 4.6). The total cost of healthcare for patients treated with Beers Criteria was $14,987 per patient during the follow up period compared to $8,580 total healthcare costs per patient treated with medications not in Beers Criteria (p-value

<0.0001). Total healthcare costs generated during the nine month follow up period were higher on average for patients that received Beers Criteria medications in 2013.

We used a Gamma distributed generalized linear model with a logarithmic link function to calculate the adjusted total healthcare costs generated during the follow up period for treated and control patients. Differences in the unadjusted and adjusted costs were not statistically significant. After controlling for age, gender, geographic region, hospital admission, member days, frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators, the adjusted total healthcare cost per patient for those that received Beers Criteria medications was $13,404. The adjusted total healthcare cost per patient for controls was $7,310 (p-value <0.0001) (Table 4.5; Figure 4.6). Based on the per patient total cost, and considering the total study population, we estimate that $23.2 billion in inpatient, outpatient, and medication costs were attributed to patients that received Beers Criteria medications in 2013, compared to $12.6 billion annual healthcare costs attributed to control patients.

Figure 4.6: Average Total Healthcare Costs During Follow Up Period



4.4 Summary

After matching patients treated with Beers Criteria medications and controls that did not receive Beers Criteria medications through 1:1 PSM methods, the treatment and control groups were similar with respect to age, gender, geographical region, hospital admission, number of days enrolled in insurance plan (member days), frailty, Charlson Comorbidity Score, and 26 Elixhauser Comorbidity Indicators. All 39 potentially biasing factors included in the matching model were well balanced after matching. We can conclude that our observational study is comprised of well-matched treatment and control groups and is unlikely to have much selection bias.

Using medications included in Beers Criteria is associated with greater odds of hospital admission. Of those that are hospitalized, patients using Beers Criteria medications have a greater risk of more hospital admissions and a greater risk of spending more days in the hospital compared to patients treated with medications not in Beers Criteria. The total adjusted healthcare costs were significantly higher in the cohort of patients treated with Beers Criteria medications compared to controls treated with medications not in Beers Criteria. Using medications included in Beers Criteria is also associated with significantly higher annual inpatient, outpatient, and medication costs.

V. Discussion

The primary objective of this retrospective cohort study was to quantify healthcare resource utilization and healthcare costs attributable to using PIMs included in 2012 Beers Criteria. A total of 73,644 individual NDC codes representing 138 medications from eight therapeutic areas were used to identify 2012 Beers Criteria medications. We compared hospital admissions, days spent in the hospital, and total healthcare costs generated from inpatient and outpatient visits and prescription medication use for patients that received PIMs in Beers Criteria compared to a well-matched group of patients that received medications not included in Beers Criteria. The aims of this study are innovative in that risk of hospitalization, hospitalization rates, days admitted to the hospital, and total costs attributable to all PIMs listed in Beers Criteria have not been previously published. Additionally, these outcomes have also not been compared to a well-matched group of patients that received medications not included in Beers Criteria.

To address the aims of this research, a specialized set of methodological approaches was required. PSM was used to create a control group where a control did not otherwise exist to design a quasi-randomized study structure (Rosenbaum & Rubin, 1983). We used this technique to equally distribute measured bias and hidden bias correlated with any covariates across both groups, ensuring that the non-random sample represented in Marketscan® behaved more like a randomized design with selection bias control. Few studies of Beers Criteria have used PSM techniques. To our knowledge, our study is the first to employ PSM techniques while using a current version of Beers Criteria.

Fu et al. (2007) and Stockl et al. (2010) are the only studies of Beers Criteria identified that incorporated PSM techniques. Although both studies also employed 1:1 PSM techniques, the sample size of patients exposed and unexposed to 2003 Beers Criteria PIMs in these previous studies varied considerably compared to our sample size of matched treated and control patients. In the Fu et al. (2007) study, the final sample population included 103 patients in the exposed and unexposed groups. Stockl et al. (2010) included 37,358 controls and patients exposed to Anticholinergics, 395 controls and patients exposed to Narcotics, 1,085 controls and patients exposed to Trimethobenzamide Hydrochloride, and 13,542 controls and patients exposed to Sedative Hypnotics. In comparison, our study sample was comprised of 1,297,627 matched patients in the treatment and control groups. Additionally, the number of covariates included in PSM varied between previous studies and our study. Whereas Fu et al. (2007) included 14 covariates and Stockl et al. (2010) included 11 variables in PSM, our study included 39 potentially biasing patient demographic and baseline health covariates.

Consistent with previous studies of medication use in the elderly, our research indicates that prescription medication use in older adults remains prevalent. Nearly 85% of patients aged 65 and older included in this study had at least one prescription medication claim during a three-month baseline period in 2013. Older people have more health problems, take more medications, and are more likely to experience negative health outcomes that require hospitalization (Budnitz, Lovegrove, Shehab, & Richards, 2011). Even more concerning, older adults are often prescribed medications that are not medically necessary. Incidence of Beers Criteria medication use in the elderly has been well established in previous research.

Despite the adoption of Beers Criteria among a variety of healthcare professionals and settings associated with geriatric care, PIM prescribing in the elderly remains prevalent (Page, Linnebur, Bryant, & Ruscin, 2010). Recent studies of Medicare claims generated by community-dwelling elderly patients using medications included in 2012 Beers Criteria support the claim that PIM use in older adults continues to be prevalent nearly 30 years after the introduction of Beers Criteria guidelines, and our study results are aligned with these findings (Davidoff et al., 2015; Jirón et al., 2016). Davidoff and colleagues (2015) reported nearly 43% of older adults that filled a prescription for at least one PIM included on 2012 Beers Criteria. Jirón and colleagues (2016) reported over 34% of elderly patients used a 2012 Beers Criteria medication during a one month baseline period in 2012. Although not one of our primary objectives, findings from our study are consistent with prevalence rates presented in recent studies. We identified 37% of patients receiving prescription medications were prescribed at least one PIM included in 2012 Beers Criteria during a three-month baseline period in 2013.

Our study offers several advantages and novel design approaches that have not been previously incorporated in research of Beers Criteria. We used a current version of Beers Criteria that coincides with recent prescribing practices among clinicians treating elderly patients. More importantly, we included all medications in Beers Criteria classified as potentially inappropriate for all older adults. This is especially innovative as most previous studies have used a limited number of medications included in Beers Criteria. Including all medications in Beers Criteria classified as potentially inappropriate for all older adults was also advantageous in that we had a very large sample size, even after matching, compared to previous studies. Using PSM, a technique not frequently used in Beers Criteria research,

allowed us to control for most sources of selection bias and to make causal inferences where there was non-random assignment (Heckman, Ichimura, Smith, & Todd, 1996). We also accounted for many potentially biasing demographic and health factors through PSM and in our outcomes analyses. To our knowledge, no study has been published that has incorporated all of these design factors to analyze unadjusted and adjusted hospitalization rates, describe risk of hospitalization, determine the marginal number days PIM users are hospitalized, calculate unadjusted inpatient, outpatient, and prescription drug costs, and report adjusted total costs for patients treated with Beers Criteria medications compared to patients treated with alternative medications. As a result, this study provides stronger evidence compared to previous studies that prescribing PIMs included in 2012 Beers Criteria has a significant effect on risk of hospitalization, number of hospital admissions, days spent hospitalized, inpatient visit costs, outpatient visit costs, and total annual costs to payers.

5.1 Aim 1 Discussion

The first aim of this study was to examine the healthcare resource utilization for Medicare patients who received medications included in Beers Criteria compared to a well-matched group of Medicare patients who did not receive medications included in Beers Criteria. Healthcare utilization outcomes of interest included any hospital admission, number of hospital admissions (of those that were admitted), and total days in the hospital (of those that were admitted). The unadjusted risk for hospitalization was significantly higher in the sample of patients treated with Beers Criteria medications. A greater proportion of treated patients experienced at least one hospital admission during the follow-up period compared to control patients. Of those treated and control patients that were

admitted to the hospital, patients that received Beers Criteria medications had more hospital visits on average during follow up compared to those that received medications not in Beers Criteria.

Results from a much earlier study of utilization also support the notion that healthcare utilization is greater among patients using Beers Criteria medications. A retrospective review of administrative claims data for a sample of Medicare managed care patients revealed that patients using 1997 Beers Criteria medications had, on average, a greater number of inpatient, ED, and outpatient visits (Fick et al., 2001). Case and comparison groups were generated based on whether patients filled a prescription for a PIM included in 1997 Beers Criteria, however, these groups were not equal in sample size (Fick et al., 2001). Unlike our study, patients were not matched using PSM. Baseline health measures were more limited compared to our study. Our study accounted for inpatient and outpatient comorbid conditions and frailty, and Fick and colleagues (2001) only used the Charlson Comorbidity Index. Despite these design and sample size differences, Fick et al. (2001) also found that patients using Beers Criteria PIMs had higher healthcare resource utilization. We reported that patients receiving Beers Criteria medications had an average of 1.26 hospital admissions, which is higher than the average number of hospital admissions PIM users experienced as reported in Fick et al. (2001). The mean number of hospital admissions for patients using Beers Criteria medications in the Fick et al. (2001) study was 0.58, and, like our study, this was significantly higher than the mean number of inpatient visits for patients not using Beers Criteria medications.

While our study results are limited to the U.S. population, it is important to highlight that higher rates of hospitalization associated with using medications in Beers

Criteria have been identified in other parts of the world as well. A population-based, longitudinal study of community-dwelling residents of rural Sweden found an association between using PIMs in 1997 Beers Criteria and risk of hospitalization. Analysis of three years of hospitalization and mortality data confirmed that PIM use was associated with an increased-risk for hospitalization (Klarin et al., 2006). Eight PIMs represented in 2003 Beers Criteria were included in an analysis of pharmaceutical claims for 251,305 older adults residing in Australia. Results from this study indicate that all included medications (amiodarone, diazepam, digoxin, ferrous sulphate, indomethacin, naproxen, oxazepam, and temazepam) were associated with an increased risk of hospitalization (Price et al., 2014). Not all medications included in Beers Criteria are available or used in other countries, and there are likely differences in prescribing practices, use of healthcare resources, and other factors that make it difficult to compare international studies of Beers Criteria to our study or to other studies conducted within the U.S. Regardless, we found it important to highlight these studies to demonstrate that healthcare resource utilization associated with PIM use is not just problematic in the U.S.

Patients included in our study that used Beers Criteria medications had 77.5% higher odds of a hospital admission compared to patients not using Beers Criteria medications. Community-dwelling patients that used a PIM in 1997 Beers Criteria had a 20% greater risk of hospitalization (Fillenbaum et al., 2004). Results from a retrospective cohort study of managed care administrative data for 174,275 commercially insured older adults showed that using PIMs included in 2003 and 2012 Beers Criteria was associated with anywhere from two to three times greater risk for hospitalization and ED visits (Brown et al., 2016). Caution should be used when comparing previous hospitalization risk rates to

our results. Unlike our study, previous studies used what are now outdated versions of Beers Criteria or did not account for all medications included in Beers Criteria. Considering that our study accounts for risk of hospitalization associated with all medications classified as potentially inappropriate in Beers Criteria, the underlying issue remains clear that any PIM use is associated with increased risk of hospitalization.

Our study included community-dwelling patients, but a study of nursing home patients provides evidence that risk of hospitalization among institutionalized patients using Beers Criteria medications is also of concern. Results from a study using 1991 and 1997 Beers Criteria and data from the 1996 Medical Expenditure Panel Survey Nursing Home Component revealed that patients institutionalized for three consecutive months or longer that received a PIM included in Beers Criteria had over 1.2 greater odds of being hospitalized compared to patients that were not using a PIM (Lau et al., 2005). Continued PIM use (defined as using PIMs for two consecutive months) was associated with nearly a 30% greater risk for hospitalization (Lau et. al, 2005). Additionally, patients using Beers Criteria PIMs had a 28% greater risk of death compared to patients not using PIMs (Lau et al., 2005). Results from Lau et al. (2005) study are dated, but this study justifies the concern regarding inappropriate medication use across all elderly populations. More current research is needed to determine if hospitalization and death rates remain higher among institutionalized PIM users compared to those using alternative medications.

Results from our study demonstrate that patients that received Beers Criteria medications spent on average more days in the hospital during follow up compared to control patients. The sample of patients that received Beers Criteria medications were in the hospital a total of 1,380,543 days during follow up in 2013 compared to controls that

were hospitalized a total of 768,123 days during follow up. Unlike previous studies of healthcare resource use, we were also interested in determining the marginal number of days patients were hospitalized. The number of hospital days that may have been saved in 2013 if patients were not prescribed Beers Criteria medications was an astounding 612,420 days. These additional days spent in the hospital are unnecessary and preventable with appropriate medication management. More important to note, though, is the increased burden that unnecessary hospitalizations have on patients and caregivers as well as the healthcare system. These visits are costly to payers and determinantal to patient quality of life.

Our study provides more current hospitalization rates, risk of hospital admission, and length of stay that are aligned with recent prescribing guidelines presented in 2012 Beers Criteria. Results from this study and results from preceding studies of earlier versions of Beers Criteria provide historical evidence that risk of hospitalization remains high and hospitalization rates associated with PIM use has not improved over the years even though Beers Criteria guidelines have been in place for nearly 30 years.

5.2 Aim 2 Discussion

The second aim of this study was to determine the total healthcare costs for Medicare patients who receive medications included in Beers Criteria during the follow up period compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria. We defined cost outcomes of interest from the perspective of an insurer. For the purposes of this study, insurance payments were denoted as costs and measured as the aggregated total in insurance payments captured for each patient during the follow up period in 2013. Inpatient visit costs, outpatient visit costs,

prescription medication costs, total unadjusted costs, and total adjusted costs during the follow-up period were anaylized for the treatment and control groups.

Total inpatient, outpatient, and prescription drug costs were higher on average for patients that received Beers Criteria medications during the follow up period. The average total cost of inpatient visits for patients treated with Beers Criteria was $4,760 compared to $2,566 average total inpatient cost for the control group. Average outpatient visit costs in the treated sample was $7,492 and $4,912 in the control group. Those treated with Beers Criteria medications during the follow up period had an average of $2,734 in prescription drug costs compared to $1,102 average prescription drug costs in the control group.

A previous analysis of facility, provider, and prescription drug payments based on 1997 Beers Criteria supports our results that PIM use is associated with higher costs (Fick et al., 2001). In this study, claims for patients with continuous health maintenance organization enrollment from June 1, 1997, through October 31, 1998 were analyzed, and all three cost measures were higher in patients treated with select PIMs included in Beers Criteria ($2,629 inpatient costs, $1,555 average outpatient costs, and $401 average drug costs) (Fick et al., 2001). The outpatient and prescription drug cost differences between the two groups were not statistically significant as they were in our study.

There are several differences between our study and the Fick et al. (2001) study that are important to note. A limited number of Beers Criteria medications were included in their study, and these medications are from what is now an outdated version of Beers Criteria. The sample size varies considerably, with 1,297,627 treated and control patients included in our study compared to 541 treated and 1,795 control patients included in Fick et al. (2001). Fick and colleagues (2001) controlled for sex, Charlson Comorbidity Index,

and total number of prescriptions in their cost analyses, whereas we controlled for age, gender, geographic region, hospital admissions, member days, frailty, Charlson Comorbidity Score, and Elixhauser Comorbidity Indicators in our analyses. Different statistical methods were also used to analyze cost. Fick et al. (2001) used analysis of covariance models to assess whether total, provider, facility, and prescription costs differed between their treated and control groups. We used generalized linear modeling to determine if Beers Criteria medications are associated with higher healthcare costs compared to non-Beers Criteria medications. Studies using generalized linear modeling for cost analysis have shown good distributional fit when using the gamma response distribution with a log link function (Moran, Solomon, Peisach, & Martin, 2007). The results from Fick et al. (2001) may not be directly comparable to our results, but their study does offer evidence that PIM use is associated with higher inpatient, outpatient, and drug costs in general.

We used inpatient, outpatient, and prescription costs to calculate the average unadjusted total cost of care for patients using Beers Criteria medications in 2013. Controlling for age, gender, geographic region, hospital admissions, member days, frailty, Charlson Comorbidity Score, and Elixhauser Comorbidity Indicators, we determined the adjusted total cost of healthcare per patient for those treated with Beers Criteria during follow up to be $13,404 compared to $7,310 adjusted average total cost of healthcare per patient for those treated with medications not in Beers Criteria.

Stockl and colleagues (2010) analyzed claims data to determine pharmacy costs and medical charges for managed care patients that experienced an adverse drug event while using anticholinergics, narcotics, trimethobenzamide hydrochloride, or sedative

hypnotics included in 2003 Beers Criteria. Costs were measured for 360 days. Similar to our study, adjusted costs were also calculated using generalized linear modeling with a gamma response distribution with a log link function while adjusting for age, sex, health plan type, geographic state, Charlson Comorbidity Index, and baseline costs (Stockl et al., 2010). Annual adjusted total healthcare costs were significantly higher for patients in each of the four Beers Criteria medication groups compared to controls in each group (Stockl et al., 2010).

As is the case with Fick et al. (2001), these results may not be directly comparable to our study. The results from Stockl et al. (2010) are based on a small number of Beers Criteria medications. The study population was also limited to a Western U.S. managed care organization. While results from that study may not be representative of all U.S. elderly patients receiving similar Beers Criteria medications, this study does support our findings in that total adjusted healthcare costs are higher when patients are prescribed medications included in Beers Criteria.

Patients treated with Beers Criteria medications in our study were responsible for significantly greater annual healthcare costs in 2013. As was the case when we analyzed healthcare utilization, the burden that this particular elderly patient population has on U.S. healthcare spending is alarming. Medicare spending exceeded $585 billion in 2013 (Altman & Frist, 2015). The largest share of Medicare spending in beneficiaries over the age of 65 was on inpatient care, and inpatient service expenses increased more than 2.5 times in 66 to 89-year-old beneficiaries (Neuman et al., 2015). As the U.S. elderly population is expected to continue to rise in the years ahead, the number of Medicare beneficiaries and total Medicare spending will increase. (Neuman et al., 2015). Looking to

the years ahead, we can expect to see further strain on the Medicare system and on other payers in the U.S as PIM prescribing continues.

5.3 Study Limitations

Consistent with other studies analyzing claims data, our use of administrative claims data within Marketscan® is not without limitations. Coding is used specifically for billing purposes, and administrative claims represented in Marketscan® are collected for the purpose of making healthcare payments and are not collected for use in research (Suissa & Garbe, 2007). Variations in coding practices are a common limitation of administrative databases, and there is a possibility that the Marketscan® medical claims used in this study may be incomplete or potential errors may have occurred in diagnosis coding. It is important to note, however, that Marketscan® offers the advantage of high-quality coding, and a diagnosis is coded on 99% of all claims (Hansen & Chang, 2011). Regardless, we had to rely on coding information and billing data which may not be completely accurate, and we may have unintentionally excluded patients that should be included in the sample based on these errors and coding limitations. Coding practices may have threatened the internal validity of this study. However, many coding weaknesses were equally present in both the treatment and control groups resulting in a marginal effect estimate not biased by most coding variation.

Our study population is not inclusive of all elderly patients over the age of 65. Patients that were not community-dwelling were excluded in our study. Marketscan® does not capture data for poor or dually insured individuals, and this study did not include poor or dually insured individual patients in the study population. It is also likely that some individuals were excluded from our sample population given that medium and small

employers are not represented in Marketscan® data (Hansen & Chang, 2011). Marketscan® databases are based on a non-random sample. While there may be hidden biases in our data, administrative databases are advantageous for their large sample sizes. Despite the population limitations, we are confident that we have achieved stronger external validity than is generally seen in smaller randomized study designs (Suissa & Garbe, 2007) thus allowing us to generalize our results to a larger elderly population.

The aim of our study was to evaluate the overall burden of healthcare utilization and cost associated with treating patients with PIMs included in Beers Criteria. Our cost analyses were conducted from the perspective of the insurance company. Thus, other factors associated with cost, such as premiums, deductibles, co-insurance, and self-paid expenses, were not included in our analyses. Our focus on healthcare utilization included inpatient and outpatient visits for community-dwelling individuals. We did not capture expenditures related to skilled nursing, long-term, palliative, or hospice care. It is likely that treatment plans and medication regimens are vastly different in individuals receiving palliative and hospice care compared to community-dwelling patients. In the case of palliative and hospice care, it may be more important to control the patient's symptoms (which may require the use of PIMs listed in Beers Criteria) rather than simply avoiding the use of PIMs all together (American Geriatrics Society, 2012). The healthcare utilization and cost of using PIMs listed in Beers Criteria may differ when used within special populations compared to PIM use in community-dwelling older adults.

We excluded two categories of medications included in Beers Criteria. We did not include medications classified in Beers Criteria as those to use in caution in older adults or medications that, if used in older patients, may exacerbate an existing disease or syndrome.

Medication use within these specific conditions were not the focus of our study. Unlike previous studies of Beers Criteria, however, we did include all medications classified in Beers Criteria as potentially inappropriate for use in all older adults in our analyses. Given the large volume of PIMs that were included in our study (138 individual medications across eight therapeutic areas and 73,644 individual NDC codes), results from this study offer significant value and a greater understanding of the association between using Beers Criteria medications and increased healthcare resource utilization and annual costs.

Although we controlled for many demographic and baseline health measures in our study, there are factors that we did not control for. We did not control for duration of medication exposure during the baseline period. Instead, we examined days exposed to each Beers Criteria medication in the follow up period and after PSM. In the baseline period, we described inappropriate medication use as a binary variable, categorizing patients as yes/no if they received any Beers medication (AnyBeers). We did not control for using individual Beers Criteria medications as analyzing utilization and cost for all individual Beers Criteria medications was not the purpose of our study. To achieve the aims of this study, we did control for many common indications that are known to be risk factors associated with increased use in healthcare resources.

It should be noted that there are other factors related to medication use in the elderly that could impact healthcare utilization and cost that were not addressed in analyses of this study. Elderly patients may receive multiple medications or medications that may not be medically necessary in order to treat a growing number of health problems as they age (Maher et al., 2013; Hajjar, Cafiero, & Hanlon, 2007). The use of multiple medications puts the elderly at an increased risk for interactions between drugs (Hajjar, Cafiero, &

Hanlon, 2007). Medication non-adherence is associated with poor clinical outcomes and has significant clinical and economic implications. Poorly treated health conditions require additional medical treatment and often hospitalization (Hughes, 2004). These factors can also impact healthcare resource utilization. Inpatient and outpatient visit costs and prescription drug costs associated with treating medical complications due to drug-drug interactions and medication non-adherence can also impact total annual healthcare costs associated with PIM use. However, these factors were not the focus of our study.

5.4 Future Directions

Before we can expect a significant clinical change in PIM management in the elderly population, we first needed to understand the impact using PIMs included in Beers Criteria has on healthcare resource utilization and costs compared to using alternative medications not listed in Beers Criteria. Results from this study suggest that elderly patients that are prescribed medications included in Beers Criteria have a greater risk of hospital admission compared to patients that use alternative medications not included in Beers Criteria. Of those patients that are hospitalized, using Beers Criteria medications is also associated with experiencing more hospital admissions and spending more days in the hospital compared to using medications not in Beers Criteria. Our results indicate that significantly higher inpatient, outpatient, medication costs, and annual healthcare costs are expected when clinicians prescribe medications included in Beers Criteria compared to patients treated with medications not in Beers Criteria. Results from this study are meaningful for providers that provide care to the elderly population, pharmacists, older adults and their caregivers, healthcare administrators and policy makers, and payers. These findings have implications for provider education, policy reform, and future research.

Beers Criteria provides a well-developed and extensive list of medications to avoid, but it does not include a list of alternative medications in the criteria (American Geriatrics Society, 2015). Individual patient health conditions are complex and often require specialized medication regimens to treat a variety of health problems. Beers Criteria is not intended to completely remove clinical judgment in regards to the needs and medication management of the individual patient (Molony, 2003). Instead, these complexities require individualized clinician judgment to appropriately determine if alternative, and potentially safer, medications not included in Beers Criteria would be more appropriate for each individual patient based on their health status. Results from our study suggest that providers need to consider the long-term implications that clinical judgment has on the health and well-being of patients that are prescribed PIMs included in Beers Criteria. An appropriate and thorough medication review and minimizing use of PIMs included in Beers Criteria may prevent unnecessary hospitalizations among elderly patients. Prior to this study, clinicians likely did not appreciate the impact that PIM prescribing has on outpatient resources, inpatient hospitalization rates, the number of days patients spend in the hospital, a patient's quality of life, or the long-term economic consequences on our national healthcare system.

In the short-term, we hope results from this study will be informative to clinicians who do not currently use Beers Criteria recommendations to guide their medication management decisions in elderly patients. While we cannot expect immediate clinical changes in prescription prescribing across all medication classes used by elderly patients, results from this study emphasize the importance of enhancing the training and education providers receive to ensure long-term improvements in medication management regimens

are implemented in the near future. A key next step for policymakers is to develop information dissemination plans that will encourage clinicians to perform enhanced medication reviews and modify medical interventions before prescribing PIMs included in Beers Criteria to reduce the risk of unnecessary hospitalizations of elderly patients and minimize the burden this population will have on our national healthcare system in the future.

Future studies should quantify the cost of PIM use at the patient level, specifically the potential out of pocket burden associated with PIM use. This study enabled us to understand the total annualized cost burden that using Beers Criteria medications has on the healthcare system. Future cost analyses should consider the burden PIM use has on patient out of pocket expenses such as insurance premiums, deductibles, co-insurance, and self-paid expenses. Additionally, previous studies have not quantified the current economic burden of using PIMs included in Beers Criteria in short-term rehabilitation facilities, skilled nursing facilities, or LTC facilities. Although we have a greater understanding of healthcare utilization and cost burden among community-dwelling individuals receiving Beers Criteria medications, researchers should also consider healthcare resource utilization and economic consequences for institutionalized patients receiving PIMs included in Beers Criteria.

Researchers should consider a prospective implementation study to develop new, or improve existing, medication warning systems that can be implemented into existing electronic medical record systems. These technology improvements should alert clinicians when an inappropriate medication is prescribed to an elderly patient and enable pharmacy systems to identify potential prescribing errors before the patient is issued a PIM. Future

studies should also engage policy makers and healthcare leaders to identify ways in which our healthcare system can reallocate the money saved by reducing hospitalizations attributed to PIM use and invest in medication technology system updates. The economic investment of preventing even a fraction of the number of unnecessary hospitalizations attributed to PIM use will justify the economic impact of updating electronic medical systems and implementing meaningful medication technology systems.

VI. Conclusion

This study addressed two aims through innovative research strategies not previously used in utilization and cost analyses of medications classified in 2012 Beers Criteria as inappropriate for use in older adults. Community-dwelling Medicare patients with private supplementary insurance were included in the study. Healthcare utilization and costs were analyzed using 2013 Truven Health Marketscan® Commercial Claims and Encounters Database. Previous research of Beers Criteria has predominately focused on the prevalence, potential risk factors, and health outcomes associated with PIM use in the elderly. This was the first study to analyze healthcare utilization and total healthcare costs for patients that were prescribed medications that adhere to Beers Criteria versus patients with similar health conditions that were prescribed medications that do not adhere to Beers Criteria.

The first aim of this study was to examine the healthcare resource utilization for Medicare patients who receive medications included in Beers Criteria compared to a well-matched group of Medicare patients who do not receive medications included in Beers Criteria. More specifically, we were interested in determining if treating patients with inappropriate medications included in Beers Criteria is associated with more hospital admissions and a greater risk of experiencing a hospital admission compared to patients who do not receive Beers Criteria medications. This study provides evidence that elderly patients that are prescribed medications included in Beers Criteria have a greater risk of hospital admission compared to patients that use alternative medications not included in

Beers Criteria. Of those treated and control patients that were hospitalized, we also examined whether using Beers Criteria medications is also associated with a greater number of days spent in the hospital. Results from this study indicate that of those patients that are hospitalized, using Beers Criteria medications is also associated with a greater number of hospital admissions and more days spent in the hospital compared to using medications not in Beers Criteria.

The second aim of this study was to calculate the total healthcare costs for Medicare patients who receive medications included in Beers Criteria compared patients who do not receive medications included in Beers Criteria. Inpatient visit, outpatient visit, and prescription medication costs were higher on average for patients that received Beers Criteria medications. After controlling for potentially biasing factors, we found the adjusted total cost of healthcare for patients treated with Beers Criteria to be significantly higher during the follow up period compared to patients treated with medications not in Beers Criteria. Patients treated with Beers Criteria medications were also responsible for significantly greater annual healthcare costs in 2013.

Results from our study suggest that providers should consider the long-term implications that medication selection has on the health and well-being of patients. Our results also emphasize the importance of educating providers to ensure sustainable improvements in medication management regimens are implemented in the near future. It is imperative that providers, healthcare leaders, and policy makers work together to reduce the risk of unnecessary hospitalizations of elderly patients and minimize the burden this population will have on our national healthcare system in the future.

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APPENDICES

Appendix A. Medication Appropriateness Index

To assess the appropriateness of the drug, please answer the following questions and circle the applicable score:				
1. Is there an indication for the drug? Comments:	1 Indicated	2	3 Not Indicated	9 DK†
2. Is the medication effective for the condition? Comments:	1 Effective	2	3 Ineffective	9 DK
3. Is the dosage correct? Comments:	1 Correct	2	3 Incorrect	9 DK
4. Are the directions correct? Comments:	1 Correct	2	3 Incorrect	9 DK
5. Are the directions practical? Comments:	1 Practical	2	3 Impractical	9 DK
6. Are there clinically significant drug–drug interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
7. Are there clinically significant drug–disease/condition interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
8. Is there unnecessary duplication with other drug(s)? Comments:	1 Necessary	2	3 Unnecessary	9 DK
9. Is the duration of therapy acceptable? Comments:	1 Acceptable	2	3 Unacceptable	9 DK
10. Is this drug the least expensive alternative compared to others of equal utility? Comments:	1 Least expensive	2	3 Most expensive	9 DK

*Complete instructions in the use of the scale are available upon request.
†Don't know.

Source: "A Method for Assessing Drug Therapy Appropriateness" by Hanlon, J. et al., 1992, *Journal of Clinical Epidemiology*, *45*, p. 1046.

Appendix B. Improved Prescribing in the Elderly Tool

The following medications represent potentially inappropriate prescriptions in an elderly individual:

Beta-blocker and chronic obstructive airways disease
Beta-block and congestive heart failure
Calcium channel blocker (excluding amlodipine and felodipine) and congestive heart failure
Thiazide diuretic and gout
Long half-life benzodiazepine (chlordiazepoxide, clorazepate, diazepam, flurazepam, clonazepam, nitrazepam)
Tricyclic antidepressant and glaucoma
Tricyclic antidepressant and heart block
Tricyclic antidepressant with active metabolites (imipramine, doxepin, amitriptyline)
Methylphenidate for depression
Nonsteroidal anti-inflammatory drugs* and peptic ulcer disease
Nonsteroidal anti-inflammatory drugs and hypertension
Long term use of nonsteroidal anti-inflammatory drugs for osteoarthritis
Anticholinergic drugs to treat side effects of antipsychotic medications
Long term diphenoxylate to treat diarrhea

***Consider acetylsalicylic acid as a nonsteroidal anti-inflammatory drug only if the dose is greater than 1300 mg/day*

Source: "Development and validation of an improving prescribing in the elderly tool*"* by Naugler, C.T., Brymer, C., Stolle, P., & Arcese, Z.A., 2000, *Canadian Journal of Clinical Pharmacology, 7*, p. 106.

Appendix C. STOPP (Screening Tool of Older Person's Prescriptions)

A. Cardiovascular system

1. Digoxin at a long-term dose > 125 µg/day with impaired renal function* (*increased risk of toxicity*) [Cusack et al. 1979, Gooselink et al. 1997, Haas and Young 1999].
2. Loop diuretic for dependent ankle edema only i.e. no clinical signs of heart failure (*no evidence of efficacy, compression hosiery usually more appropriate*) [Alguire and Mathes1997, Kolbach et al. 2004].
3. Loop diuretic as first-line monotherapy for hypertension (*safer, more effective alternatives available*) [Williams et al. 2004].
4. Thiazide diuretic with a history of gout (*may exacerbate gout*) [Gurwtiz et al. 1997].
5. Non-cardioselective β-blocker with Chronic Obstructive Pulmonary Disease (COPD) (*risk of increased bronchospasm*) [van der Woude et al. 2005, Salpeter et al. 2005].
6. β-blocker in combination with verapamil (*risk of symptomatic heart block*) [BNF 2006].
7. Use of diltiazem or verapamil with NYHA class III or IV heart failure (*may worsen heart failure*) [BNF 2006].
8. Calcium channel blockers with chronic constipation (*may exacerbate constipation*) [Dougall and McLay 1996].
9. Use of aspirin and warfarin in combination without histamine H_2-receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (*high risk of gastrointestinal bleeding*) [Garcia Rodriguez et al. 2001, Holbrook et al. 2005].
10. Dipyridamole as monotherapy for cardiovascular secondary prevention (*no evidence for efficacy*) [De Schryver et al. 2006].
11. Aspirin with a past history of peptic ulcer disease without histamine H_2-receptor antagonist or proton pump inhibitor (*risk of bleeding*) [Garcia Rodriguez et al. 2001].
12. Aspirin at dose > 150 mg/day (*increased bleeding risk, no evidence for increased efficacy*) [Fisher and Knappertz 2006].
13. Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event (*not indicated*).
14. Aspirin to treat dizziness not clearly attributable to cerebrovascular disease (*not indicated*).
15. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration (*no proven added benefit*) [Pinede et al. 2001].
16. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (*no proven benefit*) [Pinede et al. 2001].
17. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (*high risk of bleeding*) [BNF 2006].

* Serum creatinine > 150 µmol/l, or estimated GFR 20 – 50 ml/min [BNF 2006].

B. Central nervous system and psychotropic drugs

1. Tricyclic antidepressants (TCAs) with dementia (*risk of worsening cognitive impairment*) [Smith 1998, Sommer et al. 2003].
2. TCAs with glaucoma *(likely to exacerbate glaucoma)* [Smith 1998, Sommer et al. 2003].
3. TCAs with cardiac conductive abnormalities (*pro-arrhythmic effects*) [Smith 1998, Sommer et al. 2003].
4. TCAs with constipation (*likely to worsen constipation*) [Smith 1998, Sommer et al. 2003].
5. TCAs with an opiate or calcium channel blocker (*risk of severe constipation*) [Smith 1998, Sommer et al. 2003].
6. TCA's with prostatism or prior history of urinary retention (*risk of urinary retention*) [Smith 1998, Sommer et al. 2003].
7. Long-term (i.e. > 1 month), long-acting benzodiazepines, e.g. chlordiazepoxide, fluazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites, e.g. diazepam (*risk of prolonged sedation, confusion, impaired balance, falls*) [Gray et al. 2006, Hanlon et al. 1998, Tamblyn et al. 2005].
8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics (*risk of confusion, hypotension, extrapyramidal side effects, falls*) [Alexopoulos et al. 2004, Maixner et al. 1999].
9. Long-term neuroleptics (> 1 month) in those with parkinsonism (*likely to worsen extrapyramidal symptoms*) [Smith 1998, van de Vijver et al. 2002].
10. Phenothiazines in patients with epilepsy (*may lower seizure threshold*) [Alexopoulos et al. 2004, BNF 2006].
11. Anticholinergics to treat extrapyramidal sideeffects of neuroleptic medications (*risk of anticholinergic toxicity*) [Mintzer and Burns 2000, Tune 2001].
12. Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatremia (*non-iatrogenic hyponatremia < 130 mmol/l within the previous 2 months*) [Jacob and Spinler 2006].
13. Prolonged use (> 1 week) of first-generation antihistamines, i.e. diphenhydramine, chlorpheniramine, cyclizine, promethazine (*risk of sedation and anti-cholinergic side effects*) [Sutter et al. 2003].

C. Gastrointestinal system

1. Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhea of unknown cause (*risk of delayed diagnosis, may exacerbate constipation with overflow diarrhea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis*) [Lustman et al. 1987, Thielman and Guerrant 2004].
2. Diphenoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis, i.e. bloody diarrhea, high fever or severe systemic toxicity (*risk of exacerbation or protraction of infection*) [Thielman and Guerrant 2004].
3. Prochlorperazine (Stemetil) or metoclopramide with parkinsonism (*risk of exacerbating parkinsonism*) [Smith 1998].
4. PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks (*dose reduction or earlier discontinuation indicated*) [BNF 2006, NICE guideline 2000/022].
5. Anticholinergic antispasmodic drugs with chronic constipation (*risk of exacerbation of constipation*) [Bosshard et al. 2004].

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* Serum creatinine > 150 µmol/l, or estimated GFR 20 – 50 ml/min [BNF 2006].

D. Respiratory system

1. Theophylline as monotherapy for COPD (*safer, more effective alternative; risk of adverse effects due to narrow therapeutic index*) [Ramsdell 1995].
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-to-severe COPD (*unnecessary exposure to long-term side effects of systemic steroids*) [Buist et al. 2006, McEvoy and Niewoehner 1997].
3. Nebulized ipratropium with glaucoma (*may exacerbate glaucoma*) [BNF 2006].

E. Musculoskeletal system

1. Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H_2 -receptor antagonist, PPI or misoprostol (*risk of peptic ulcer relapse*) [Hooper et al. 2004].
2. NSAID with moderate-to-severe hypertension (*risk of exacerbation of hypertension*) [Whelton 2006].
3. NSAID with heart failure (*risk of exacerbation of heart failure*) [Slørdal and Spigest 2006].
4. Long-term use of NSAID (> 3 months) for symptom relief of mild osteoarthritis (*simple analgesics preferable and usually as effective for pain relief*) [Altman et al. 2000].
5. Warfarin and NSAID together (*risk of gastrointestinal bleeding*) [Battistella et al. 2005].
6. NSAID with chronic renal failure* (*risk of deterioration in renal function*) [Cheng and Harris 2005].
7. Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthrtitis or osterarthritis (*risk of major systemic corticosteroid side-effects*) [Altman et al. 2000, Kwoh et al. 2002, Lee and Weinblatt 2001].
8. Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol (*allopurinol first-choice prophylactic drug in gout*) [Schlesinger 2004, Terkeltaub 2004].

F. Urogenital system

1. Bladder antimuscarinic drugs with dementia (*risk of increased confusion, agitation*) [Kay et al. 2005, Staskin 2005].
2. Antimuscarinic drugs with chronic glaucoma (*risk of acute exacerbation of glaucoma*) [Staskin 2005].
3. Antimuscarinic drugs with chronic constipation (*risk of exacerbation of constipation*) [Staskin 2005].
4. Antimuscarinic drugs with chronic prostatism (*risk of urinary retention*) [Staskin 2005].
5. α-blockers in males with frequent incontinence, i.e. one or more episodes of incontinence daily (*risk of urinary frequency and worsening of incontinence*) [Sarkar and Ritch 2000].
6. α-blockers with long-term urinary catheter in situ, i.e. more than 2 months (*drug not indicated*).

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* Serum creatinine > 150 µmol/l, or estimated GFR 20 – 50 ml/min [BNF 2006].

G. Endocrine system

1. Glibenclamide or chlorpropamide with type 2 diabetes mellitus (*risk of prolonged hypoglycemia*) [Cheillah and Burge 2004].
2. β-blockers in those with diabetes mellitus and frequent hypoglycemic episodes i.e. ≥ 1 episode per month (*risk of masking hypoglycemic symptoms*) [Cheillah and Burge 2004].
3. Estrogens with a history of breast cancer or venous thromboembolism (*increased risk of recurrence*) [Beral et al. 2002, Collaborative Group on Hormonal Factors in Breast Cancer 1997, Grady and Sawaya 1998].
4. Estrogens without progestogen in patients with intact uterus (*risk of endometrial cancer*) [Lethaby et al. 2000].

H. Drugs that adversely affect fallers

1. Benzodiazepines (*sedative, may cause reduced sensorium, impair balance*) [Tinetti 2003].
2. Neuroleptic drugs (*may cause gait dyspraxia, parkinsonism*) [Tinetti 2003].
3. First-generation antihistamines (*sedative, may impair sensorium*) [Sutter et al. 2003].
4. Vasodilator drugs with persistent postural hypotension, i.e. recurrent > 20 mmHg drop in systolic blood pressure (*risk of syncope, falls*) [Leipzig et al. 1999].
5. Long-term opiates in those with recurrent falls (*risk of drowsiness, postural hypotension, vertigo*) [American Geriatrics Society Panel on Persistent Pain in Older Persons 2002, Leipzig et al. 1999].

I. Analgesic drugs

1. Use of long-term powerful opiates, e.g. morphine or fentanyl as first-line therapy for mild-to-moderate pain (*World Health Organization analgesic ladder not observed*) [American Geriatrics Society Panel on Persistent Pain in Older Persons 2002].
2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (*risk of severe constipation*) [Walsh 1999].
3. Long-term opiates in those with dementia unless indicated for palliative care or management of moderate/severe chronic pain syndrome (*risk of exacerbation of cognitive impairment*) [American Geriatrics Society Panel on Persistent Pain in Older Persons 2002].

J. Duplicate drug classes

Any duplicate drug class prescription, e.g. two concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors (*optimization of monotherapy within a single drug class should be observed prior to considering a new class of drug*).

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* Serum creatinine > 150 μmol/l, or estimated GFR 20 – 50 ml/min [BNF 2006].

Source: "STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) Consensus validation" by Gallagher, P., Ryan, C., Byrne, S., Kennedy, J., & O'Mahony D., 2008, *International Journal of Clinical Pharmacology and Therapeutics, 46*, p. 76-78.

Appendix D. START (Screening Tool to Alert doctors to Right Treatment)

A. Cardiovascular system

1. Warfarin in the presence of chronic atrial fibrillation [Hart et al. 1999, Ross et al. 2005, Mant et al. 2007].
2. Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin [Hart et al. 1999, Ross et al. 2005].
3. Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm [Smith et al. 2006].
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg [Williams et al. 2004, Papademetriou et al. 2004, Skoog et al. 2004, Trenkwalder et al. 2005].
5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is greater than 5 years [Brown and Moussa 2003, Amarenco et al. 2004, Smith et al. 2006].
6. Angiotensin converting enzyme (ACE) inhibitor with chronic heart failure [Hunt et al. 2005].
7. ACE inhibitor following acute myocardial infarction [ACE Inhibitor Myocardial Infarction Collaborative Group 1998, Antman et al. 2004].
8. β-blocker with chronic stable angina [Gibbons et al. 2003].

B. Respiratory system

1. Regular inhaled β_2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD [Buist et al. 2006].
2. Regular inhaled corticosteroid for moderate/severe asthma or COPD, where predicted $FEV_1 < 50\%$ [Buist et al. 2006].
3. Home continuous oxygen with documented chronic type 1 respiratory failure ($pO_2 < 8.0$ kPa, $pCO_2 < 6.5$ kPa) or type 2 respiratory failure ($pO_2 < 8.0$ kPa, $pCO_2 > 6.5$ kPa) [Cranston et al. 2005, Buist et al. 2006].

C. Central nervous system

1. L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability [Kurlan 1998, Danisi 2002].
2. Antidepressant drug in the presence of moderate/severe depressive symptoms lasting at least three months [Lebowitz et al. 1997, Wilson et al. 2006].

D. Gastrointestinal system

1. Proton pump inhibitor with severe gastroesophageal acid reflux disease or peptic stricture requiring dilation [Hungin and Raghunath 2004].
2. Fiber supplement for chronic, symptomatic diverticular disease with constipation [Aldoori et al. 1994].

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* Serum creatinine > 150 µmol/l, or estimated GFR 20 – 50 ml/min [BNF 2006].

E. Musculoskeletal system

1. Disease-modifying antirheumatic drug (DMARD) with active moderate/severe rheumatoid disease lasting > 12 weeks [Kwoh et al. 2002].
2. Bisphosphonates in patients taking maintenance corticosteroid therapy [Buckley et al. 2001].
3. Calcium and vitamin D supplement in patients with known osteoporosis (previous fragility fracture, acquired dorsal kyphosis) [Gass and Dawson Hughes 2006].

F. Endocrine system

1. Metformin with type 2 diabetes ± metabolic syndrome (in the absence of renal impairment*) [Mooradian 1996, Johansen 1999].
2. ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy, i.e. overt urinalysis proteinuria or microalbuminuria (> 30 mg/24 hours) ± serum biochemical renal impairment* [Sigal et al. 2005].
3. Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors (hypertension, hypercholesterolemia, smoking history) [Sigal et al. 2005].
4. Statin therapy in diabetes mellitus if coexisting major cardiovascular risk factors present [Sigal et al. 2005].

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* Serum creatinine > 150 µmol/l, or estimated GFR 20 – 50 ml/min [BNF 2006].

Source: "STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) Consensus validation" by Gallagher, P., Ryan, C., Byrne, S., Kennedy, J., & O'Mahony D., 2008, *International Journal of Clinical Pharmacology and Therapeutics*, *46*, p. 79.

Appendix E. 1991 Beers Criteria

Table 3.—Criteria for Inappropriate Use*

Drug Name or Class	Statement
Sedative-hypnotics	
Long-acting benzodiazepines: chlordiazepoxide, diazepam, flurazepam	All use should be avoided; use short-acting benzodiazepines if needed
Meprobamate	All use should be avoided, except in those already addicted
Oxazepam	Any single dose >30 mg should be avoided
Short-acting benzodiazepines: oxazepam, triazolam, alprazolam	Nightly use for >4 wk should be avoided
Short-duration barbiturates: pentobarbital, secobarbital	All use should be avoided, except in those already addicted; safer sedative-hypnotics are available
Triazolam	Any single dose >0.25 mg should be avoided
Antidepressants	
Amitriptyline	All use should be avoided; use less anticholinergic antidepressant if needed
Combination antidepressants-antipsychotics, eg, amitriptyline-perphenazine (Triavil)	All use should be avoided; if needed, prescribe individual components at proper geriatric doses; avoid amitriptyline
Antipsychotics	
Haloperidol	Doses >3 mg/d should be avoided; patients with known psychotic disorders may require higher doses
Thioridazine	Doses >30 mg/d should be avoided; patients with known psychotic disorders may require higher doses
Antihypertensives	
Hydrochlorothiazide	Doses >50 mg/d should be avoided
Methyldopa	All use should be avoided; safer antihypertensives are available
Propranolol	All use should be avoided, except if used to control violent behaviors; other β-blockers offer less CNS penetration or more β selectivity
Reserpine	All use should be avoided; safer antihypertensives are available
NSAIDs	
Indomethacin	All use should be avoided; other NSAIDs cause less CNS toxic reaction
Phenylbutazone	All use should be avoided; other NSAIDs are less toxic

Table 3.—Criteria for Inappropriate Use* (cont)

Drug Name or Class	Statement
Oral hypoglycemics	
Chlorpropamide	All use should be avoided; other oral hypoglycemics have shorter half-lives and do not cause SIADH
Analgesics	
Propoxyphene	All use should be avoided; other analgesics are safer and more effective
Pentazocine	All use should be avoided; other narcotics are more effective and safer
Dementia treatments	
Cyclandelate	All use should be avoided; effectiveness is in doubt
Isoxsuprine	All use should be avoided; effectiveness is in doubt
Platelet Inhibitors	
Dipyridamole	All use should be avoided; effectiveness at low doses is in doubt; toxic reaction is high at higher doses; aspirin is safer alternative
Histamine, blockers	
Cimetidine	Doses >900 mg/d and therapy beyond 12 wk should be avoided
Ranitidine	Doses >300 mg/d and therapy beyond 12 wk should be avoided
Antibiotics	
Oral antibiotics	Therapy >4 wk should be avoided except when treating osteomyelitis, prostatitis, tuberculosis, or endocarditis
Decongestants	
Oxymetazoline, phenylephrine, pseudoephedrine	Daily use for >2 wk should be avoided
Iron	Doses >325 mg/d should be avoided; they do not substantially increase iron absorption and increase side effects
Muscle relaxants-antispasmodics	
Cyclobenzaprine, orphenidrate, methocarbamol, carisoprodol	All use should be avoided; potential for toxic reaction is greater than potential benefit
GI antispasmodics	All long-term use should be avoided; potential for toxic reaction is greater than potential benefit
Antiemetics	
Trimethobenzamide	All use should be avoided

*CNS indicates central nervous system; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion; and GI, gastrointestinal.

Source: "Explicit criteria for determining inappropriate medication use in nursing home residents" by Beers, M. H., Ouslander, J. G., Rollingher, I., Reuben, D. B., Brooks, J., & Beck, J. C., 1991, *Archives of Internal Medicine, 151,* p. 1829.

Appendix F. 1997 Beers Criteria

Summary of Prescribing Concern	Applicable Medications†	High Severity
Propoxyphene should generally be avoided in the elderly. It offers few analgesic advantages over acetaminophen, yet has the side effects of other narcotic drugs.	Propoxyphene and combination products	No
Of all available nonsteroidal, anti-inflammatory drugs, indomethacin produces the most central nervous system side effects and should, therefore, be avoided in the elderly.	Indomethacin (Indocin, Indocin SR)	No
Phenylbutazone may produce serious hematological side effects and should not be used in elderly patients.	Phenylbutazone (Butazolidin)	No
Pentazocine is a narcotic analgesic that causes more central nervous system side effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist. For both reasons, its use should generally be avoided in the elderly.	Pentazocine (Talwin)	Yes
Trimethobenzamide is one of the least effective antiemetic drugs, yet it can cause extrapyramidal side effects. When possible, it should be avoided in the elderly.	Trimethobenzamide (Tigan)	No
Most muscle relaxants and antispasmodic drugs are poorly tolerated by the elderly, leading to anticholinergic side effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by the elderly is questionable. Whenever possible, they should not be used by the elderly.	Methocarbamol (Robaxin), carisoprodol (Soma), oxybutynin (Ditropan), chlorzoxazone (Paraflex), metaxalone (Skelaxin), and cyclobenzaprine (Flexeril)	No
Benzodiazepine hypnotic has an extremely long half-life in the elderly (often days), producing prolonged sedation and increasing the incidence of falls and fractures. Medium- or short-acting benzodiazepines are preferable.	Flurazepam (Dalmane)	Yes
Because of its strong anticholinergic and sedating properties, amitriptyline is rarely the antidepressant of choice for the elderly.	Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)	Yes
Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for the elderly.	Doxepin (Sinequan)	Yes
Meprobamate is a highly addictive and sedating anxiolytic. Avoid in elderly patients. Those using meprobamate for prolonged periods may be addicted and may need to be withdrawn slowly.	Meprobamate (Miltown, Equanil)	Yes if recently started‡
Because of increased sensitivity to benzodiazepines in the elderly, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the following suggested maximums	Lorazepam (Ativan), 3 mg; oxazepam (Serax), 60 mg; alprazolam (Xanax), 2 mg; temazepam (Restoril), 15 mg; zolpidem (Ambien), 5 mg; triazolam (Halcion), 0.25 mg	No
Chlordiazepoxide and diazepam have a long half-life in the elderly (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	Chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), and diazepam (Valium)	Yes
Disopyramide, of all antiarrhythmic drugs, is the most potent negative inotrope and therefore may induce heart failure in the elderly. It is also strongly anticholinergic. When appropriate, other antiarrhythmic drugs should be used.	Disopyramide (Norpace, Norpace CR)	Yes
Because of decreased renal clearance of digoxin, doses in the elderly should rarely exceed 0.125 mg daily, except when treating atrial arrhythmias.	Digoxin (Lanoxin)	Yes if recently started‡
Dipyridamole frequently causes orthostatic hypotension in the elderly. It has been proven beneficial only in patients with artificial heart valves. Whenever possible, its use in the elderly should be avoided.	Dipyridamole (Persantine)	No
Methyldopa may cause bradycardia and exacerbate depression in the elderly. Alternate treatments for hypertension are generally preferred.	Methyldopa (Aldomet); methyldopa/hydrochlorothiazide (Aldoril)	Yes if recently started‡
Reserpine imposes unnecessary risk in the elderly, inducing depression, impotence, sedation, and orthostatic hypotension. Safer alternatives exist.	Reserpine (Serpasil); reserpine hydrochlorothiazide (Hydropres)	No
Chlorpropamide has a prolonged half-life in the elderly and can cause prolonged and serious hypoglycemia. Additionally, it is the only oral hypoglycemic agent that causes SIADH. Avoid in the elderly.	Chlorpropamide (Diabinese)	Yes
Gastrointestinal antispasmodic drugs are highly anticholinergic and generally produce substantial toxic effects in the elderly. Additionally, their effectiveness at doses tolerated by the elderly is questionable. All these drugs are best avoided in the elderly, especially for long-term use.	Dicyclomine (Bentyl); hyoscyamine (Levsin, Levsinex); propantheline (Pro-Banthine); belladonna alkaloids (Donnatal and others); and clidinium-chlordiazepoxide (Librax)	Yes
All nonprescription and many prescription antihistamines have potent anticholinergic properties. Many cough and cold preparations are available without antihistamines, and these are safer substitutes in the elderly.	Examples include single and combination preparations containing chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril, Atarax), cyproheptadine (Periactin), promethazine (Phenergan), tripelennamine, and dexchlorpheniramine (Polaramine)	No

Summary of Prescribing Concern	Applicable Medications†	High Severity
Diphenhydramine is potently anticholinergic and usually should not be used as a hypnotic in the elderly. When used to treat or prevent allergic reactions, it should be used in the smallest possible dose and with great caution.	Diphenhydramine (Benadryl)	No
Hydergine (ergot mesyloids) and the cerebral vasodilators have not been shown to be effective, in the doses studied, for the treatment of dementia or any other condition.	Ergot mesyloids (Hydergine), cyclospasmol	No
Iron supplements rarely need to be given in doses exceeding 325 mg of ferrous sulfate daily. When doses are higher, total absorption is not substantially increased, but constipation is more likely to occur.	Iron supplements, >325 mg	No
Barbiturates cause more side effects than most other sedative or hypnotic drugs in the elderly and are highly addictive. They should not be started as new therapy in the elderly except when used to control seizures.	All barbiturates except phenobarbital	Yes if recently started‡
Meperidine is not an effective oral analgesic and has many disadvantages to other narcotic drugs. Avoid in the elderly.	Meperidine	Yes
Ticlopidine has been shown to be no better than aspirin in preventing clotting and is considerably more toxic. Avoid in the elderly.	Ticlopidine	Yes

** It is important to note that most package circulars produced by drug manufacturers do not include language identical to the statements presented herein. Although the adverse effects that these drugs can produce are generally listed in the package circulars, these as well as warnings and contraindications must be approved by regulatory agencies and in general are not based on consensus or surveys. SIADH indicates syndrome of inappropriate antidiuretic hormone.*

†Dose limits are total daily dose.

‡Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a 1-month period.

Source: "Explicit criteria for determining potentially inappropriate medication use by the elderly. An update" by Beers, M. H., 1997, *Archives of Internal Medicine, 157*, p. 1533-1534.

Appendix G. 2003 Beers Criteria

Table 1. 2002 Criteria for Potentially Inappropriate Medication Use in Older Adults: Independent of Diagnoses or Conditions

Drug	Concern	Severity Rating (High or Low)
Propoxyphene (Darvon) and combination products (Darvon with ASA, Darvon-N, and Darvocet-N)	Offers few analgesic advantages over acetaminophen, yet has the adverse effects of other narcotic drugs.	Low
Indomethacin (Indocin and Indocin SR)	Of all available nonsteroidal anti-inflammatory drugs, this drug produces the most CNS adverse effects.	High
Pentazocine (Talwin)	Narcotic analgesic that causes more CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist.	High
Trimethobenzamide (Tigan)	One of the least effective antiemetic drugs, yet it can cause extrapyramidal adverse effects.	High
Muscle relaxants and antispasmodics: methocarbamol (Robaxin), carisoprodol (Soma), chlorzoxazone (Paraflex), metaxalone (Skelaxin), cyclobenzaprine (Flexeril), and oxybutynin (Ditropan). Do not consider the extended-release Ditropan XL.	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these cause anticholinergic adverse effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable.	High
Flurazepam (Dalmane)	This benzodiazepine hypnotic has an extremely long half-life in elderly patients (often days), producing prolonged sedation and increasing the incidence of falls and fracture. Medium- or short-acting benzodiazepines are preferable.	High
Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)	Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients.	High
Doxepin (Sinequan)	Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for elderly patients.	High
Meprobamate (Miltown and Equanil)	This is a highly addictive and sedating anxiolytic. Those using meprobamate for prolonged periods may become addicted and may need to be withdrawn slowly.	High
Doses of short-acting benzodiazepines: doses greater than lorazepam (Ativan), 3 mg; oxazepam (Serax), 60 mg; alprazolam (Xanax), 2 mg; temazepam (Restoril), 15 mg; and triazolam (Halcion), 0.25 mg	Because of increased sensitivity to benzoadiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Long-acting benzodiazepines: chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol) clidinium-chlordiazepoxide (Librax), diazepam (Valium), quazepam (Doral), halazepam (Paxipam), and chlorazepate (Tranxene)	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	High
Disopyramide (Norpace and Norpace CR)	Of all antiarrhythmic drugs, this is the most potent negative inotrope and therefore may induce heart failure in elderly patients. It is also strongly anticholinergic. Other antiarrhythmic drugs should be used.	High
Digoxin (Lanoxin) (should not exceed >0.125 mg/d except when treating atrial arrhythmias)	Decreased renal clearance may lead to increased risk of toxic effects.	Low
Short-acting dipyridamole (Persantine). Do not consider the long-acting dipyridamole (which has better properties than the short-acting in older adults) except with patients with artificial heart valves	May cause orthostatic hypotension.	Low
Methyldopa (Aldomet) and methyldopa-hydrochlorothiazide (Aldoril)	May cause bradycardia and exacerbate depression in elderly patients.	High
Reserpine at doses >0.25 mg	May induce depression, impotence, sedation, and orthostatic hypotension.	Low
Chlorpropamide (Diabinese)	It has a prolonged half-life in elderly patients and could cause prolonged hypoglycemia. Additionally, it is the only oral hypoglycemic agent that causes SIADH.	High
Gastrointestinal antispasmodic drugs: dicyclomine (Bentyl), hyoscyamine (Levsin and Levsinex), propantheline (Pro-Banthine), belladonna alkaloids (Donnatal and others), and clidinium-chlordiazepoxide (Librax)	GI antispasmodic drugs are highly anticholinergic and have uncertain effectiveness. These drugs should be avoided (especially for long-term use).	High
Anticholinergics and antihistamines: chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril and Atarax), cyproheptadine (Periactin), promethazine (Phenergan), tripelennamine, dexchlorpheniramine (Polaramine)	All nonprescription and many prescription antihistamines may have potent anticholinergic properties. Nonanticholinergic antihistamines are preferred in elderly patients when treating allergic reactions.	High
Diphenhydramine (Benadryl)	May cause confusion and sedation. Should not be used as a hypnotic, and when used to treat emergency allergic reactions, it should be used in the smallest possible dose.	High
Ergot mesyloids (Hydergine) and cyclandelate (Cyclospasmol)	Have not been shown to be effective in the doses studied.	Low
Ferrous sulfate >325 mg/d	Doses >325 mg/d do not dramatically increase the amount absorbed but greatly increase the incidence of constipation.	Low
All barbiturates (except phenobarbital) except when used to control seizures	Are highly addictive and cause more adverse effects than most sedative or hypnotic drugs in elderly patients.	High

(continued)

Table 1. 2002 Criteria for Potentially Inappropriate Medication Use in Older Adults: Independent of Diagnoses or Conditions (cont)

Drug	Concern	Severity Rating (High or Low)
Meperidine (Demerol)	Not an effective oral analgesic in doses commonly used. May cause confusion and has many disadvantages to other narcotic drugs.	High
Ticlopidine (Ticlid)	Has been shown to be no better than aspirin in preventing clotting and may be considerably more toxic. Safer, more effective alternatives exist.	High
Ketorolac (Toradol)	Immediate and long-term use should be avoided in older persons, since a significant number have asymptomatic GI pathologic conditions.	High
Amphetamines and anorexic agents	These drugs have potential for causing dependence, hypertension, angina, and myocardial infarction.	High
Long-term use of full-dosage, longer half-life, non–COX-selective NSAIDs: naproxen (Naprosyn, Avaprox, and Aleve), oxaprozin (Daypro), and piroxicam (Feldene)	Have the potential to produce GI bleeding, renal failure, high blood pressure, and heart failure.	High
Daily fluoxetine (Prozac)	Long half-life of drug and risk of producing excessive CNS stimulation, sleep disturbances, and increasing agitation. Safer alternatives exist.	High
Long-term use of stimulant laxatives: bisacodyl (Dulcolax), cascara sagrada, and Neoloid except in the presence of opiate analgesic use	May exacerbate bowel dysfunction.	High
Amiodarone (Cordarone)	Associated with QT interval problems and risk of provoking torsades de pointes. Lack of efficacy in older adults.	High
Orphenadrine (Norflex)	Causes more sedation and anticholinergic adverse effects than safer alternatives.	High
Guanethidine (Ismelin)	May cause orthostatic hypotension. Safer alternatives exist.	High
Guanadrel (Hylorel)	May cause orthostatic hypotension.	High
Cyclandelate (Cyclospasmol)	Lack of efficacy.	Low
Isoxsurpine (Vasodilan)	Lack of efficacy.	Low
Nitrofurantoin (Macrodantin)	Potential for renal impairment. Safer alternatives available.	High
Doxazosin (Cardura)	Potential for hypotension, dry mouth, and urinary problems.	Low
Methyltestosterone (Android, Virilon, and Testrad)	Potential for prostatic hypertrophy and cardiac problems.	High
Thioridazine (Mellaril)	Greater potential for CNS and extrapyramidal adverse effects.	High
Mesoridazine (Serentil)	CNS and extrapyramidal adverse effects.	High
Short acting nifedipine (Procardia and Adalat)	Potential for hypotension and constipation.	High
Clonidine (Catapres)	Potential for orthostatic hypotension and CNS adverse effects.	Low
Mineral oil	Potential for aspiration and adverse effects. Safer alternatives available.	High
Cimetidine (Tagamet)	CNS adverse effects including confusion.	Low
Ethacrynic acid (Edecrin)	Potential for hypertension and fluid imbalances. Safer alternatives available.	Low
Desiccated thyroid	Concerns about cardiac effects. Safer alternatives available.	High
Amphetamines (excluding methylphenidate hydrochloride and anorexics)	CNS stimulant adverse effects.	High
Estrogens only (oral)	Evidence of the carcinogenic (breast and endometrial cancer) potential of these agents and lack of cardioprotective effect in older women.	Low

Abbreviations: CNS, central nervous system; COX, cyclooxygenase; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 2. 2002 Criteria for Potentially Inappropriate Medication Use in Older Adults: Considering Diagnoses or Conditions

Disease or Condition	Drug	Concern	Severity Rating (High or Low)
Heart failure	Disopyramide (Norpace), and high sodium content drugs (sodium and sodium salts [alginate bicarbonate, biphosphate, citrate, phosphate, salicylate, and sulfate])	Negative inotropic effect. Potential to promote fluid retention and exacerbation of heart failure.	High
Hypertension	Phenylpropanolamine hydrochloride (removed from the market in 2001), pseudoephedrine; diet pills, and amphetamines	May produce elevation of blood pressure secondary to sympathomimetic activity.	High
Gastric or duodenal ulcers	NSAIDs and aspirin (>325 mg) (coxibs excluded)	May exacerbate existing ulcers or produce new/additional ulcers.	High
Seizures or epilepsy	Clozapine (Clozaril), chlorpromazine (Thorazine), thioridazine (Mellaril), and thiothixene (Navane)	May lower seizure thresholds.	High
Blood clotting disorders or receiving anticoagulant therapy	Aspirin, NSAIDs, dipyridamole (Persantin), ticlopidine (Ticlid), and clopidogrel (Plavix)	May prolong clotting time and elevate INR values or inhibit platelet aggregation, resulting in an increased potential for bleeding.	High
Bladder outflow obstruction	Anticholinergics and antihistamines, gastrointestinal antispasmodics, muscle relaxants, oxybutynin (Ditropan), flavoxate (Urispas), anticholinergics, antidepressants, decongestants, and tolterodine (Detrol)	May decrease urinary flow, leading to urinary retention.	High
Stress incontinence	α-Blockers (Doxazosin, Prazosin, and Terazosin), anticholinergics, tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride, and amitriptyline hydrochloride), and long-acting benzodiazepines	May produce polyuria and worsening of incontinence.	High
Arrhythmias	Tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride, and amitriptyline hydrochloride)	Concern due to proarrhythmic effects and ability to produce QT interval changes.	High
Insomnia	Decongestants, theophylline (Theodur), methylphenidate (Ritalin), MAOIs, and amphetamines	Concern due to CNS stimulant effects.	High
Parkinson disease	Metoclopramide (Reglan), conventional antipsychotics, and tacrine (Cognex)	Concern due to their antidopaminergic/ cholinergic effects.	High
Cognitive impairment	Barbiturates, anticholinergics, antispasmodics, and muscle relaxants. CNS stimulants: dextroAmphetamine (Adderall), methylphenidate (Ritalin), methamphetamine (Desoxyn), and pemolin	Concern due to CNS-altering effects.	High
Depression	Long-term benzodiazepine use. Sympatholytic agents: methyldopa (Aldomet), reserpine, and guanethidine (Ismelin)	May produce or exacerbate depression.	High
Anorexia and malnutrition	CNS stimulants: DextroAmphetamine (Adderall), methylphenidate (Ritalin), methamphetamine (Desoxyn), pemolin, and fluoxetine (Prozac)	Concern due to appetite-suppressing effects.	High
Syncope or falls	Short- to intermediate-acting benzodiazepine and tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride, and amitriptyline hydrochloride)	May produce ataxia, impaired psychomotor function, syncope, and additional falls.	High
SIADH/hyponatremia	SSRIs: fluoxetine (Prozac), citalopram (Celexa), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft)	May exacerbate or cause SIADH.	Low
Seizure disorder	Bupropion (Wellbutrin)	May lower seizure threshold.	High
Obesity	Olanzapine (Zyprexa)	May stimulate appetite and increase weight gain.	Low
COPD	Long-acting benzodiazepines: chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), diazepam (Valium), quazepam (Doral), halazepam (Paxipam), and chlorazepate (Tranxene). β-blockers: propranolol	CNS adverse effects. May induce respiratory depression. May exacerbate or cause respiratory depression.	High
Chronic constipation	Calcium channel blockers, anticholinergics, and tricyclic antidepressant (imipramine hydrochloride, doxepin hydrochloride, and amitriptyline hydrochloride)	May exacerbate constipation.	Low

Abbreviations: CNS, central nervous systems; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; MAOIs, monoamine oxidase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRIs, selective serotonin reuptake inhibitors.

Source: Source: "Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults" by Fick, D. M., Cooper, J. W., Wade, W. E., Waller, J. L., Maclean, J. R., & Beers, M. H.., 2003, *Archives of Internal Medicine, 163*, p. 2719-2721.

Appendix H. 2012 Beers Criteria

Table 2. 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics (excludes TCAs)				
First-generation antihistamines (as single agent or as part of combination products) Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; greater risk of confusion, dry mouth, constipation, and other anticholinergic effects and toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate	Avoid	Hydroxyzine and promethazine: high; All others: moderate	Strong
Antiparkinson agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more-effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Antispasmodics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid except in short-term palliative care to decrease oral secretions	Moderate	Strong
Antithrombotics				
Dipyridamole, oral short acting* (does not apply to extended-release combination with aspirin)	May cause orthostatic hypotension; more-effective alternatives available; intravenous form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Ticlopidine*	Safer effective alternatives available	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl < 60 mL/min due to inadequate drug concentration in the urine	Avoid for long-term suppression; avoid in patients with CrCl < 60 mL/min	Moderate	Strong
Cardiovascular				
$Alpha_1$ blockers Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Alpha agonists, central Clonidine Guanabenz* Guanfacine* Methyldopa* Reserpine (> 0.1 mg/d)*	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid clonidine as a first-line antihypertensive. Avoid others as listed	Low	Strong

(Continued)

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Antiarrhythmic drugs (Class Ia, Ic, III) Amiodarone Dofetilide Dronedarone Flecainide Ibutilide Procainamide Propafenone Quinidine Sotalol	Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults. Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders, and QT- interval prolongation	Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation	High	Strong
Disopyramide*	Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or heart failure. In general, rate control is preferred over rhythm control for atrial fibrillation	Avoid in patients with permanent atrial fibrillation or heart failure	Moderate	Strong
Digoxin > 0.125 mg/d	In heart failure, higher dosages associated with no additional benefit and may increase risk of toxicity; slow renal clearance may lead to risk of toxic effects	Avoid	Moderate	Strong
Nifedipine, immediate release*	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Spironolactone > 25 mg/d	In heart failure, the risk of hyperkalemia is higher in older adults especially if taking > 25 mg/d or taking concomitant NSAID, angiotensin converting-enzyme inhibitor, angiotensin receptor blocker, or potassium supplement	Avoid in patients with heart failure or with a CrCl < 30 mL/min	Moderate	Strong
Central nervous system				
Tertiary TCAs, alone or in combination: Amitriptyline Chlordiazepoxide-amitriptyline Clomipramine Doxepin > 6 mg/d Imipramine Perphenazine-amitriptyline Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin ($\leq$6 mg/d) is comparable with that of placebo	Avoid	High	Strong
Antipsychotics, first (conventional) and second (atypical) generation (see Table 8 for full list)	Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid use for behavioral problems of dementia unless nonpharmacological options have failed and patient is threat to self or others	Moderate	Strong
Thioridazine Mesoridazine	Highly anticholinergic and risk of QT-interval prolongation	Avoid	Moderate	Strong

(Continued)

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Barbiturates Amobarbital* Butabarbital* Butalbital Mephobarbital* Pentobarbital* Phenobarbital Secobarbital*	High rate of physical dependence; tolerance to sleep benefits; risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short and intermediate acting:* Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam *Long acting:* Clorazepate Chlordiazepoxide Chlordiazepoxide-amitriptyline Clidinium-chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	Older adults have increased sensitivity to benzodiazepines and slower metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anesthesia, end-of-life care	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium	High	Strong
Chloral hydrate*	Tolerance occurs within 10 days, and risks outweigh benefits in light of overdose with doses only 3 times the recommended dose	Avoid	Low	Strong
Meprobamate	High rate of physical dependence; very sedating	Avoid	Moderate	Strong
Nonbenzodiazepine hypnotics Eszopiclone Zolpidem Zaleplon	Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); minimal improvement in sleep latency and duration	Avoid chronic use (> 90 days)	Moderate	Strong
Ergot mesylates* Isoxsuprine*	Lack of efficacy	Avoid	High	Strong
Endocrine				
Androgens Methyltestosterone* Testosterone	Potential for cardiac problems and contraindicated in men with prostate cancer	Avoid unless indicated for moderate to severe hypogonadism	Moderate	Weak
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women Evidence that vaginal estrogens for treatment of vaginal dryness is safe and effective in women with breast cancer, especially at dosages of estradiol < 25 μg twice weekly	Avoid oral and topical patch. Topical vaginal cream: acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms	Oral and patch: high Topical: moderate	Oral and patch: strong Topical: weak
Growth hormone	Effect on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except as hormone replacement after pituitary gland removal	High	Strong

(Continued)

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long duration Chlorpropamide Glyburide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion. Glyburide: greater risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
Gastrointestinal				
Metoclopramide	Can cause extrapyramidal effects including tardive dyskinesia; risk may be even greater in frail older adults	Avoid, unless for gastroparesis	Moderate	Strong
Mineral oil, oral	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
Trimethobenzamide	One of the least effective antiemetic drugs; can cause extrapyramidal adverse effects	Avoid	Moderate	Strong
Pain				
Meperidine	Not an effective oral analgesic in dosages commonly used; may cause neurotoxicity; safer alternatives available	Avoid	High	Strong
Non–COX-selective NSAIDs, oral Aspirin > 325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increases risk of GI bleeding and peptic ulcer disease in high-risk groups, including those aged > 75 or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. Use of proton pump inhibitor or misoprostol reduces but does not eliminate risk. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months and in approximately 2–4% of patients treated for 1 year. These trends continue with longer duration of use	Avoid chronic use unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	Moderate	Strong
Indomethacin Ketorolac, includes parenteral	Increases risk of GI bleeding and peptic ulcer disease in high-risk groups. (See above Non-COX selective NSAIDs.) Of all the NSAIDs, indomethacin has most adverse effects	Avoid	Indomethacin: moderate Ketorolac: high	Strong

(Continued)

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Pentazocine*	Opioid analgesic that causes CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs; is also a mixed agonist and antagonist; safer alternatives available	Avoid	Low	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture; effectiveness at dosages tolerated by older adults is questionable	Avoid	Moderate	Strong

The primary target audience is the practicing clinician. The intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health-outcome, quality of care, cost, and utilization data.

* Infrequently used drugs.

CNS = central nervous system; COX = cyclooxygenase; CrCl = creatinine clearance; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressant.

Correction made after online publication February 29, 2012: Table 2 has been updated.

Table 3. 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug–Disease or Drug–Syndrome Interactions That May Exacerbate the Disease or Syndrome

Disease or Syndrome	Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular					
Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (avoid only for systolic heart failure) Diltiazem Verapamil Pioglitazone, rosiglitazone Cilostazol Dronedarone	Potential to promote fluid retention and exacerbate heart failure	Avoid	NSAIDs: moderate CCBs: moderate Thiazolidinediones (glitazones): high Cilostazol: low Dronedarone: moderate	Strong
Syncope	AChEIs Peripheral alpha blockers Doxazosin Prazosin Terazosin Tertiary TCAs Chlorpromazine, thioridazine, and olanzapine	Increases risk of orthostatic hypotension or bradycardia	Avoid	Alpha blockers: high TCAs, AChEIs, and antipsychotics: moderate	AChEIs and TCAs: strong Alpha blockers and antipsychotics: weak
Central nervous system					
Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Lowers seizure threshold; may be acceptable in patients with well-controlled seizures in whom alternative agents have not been effective	Avoid	Moderate	Strong
Delirium	All TCAs Anticholinergics (see Table 9 for full list) Benzodiazepines Chlorpromazine Corticosteroids H_2-receptor antagonist Meperidine Sedative hypnotics Thioridazine	Avoid in older adults with or at high risk of delirium because of inducing or worsening delirium in older adults; if discontinuing drugs used chronically, taper to avoid withdrawal symptoms	Avoid	Moderate	Strong
Dementia and cognitive impairment	Anticholinergics (see Table 9 for full list) Benzodiazepines H_2-receptor antagonists Zolpidem Antipsychotics, chronic and as-needed use	Avoid because of adverse CNS effects. Avoid antipsychotics for behavioral problems of dementia unless nonpharmacological options have failed, and patient is a threat to themselves or others. Antipsychotics are associated with an increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid	High	Strong
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine hypnotics Eszopiclone Zaleplon Zolpidem TCAs and selective serotonin reuptake inhibitors	Ability to produce ataxia, impaired psychomotor function, syncope, and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones	Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure disorders	High	Strong

(Continued)

Disease or Syndrome	Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Insomnia	Oral decongestants Pseudoephedrine Phenylephrine Stimulants Amphetamine Methylphenidate Pemoline Theobromines Theophylline Caffeine	CNS stimulant effects	Avoid	Moderate	Strong
Parkinson's disease	All antipsychotics (see Table 8 for full list, except for quetiapine and clozapine) Antiemetics Metoclopramide Prochlorperazine Promethazine	Dopamine receptor antagonists with potential to worsen parkinsonian symptoms. Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson's disease	Avoid	Moderate	Strong
Gastrointestinal					
Chronic constipation	Oral antimuscarinics for urinary incontinence Darifenacin Fesoterodine Oxybutynin (oral) Solifenacin Tolterodine Trospium Nondihydropyridine CCB Diltiazem Verapamil First-generation antihistamines as single agent or part of combination products Brompheniramine (various) Carbinoxamine Chlorpheniramine Clemastine (various) Cyproheptadine Dexbrompheniramine Dexchlorpheniramine (various) Diphenhydramine Doxylamine Hydroxyzine Promethazine Triprolidine Anticholinergics and antispasmodics (see Table 9 for full list of drugs with strong anticholinergic properties) Antipsychotics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine Tertiary TCAs (amitriptyline, clomipramine, doxepin, imipramine, and trimipramine)	Can worsen constipation; agents for urinary incontinence: antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops	Avoid unless no other alternatives	For urinary incontinence: high All others: Moderate to low	Weak

(Continued)

Disease or Syndrome	Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
History of gastric or duodenal ulcers	Aspirin (>325 mg/d) Non–COX-2 selective NSAIDs	May exacerbate existing ulcers or cause new or additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	Moderate	Strong
Kidney and urinary tract					
Chronic kidney disease Stages IV and V	NSAIDs Triamterene (alone or in combination)	May increase risk of kidney injury	Avoid	NSAIDs: moderate Triamterene: low	NSAIDs: strong Triamterene: weak
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen)	Aggravation of incontinence	Avoid in women	High	Strong
Lower urinary tract symptoms, benign prostatic hyperplasia	Inhaled anticholinergic agents Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 9 for complete list)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Inhaled agents: strong All others: weak
Stress or mixed urinary incontinence	Alpha blockers Doxazosin Prazosin Terazosin	Aggravation of incontinence	Avoid in women	Moderate	Strong

The primary target audience is the practicing clinician. The intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health-outcome, quality of care, cost, and utilization data.

CCB = calcium channel blocker; AChEI = acetylcholinesterase inhibitor; CNS = central nervous system; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressant.

Table 4. 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults

Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiac events	Lack of evidence of benefit versus risk in individuals aged ≥80	Use with caution in adults aged ≥80	Low	Weak
Dabigatran	Greater risk of bleeding than with warfarin in adults aged ≥75; lack of evidence for efficacy and safety in individuals with CrCl < 30 mL/min	Use with caution in adults aged ≥75 or if CrCl < 30 mL/min	Moderate	Weak
Prasugrel	Greater risk of bleeding in older adults; risk may be offset by benefit in highest-risk older adults (e.g., with prior myocardial infarction or diabetes mellitus)	Use with caution in adults aged ≥75	Moderate	Weak
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine Serotonin–norepinephrine reuptake inhibitor Selective serotonin reuptake inhibitor Tricyclic antidepressants Vincristine	May exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia; need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk	Use with caution	Moderate	Strong
Vasodilators	May exacerbate episodes of syncope in individuals with history of syncope	Use with caution	Moderate	Weak

The primary target audience is the practicing clinician. The intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health-outcome, quality of care, cost, and utilization data.
CrCl = creatinine clearance.

Source: "American geriatrics society updated beers criteria for potentially inappropriate medication use in older adults" by the American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012, *Journal of the American Geriatrics Society*, *60*, p. 619-627.

Table 2. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics				
First-generation antihistamines Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate	Avoid	Moderate	Strong
Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more-effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Antispasmodics Atropine (excludes ophthalmic) Belladonna alkaloids Clidinium-Chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong
Antithrombotics				
Dipyridamole, oral short-acting (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; intravenous form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Ticlopidine	Safer, effective alternatives available	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression of bacteria	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk–benefit profile	Avoid use as an antihypertensive	Moderate	Strong

(Continued)

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Central alpha blockers Clonidine Guanabenz Guanfacine Methyldopa Reserpine (>0.1 mg/d)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid clonidine as first-line antihypertensive Avoid others as listed	Low	Strong
Disopyramide	Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or severe or recently decompensated heart failure	Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure	High	Strong
Digoxin	Use in atrial fibrillation: should not be used as a first-line agent in atrial fibrillation, because more-effective alternatives exist and it may be associated with increased mortality	Avoid as first-line therapy for atrial fibrillation	Atrial fibrillation: moderate	Atrial fibrillation: strong
	Use in heart failure: questionable effects on risk of hospitalization and may be associated with increased mortality in older adults with heart failure; in heart failure, higher dosages not associated with additional benefit and may increase risk of toxicity	Avoid as first-line therapy for heart failure	Heart failure: low	Heart failure: strong
	Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in patients with Stage 4 or 5 chronic kidney disease	If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/d	Dosage >0.125 mg/d: moderate	Dosage >0.125 mg/d: strong
Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Amiodarone is effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; it may be reasonable first-line therapy in patients with concomitant heart failure or substantial left ventricular hypertrophy if rhythm control is preferred over rate control	Avoid amiodarone as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	High	Strong
Central nervous system				

(Continued)

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Antidepressants, alone or in combination Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/d Imipramine Nortriptyline Paroxetine Protriptyline Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/d) comparable with that of placebo	Avoid	High	Strong
Antipsychotics, first- (conventional) and second- (atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible ***and*** the older adult is threatening substantial harm to self or others	Avoid, except for schizophrenia, bipolar disorder, or short-term use as antiemetic during chemotherapy	Moderate	Strong
Barbiturates Amobarbital Butabarbital Butalbital Mephobarbital Pentobarbital Phenobarbital Secobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short- and intermediate- acting* Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults	Avoid	Moderate	Strong

(Continued)

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Long-acting Clorazepate Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) Clonazepam Diazepam Flurazepam Quazepam	May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia			
Meprobamate	High rate of physical dependence; very sedating	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone Zolpidem Zaleplon	Benzodiazepine-receptor agonists have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); increased emergency department visits and hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid	Moderate	Strong
Ergoloid mesylates (dehydrogenated ergot alkaloids) Isoxsuprine	Lack of efficacy	Avoid	High	Strong
Endocrine				
Androgens Methyltestosterone Testosterone	Potential for cardiac problems; contraindicated in men with prostate cancer	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	Moderate	Weak
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risk and benefits of low-dose vaginal estrogen (dosages of estradiol <25 μg twice weekly) with their healthcare provider	Avoid oral and topical patch Vaginal cream or tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, lower urinary tract infections, and other vaginal symptoms	Oral and patch: high Vaginal cream or tablets: moderate	Oral and patch: strong Topical vaginal cream or tablets: weak
Growth hormone	Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except as hormone replacement after pituitary gland removal	High	Strong

(Continued)

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting; refers to sole use of short- or rapid-acting insulins to manage or avoid hyperglycemia in absence of basal or long-acting insulin; does not apply to titration of basal insulin or use of additional short- or rapid-acting insulin in conjunction with scheduled insulin (i.e., correction insulin)	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long-duration				
Chlorpropamide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion	Avoid	High	Strong
Glyburide	Glyburide: higher risk of severe prolonged hypoglycemia in older adults			
Gastrointestinal				
Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults	Avoid, unless for gastroparesis	Moderate	Strong
Mineral oil, given orally	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
Proton-pump inhibitors	Risk of *Clostridium difficile* infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (e.g., oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (e.g., due to failure of drug discontinuation trial or H_2 blockers)	High	Strong
Pain medications				
Meperidine	Not effective oral analgesic in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid, especially in individuals with chronic kidney disease	Moderate	Strong

(Continued)

Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Non-cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those aged >75 or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months and in ~2–4% of patients treated for 1 year; these trends continue with longer duration of use	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)	Moderate	Strong
Indomethacin	Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid	Moderate	Strong
Ketorolac, includes parenteral	Increased risk of gastrointestinal bleeding, peptic ulcer disease, and acute kidney injury in older adults			
Pentazocine	Opioid analgesic that causes CNS adverse effects, including confusion and hallucinations, more commonly than other opioid analgesic drugs; is also a mixed agonist and antagonist; safer alternatives available	Avoid	Low	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
Genitourinary Desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

The primary target audience is practicing clinicians. The intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health-outcome, quality-of-care, cost, and utilization data.
CNS = central nervous system; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 3. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug–Disease or Drug–Syndrome Interactions That May Exacerbate the Disease or Syndrome

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular					
Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (diltiazem, verapamil)—avoid only for heart failure with reduced ejection fraction Thiazolidinediones (pioglitazone, rosiglitazone) Cilostazol Dronedarone (severe or recently decompensated heart failure)	Potential to promote fluid retention and exacerbate heart failure	Avoid	NSAIDs: moderate CCBs: moderate Thiazolidinediones: high Cilostazol: low Dronedarone: high	Strong
Syncope	AChEIs Peripheral alpha-1 blockers Doxazosin Prazosin Terazosin Tertiary TCAs Chlorpromazine Thioridazine Olanzapine	Increases risk of orthostatic hypotension or bradycardia	Avoid	Peripheral alpha-1 blockers: high TCAs, AChEIs, antipsychotics: moderate	AChEIs, TCAs: strong Peripheral alpha-1 blockers, antipsychotics: weak
Central nervous system					
Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Lowers seizure threshold; may be acceptable in individuals with well-controlled seizures in whom alternative agents have not been effective	Avoid	Low	Strong
Delirium	Anticholinergics (see Table 7 for full list) Antipsychotics Benzodiazepines Chlorpromazine Corticosteroids[a] H_2-receptor antagonists Cimetidine Famotidine Nizatidine Ranitidine Meperidine Sedative hypnotics	Avoid in older adults with or at high risk of delirium because of the potential of inducing or worsening delirium Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible ***and*** the older adult is threatening substantial harm to self or others Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid	Moderate	Strong

(Continued)

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Dementia or cognitive impairment	Anticholinergics (see Table 7 for full list) Benzodiazepines H_2-receptor antagonists Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone Zolpidem Zaleplon Antipsychotics, chronic and as-needed use	Avoid because of adverse CNS effects Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible ***and*** the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid	Moderate	Strong
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopiclone Zaleplon Zolpidem TCAs SSRIs Opioids	May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (i.e., anticonvulsants, opioid-receptor agonists, antipsychotics, antidepressants, benzodiazepine-receptor agonists, other sedatives and hypnotics) and implement other strategies to reduce fall risk	Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure and mood disorders Opioids: avoid, excludes pain management due to recent fractures or joint replacement	High Opioids: moderate	Strong Opioids: strong
Insomnia	Oral decongestants Pseudoephedrine Phenylephrine Stimulants Amphetamine Armodafinil Methylphenidate Modafinil Theobromines Theophylline Caffeine	CNS stimulant effects	Avoid	Moderate	Strong

(Continued)

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Parkinson disease	All antipsychotics (except aripiprazole, quetiapine, clozapine) Antiemetics Metoclopramide Prochlorperazine Promethazine	Dopamine-receptor antagonists with potential to worsen parkinsonian symptoms Quetiapine, aripiprazole, clozapine appear to be less likely to precipitate worsening of Parkinson disease	Avoid	Moderate	Strong
Gastrointestinal					
History of gastric or duodenal ulcers	Aspirin (>325 mg/d) Non-COX-2 selective NSAIDs	May exacerbate existing ulcers or cause new or additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (i.e., proton-pump inhibitor or misoprostol)	Moderate	Strong
Kidney and urinary tract					
Chronic kidney disease Stages IV or less (creatinine clearance <30 mL/min)	NSAIDs (non-COX and COX-selective, oral and parenteral)	May increase risk of acute kidney injury and further decline of renal function	Avoid	Moderate	Strong
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen) Peripheral alpha-1 blockers Doxazosin Prazosin Terazosin	Aggravation of incontinence	Avoid in women	Estrogen: high Peripheral alpha-1 blockers: moderate	Estrogen: strong Peripheral alpha-1 blockers: strong
Lower urinary tract symptoms, benign prostatic hyperplasia	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 7 for complete list)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Strong

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[a] Excludes inhaled and topical forms. Oral and parenteral corticosteroids may be required for conditions such as exacerbations of chronic obstructive pulmonary disease but should be prescribed in the lowest effective dose and for the shortest possible duration.

CCB = calcium channel blocker; AChEI = acetylcholinesterase inhibitor; CNS = central nervous system; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant.

Table 4. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults

Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Aspirin for primary prevention of cardiac events	Lack of evidence of benefit versus risk in adults aged ≥80	Use with caution in adults aged ≥80	Low	Strong
Dabigatran	Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other target-specific oral anticoagulants in adults aged ≥75; lack of evidence of efficacy and safety in individuals with CrCl <30 mL/min	Use with caution in in adults aged ≥75 and in patients with CrCl <30 mL/min	Moderate	Strong
Prasugrel	Increased risk of bleeding in older adults; benefit in highest-risk older adults (e.g., those with prior myocardial infarction or diabetes mellitus) may offset risk	Use with caution in adults aged ≥75	Moderate	Weak
Antipsychotics Diuretics Carbamazepine Carboplatin Cyclophosphamide Cisplatin Mirtazapine Oxcarbazepine SNRIs SSRIs TCAs Vincristine	May exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution	Moderate	Strong
Vasodilators	May exacerbate episodes of syncope in individuals with history of syncope	Use with caution	Moderate	Weak

The primary target audience is the practicing clinician. The intentions of the criteria are to improve selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health-outcome, quality-of-care, cost, and utilization data.

CrCl = creatinine clearance; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Table 5. 2015 American Geriatrics Society Beers Criteria for Potentially Clinically Important Non-Anti-infective Drug–Drug Interactions That Should Be Avoided in Older Adults

Object Drug and Class	Interacting Drug and Class	Risk Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
ACEIs	Amiloride or triamterene	Increased risk of Hyperkalemia	Avoid routine use; reserve for patients with demonstrated hypokalemia while taking an ACEI	Moderate	Strong
Anticholinergic	Anticholinergic	Increased risk of Cognitive decline	Avoid, minimize number of anticholinergic drugs (Table 7)	Moderate	Strong
Antidepressants (i.e., TCAs and SSRIs)	≥2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of ≥3 CNS-active drugs[a]; minimize number of CNS-active drugs	Moderate	Strong
Antipsychotics	≥2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of ≥3 CNS-active drugs[a]; minimize number of CNS-active drugs	Moderate	Strong
Benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	≥2 other CNS-active drugs[a]	Increased risk of Falls and fractures	Avoid total of ≥3 CNS-active drugs[a]; minimize number of CNS-active drugs	High	Strong
Corticosteroids, oral or parenteral	NSAIDs	Increased risk of Peptic ulcer disease or gastrointestinal bleeding	Avoid; if not possible, provide gastrointestinal protection	Moderate	Strong
Lithium	ACEIs	Increased risk of Lithium toxicity	Avoid, monitor lithium concentrations	Moderate	Strong
Lithium	Loop diuretics	Increased risk of Lithium toxicity	Avoid, monitor lithium concentrations	Moderate	Strong
Opioid receptor agonist analgesics	≥2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of ≥3 CNS-active drugs[a]; minimize number of CNS drugs	High	Strong
Peripheral Alpha-1 blockers	Loop diuretics	Increased risk of Urinary incontinence in older women	Avoid in older women, unless conditions warrant both drugs	Moderate	Strong
Theophylline	Cimetidine	Increased risk of Theophylline toxicity	Avoid	Moderate	Strong
Warfarin	Amiodarone	Increased risk of Bleeding	Avoid when possible; monitor international normalized ratio closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of Bleeding	Avoid when possible; if used together, monitor for bleeding closely	High	Strong

[a]Central nervous system (CNS)-active drugs: antipsychotics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; tricyclic antidepressants (TCAs); selective serotonin reuptake inhibitors (SSRIs); and opioids.
ACEI = angiotensin-converting enzyme inhibitor; NSAID = nonsteroidal anti-inflammatory drug.

Table 6. 2015 American Geriatrics Society Beers Criteria for Non-Anti-Infective Medications That Should Be Avoided or Have Their Dosage Reduced with Varying Levels of Kidney Function in Older Adults

Medication Class and Medication	Creatinine Clearance, mL/min, at Which Action Required	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Cardiovascular or hemostasis					
Amiloride	<30	Increased potassium, and decreased sodium	Avoid	Moderate	Strong
Apixaban	<25	Increased risk of bleeding	Avoid	Moderate	Strong
Dabigatran	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Edoxaban	30–50	Increased risk of bleeding	Reduce dose	Moderate	Strong
	<30 or >95		Avoid		
Enoxaparin	<30	Increased risk of bleeding	Reduce dose	Moderate	Strong
Fondaparinux	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Rivaroxaban	30–50	Increased risk of bleeding	Reduce dose	Moderate	Strong
	<30		Avoid		
Spironolactone	<30	Increased potassium	Avoid	Moderate	Strong
Triamterene	<30	Increased potassium, and decreased sodium	Avoid	Moderate	Strong
Central nervous system and analgesics					
Duloxetine	<30	Increased Gastrointestinal adverse effects (nausea, diarrhea)	Avoid	Moderate	Weak
Gabapentin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Levetiracetam	≤80	CNS adverse effects	Reduce dose	Moderate	Strong
Pregabalin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Tramadol	<30	CNS adverse effects	Immediate release: reduce dose Extended release: avoid	Low	Weak
Gastrointestinal					
Cimetidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Famotidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Nizatidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Ranitidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Hyperuricemia					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<30	Loss of effectiveness	Avoid	Moderate	Strong

CNS = central nervous system.

Table 7. Drugs with Strong Anticholinergic Properties

Antihistamines	Antiparkinsonian agents	Skeletal muscle relaxants
Brompheniramine	Benztropine	Cyclobenzaprine
Carbinoxamine	Trihexyphenidyl	Orphenadrine
Chlorpheniramine		
Clemastine		
Cyproheptadine		
Dexbrompheniramine		
Dexchlorpheniramine		
Dimenhydrinate		
Diphenhydramine (oral)		
Doxylamine		
Hydroxyzine		
Meclizine		
Triprolidine		
Antidepressants	Antipsychotics	Antiarrhythmic
Amitriptyline	Chlorpromazine	Disopyramide
Amoxapine	Clozapine	
Clomipramine	Loxapine	
Desipramine	Olanzapine	
Doxepin (>6 mg)	Perphenazine	
Imipramine	Thioridazine	
Nortriptyline	Trifluoperazine	
Paroxetine		
Protriptyline		
Trimipramine		
Antimuscarinics (urinary incontinence)	Antispasmodics	Antiemetic
Darifenacin	Atropine (excludes ophthalmic)	Prochlorperazine
Fesoterodine	Belladonna alkaloids	Promethazine
Flavoxate	Clidinium-chlordiazepoxide	
Oxybutynin	Dicyclomine	
Solifenacin	Homatropine (excludes ophthalmic)	
Tolterodine	Hyoscyamine	
Trospium	Propantheline	
	Scopolamine (excludes ophthalmic)	

Source: "American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults" by the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015, *Journal of the American Geriatrics Society, 63*, p. 2231-2243.

Appendix J. PIMs to avoid in older adults represented in 1991, 1997, 2003, 2012, and 2015 Beers Criteria

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Brompheniramine	Anticholinergics	Antihistamines (1st generation)	-	-	-	✓	✓
Carbinoxamine	Anticholinergics	Antihistamines (1st generation)	-	-	-	✓	✓
Chlorpheniramine	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	✓	✓
Clemastine	Anticholinergics	Antihistamines (1st generation)	-	-	-	✓	✓
Cyproheptadine	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	✓	✓
Dexbrompheniramine	Anticholinergics	Antihistamines (1st generation)	-	-	-	✓	✓
Dexchlorpheniramine	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	✓	✓
Diphenhydramine (oral)	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	✓	✓
Doxylamine	Anticholinergics	Antihistamines (1st generation)	-	-	-	✓	✓
Hydroxyzine	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	✓	✓
Meclizine	Anticholinergics	Antihistamines (1st generation)	-	-	-	-	✓
Promethazine	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	✓	✓
Tripelennamine	Anticholinergics	Antihistamines (1st generation)	-	✓	✓	-	-
Triprolidine	Anticholinergics	Antihistamines (1st generation)	-	-	-	✓	✓
Benztropine (oral)	Anticholinergics	Antiparkinson agents	-	-	-	✓	✓
Trihexyphenidyl	Anticholinergics	Antiparkinson agents	-	-	-	✓	✓
Atropine	Anticholinergics	Antispasmodics	-	-	-	✓	✓
Belladonna alkaloids	Anticholinergics	Antispasmodics	-	✓	✓	✓	✓
Clidinium-Chlordiazepoxide	Anticholinergics	Antispasmodics	-	✓	✓	✓	✓
Dicyclomine	Anticholinergics	Antispasmodics	-	✓	✓	✓	✓
Hyoscyamine	Anticholinergics	Antispasmodics	-	✓	✓	✓	✓
Propantheline	Anticholinergics	Antispasmodics	-	✓	✓	✓	✓
Scopolamine	Anticholinergics	Antispasmodics	-	-	-	✓	✓
Dipyridamole (oral, short acting)	Antithrombotics	Platelet Inhibitor	✓	✓	✓	✓	✓
Ticlopidine	Antithrombotics	Platelet Inhibitor	-	✓	✓	✓	✓

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Nitrofurantoin	Anti-infective drugs	Antibiotic	-	-	✓	✓	✓
Doxazosin	Cardiovascular drugs	Peripheral alpha-1 blocker	-	-	✓	✓	✓
Prazosin	Cardiovascular drugs	Peripheral alpha-1 blocker	-	-	-	✓	✓
Terazosin	Cardiovascular drugs	Peripheral alpha-1 blocker	-	-	-	✓	✓
Clonidine	Cardiovascular drugs	Central alpha blocker	-	-	✓	✓	✓
Guanabenz	Cardiovascular drugs	Central alpha blocker	-	-	-	✓	✓
Guanfacine	Cardiovascular drugs	Central alpha blocker	-	-	-	✓	✓
Methyldopa	Cardiovascular drugs	Central alpha blocker	✓	✓	✓	✓	✓
Methyldopa-hydrochlorothiazide	Cardiovascular drugs	Central alpha blocker	✓	✓	✓	-	-
Reserpine	Cardiovascular drugs	Central alpha blocker	✓	✓	✓	✓	✓
Amiodarone	Cardiovascular drugs	Antiarrhythmic drugs	-	-	✓	✓	✓
Disopyramide	Cardiovascular drugs	Antiarrhythmic drugs	-	✓	✓	✓	✓
Dofetilide	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Dronedarone	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	✓
Digoxin	Cardiovascular drugs	Antiarrhythmic drugs	-	✓	✓	✓	✓
Flecainide	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Ibutilide	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Procainamide	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Propafenone	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Quinidine	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Sotalol	Cardiovascular drugs	Antiarrhythmic drugs	-	-	-	✓	-
Propranolol	Cardiovascular drugs	Beta blocker	✓	-	-	-	-
Nifedipine (immediate release)	Cardiovascular drugs	Calcium channel blockers	-	-	✓	✓	✓
Ethacrynic acid	Cardiovascular drugs	Diuretic	-	-	✓	-	-
Spironolactone (>25 mg/day)	Cardiovascular drugs	Diuretic	-	-	-	✓	-
Guanethidine	Cardiovascular drugs	Antihypertensive	-	-	✓	-	-
Guanadrel	Cardiovascular drugs	Antihypertensive	-	-	✓	-	-

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Amitriptyline	Central Nervous System	Antidepressants (TCAs)	✓	✓	✓	✓	✓
Amoxapine	Central Nervous System	Antidepressants (TCAs)	-	-	-	✓	✓
Chlordiazepoxide-amitriptyline	Central Nervous System	Antidepressants (TCAs)	-	✓	✓	✓	✓
Clomipramine	Central Nervous System	Antidepressants	-	-	-	✓	✓
Desipramine	Central Nervous System	Antidepressants (TCAs)	-	-	-	-	✓
Doxepin	Central Nervous System	Antidepressants (TCAs)	-	✓	✓	✓	✓
Imipramine	Central Nervous System	Antidepressants (TCAs)	-	-	-	✓	✓
Nortriptyline	Central Nervous System	Antidepressants (TCAs)	-	-	-	-	✓
Paroxetine	Central Nervous System	Antidepressants (SSRI)	-	-	-	-	✓
Perphenazine-amitriptyline	Central Nervous System	Antidepressants (TCAs)	✓	✓	✓	✓	✓
Protriptyline	Central Nervous System	Antidepressants (TCAs)	-	-	-	-	✓
Trimipramine	Central Nervous System	Antidepressants (TCAs)	-	-	-	✓	✓
Fluoxetine (daily)	Central Nervous System	SSRI antidepressant	-	-	✓	-	-
Chlorpromazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Fluphenazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Haloperidol	Central Nervous System	Antipsychotic drugs (1st generation)	✓	-	-	✓	✓
Loxapine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Mesoridazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	✓	✓	-
Molindone	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Perphenazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Pimozide	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Promazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Thioridazine	Central Nervous System	Antipsychotic drugs (1st generation)	✓	-	✓	✓	✓
Thiothixene	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Trifluoperazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Triflupromazine	Central Nervous System	Antipsychotic drugs (1st generation)	-	-	-	✓	✓
Aripiprazole	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Asenapine	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Clozapine	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Iloperidone	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Lurasidone	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Olanzapine	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Paliperidone	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Quetiapine	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Risperidone	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Ziprasidone	Central Nervous System	Antipsychotic drugs (2nd generation)	-	-	-	✓	✓
Amobarbital	Central Nervous System	Barbiturates	-	✓	✓	✓	✓
Butabarbital	Central Nervous System	Barbiturates	-	✓	✓	✓	✓
Butalbital	Central Nervous System	Barbiturates	-	✓	✓	✓	✓
Mephobarbital	Central Nervous System	Barbiturates	-	✓	✓	✓	✓
Pentobarbital	Central Nervous System	Barbiturates	✓	✓	✓	✓	✓
Phenobarbital	Central Nervous System	Barbiturates	-	-	-	✓	✓
Secobarbital	Central Nervous System	Barbiturates	✓	✓	✓	✓	✓
Alprazolam	Central Nervous System	Benzodiazepines (Short-acting)	✓	✓	✓	✓	✓
Estazolam	Central Nervous System	Benzodiazepines (Short-acting)	-	-	-	✓	✓
Lorazepam	Central Nervous System	Benzodiazepines (Short-acting)	-	✓	✓	✓	✓
Oxazepam	Central Nervous System	Benzodiazepines (Short-acting)	✓	✓	✓	✓	✓
Temazepam	Central Nervous System	Benzodiazepines (Short-acting)	-	✓	✓	✓	✓
Triazolam	Central Nervous System	Benzodiazepines (Short-acting)	✓	✓	✓	✓	✓
Chlordiazepoxide	Central Nervous System	Benzodiazepines (Long-acting)	✓	✓	✓	✓	✓
Clonazepam	Central Nervous System	Benzodiazepines (Long-acting)	-	-	-	✓	✓
Clorazepate	Central Nervous System	Benzodiazepines (Long-acting)	-	✓	✓	✓	✓
Chlordiazepoxide-amitriptyline	Central Nervous System	Benzodiazepines (Long-acting)	-	✓	✓	✓	-
Clidinium-chlordiazepoxide	Central Nervous System	Benzodiazepines (Long-acting)	-	✓	✓	✓	✓

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Diazepam	Central Nervous System	Benzodiazepines (Long-acting)	✓	✓	✓	✓	✓
Flurazepam	Central Nervous System	Benzodiazepines (Long-acting)	✓	✓	✓	✓	✓
Halazepam	Central Nervous System	Benzodiazepines (Long-acting)	-	✓	✓	-	-
Quazepam	Central Nervous System	Benzodiazepines (Long-acting)	-	✓	✓	✓	✓
Chloral hydrate	Central Nervous System	Nonbarbiturate sedative and hypnotic	-	-	-	✓	-
Meprobamate	Central Nervous System	Anxiolytic	✓	✓	✓	✓	✓
Eszopiclone	Central Nervous System	Nonbenzodiazepine sedative	-	-	-	✓	✓
Zaleplon	Central Nervous System	Nonbenzodiazepine sedative	-	-	-	✓	✓
Zolpidem	Central Nervous System	Nonbenzodiazepine sedative	-	-	-	✓	✓
Ergoloid mesylates	Central Nervous System	Ergoloid	-	✓	✓	✓	✓
Cyclandelate	Central Nervous System	Vasodilator	✓	-	✓	-	-
Isoxsuprine	Central Nervous System	Vasodilator	-	-	✓	✓	✓
Amphetamines	Central Nervous System	Stimulant	-	-	✓	-	-
Methyltestosterone	Endocrine system	Androgens (hormones)	-	-	✓	✓	✓
Testosterone	Endocrine system	Androgens (hormones)	-	-	-	✓	✓
Desiccated thyroid	Endocrine system	Hormones	-	-	✓	✓	✓
Estrogens with or without progestins	Endocrine system	Hormones	-	-	✓	✓	✓
Growth hormone	Endocrine system	Hormones	-	-	-	✓	✓
Insulin, sliding scale	Endocrine system	Hormones	-	-	-	✓	✓
Megestrol	Endocrine system	Hormones	-	-	-	✓	✓
Chlorpropamide	Endocrine system	Sulfonylureas, long-duration	✓	✓	✓	✓	✓
Glyburide	Endocrine system	Sulfonylureas, long-duration	-	-	-	✓	✓
Metoclopramide	Gastrointestinal	Gut motility stimulator	-	-	-	✓	✓
Bisacodyl	Gastrointestinal	Laxative	-	-	✓	-	-
Cascara Sagrada	Gastrointestinal	Laxative	-	-	✓	-	-
Mineral oil (oral)	Gastrointestinal	Laxative	-	-	✓	✓	✓
Neoloid	Gastrointestinal	Laxative	-	-	✓	-	-

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Cimetidine	Gastrointestinal	Antihistamine	✓	-	✓	-	-
Ranitidine	Gastrointestinal	Antihistamine	✓	-	-	-	-
Trimethobenzamide	Gastrointestinal	Antiemetics	✓	✓	✓	✓	-
Proton-pump inhibitors*	Gastrointestinal	Proton-pump inhibitors	-	-	-	-	✓
Ferrous sulfate	Gastrointestinal	Minerals & Electrolytes - Iron deficiency	-	-	✓	-	-
Iron supplements	Gastrointestinal	Minerals & Electrolytes - Iron deficiency	✓	✓	-	-	-
Meperidine	Pain Medications	Narcotic	-	✓	✓	✓	✓
Aspirin (doses > 325 mg/day)	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Diclofenac	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Diflunisal	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Etodolac	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Fenoprofen	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Ibuprofen	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Ketoprofen	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Meclofenamate	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Mefenamic acid	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Meloxicam	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Nabumetone	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Naproxen	Pain Medications	NSAIDs, oral (Non-COX)	-	-	✓	✓	✓
Oxaprozin	Pain Medications	NSAIDs, oral (Non-COX)	-	-	✓	✓	✓
Piroxicam	Pain Medications	NSAIDs, oral (Non-COX)	-	-	✓	✓	✓
Sulindac	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Tolmetin	Pain Medications	NSAIDs, oral (Non-COX)	-	-	-	✓	✓
Indomethacin	Pain Medications	NSAIDs	✓	✓	✓	✓	✓
Ketorolac	Pain Medications	NSAIDs	-	-	✓	✓	✓
Phenylbutazone	Pain Medications	NSAIDs	✓	✓	-	-	-
Pentazocine	Pain Medications	Narcotic	✓	✓	✓	✓	✓

Beers Drug	Drug Category/ Area affected	Drug class	1991	1997	2003	2012	2015
Propoxyphene	Pain Medications	Narcotic	✓	✓	✓	-	-
Carisoprodol	Pain Medications	Skeletal muscle relaxants	✓	✓	✓	✓	✓
Chlorzoxazone	Pain Medications	Skeletal muscle relaxants	-	✓	✓	✓	✓
Cyclobenzaprine	Pain Medications	Skeletal muscle relaxants	✓	✓	✓	✓	✓
Metaxalone	Pain Medications	Skeletal muscle relaxants	-	✓	✓	✓	✓
Methocarbamol	Pain Medications	Skeletal muscle relaxants	✓	✓	✓	✓	✓
Orphenadrine	Pain Medications	Skeletal muscle relaxants	-	-	✓	✓	✓
Oxybutynin	Pain Medications	Skeletal muscle relaxants	-	✓	✓	-	-
Desmopressin	Pain Medications	Clotting promoter and antidiuretic	-	-	-	-	✓
Oxymetazoline	Upper respiratory	Decongestant	✓	-	-	-	-
Phenylephrine	Upper respiratory	Decongestant	✓	-	-	-	-
Pseudoephedrine	Upper respiratory	Decongestant	✓	-	-	-	-

Appendix K. PIMs to avoid in older adults due to drug–disease or drug–syndrome interactions that may exacerbate the disease represented in 1997, 2003, 2012, and 2015 Beers Criteria

Beers Drug	Disease/Syndrome	1991	1997	2003	2012	2015
Amitriptyline hydrochloride	Arrhythmias	-	✓	✓	-	-
Doxepin hydrochloride	Arrhythmias	-	✓	✓	-	-
Imipramine hydrochloride	Arrhythmias	-	✓	✓	-	-
Beta Blockers	Asthma	-	✓	-	-	-
Anticholinergic antihistamines	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Gastrointestinal antispasmodic drugs	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Muscle relaxants	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Narcotic drugs	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Flavoxate	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Oxybutynin	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Bethanechol	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Anticholinergic antidepressant drugs	Benign prostatic hyperplasia (BPH)	-	✓	-	-	-
Aspirin	Blood Clotting Disorders/Anticoagulant therapy	-	✓	✓	-	-
NSAIDs	Blood Clotting Disorders/Anticoagulant therapy	-	✓	✓	-	-
Dipyridamole	Blood Clotting Disorders/Anticoagulant therapy	-	✓	✓	-	-
Ticlopidine	Blood Clotting Disorders/Anticoagulant therapy	-	✓	✓	-	-
Clopidogrel	Blood Clotting Disorders/Anticoagulant therapy	-	-	✓	-	-
NSAIDs and Cox-2 inhibitors*	Cardiovascular (heart failure)	-	-	-	✓	✓
Diltiazem	Cardiovascular (heart failure)	-	-	-	✓	✓
Verapamil	Cardiovascular (heart failure)	-	-	-	✓	✓
Pioglitazone	Cardiovascular (heart failure)	-	-	-	✓	✓
Rosiglitazone	Cardiovascular (heart failure)	-	-	-	✓	✓
Cilostazol	Cardiovascular (heart failure)	-	-	-	✓	✓
Disopyramide	Cardiovascular (heart failure)	-	✓	✓	-	-
Dronedarone	Cardiovascular (heart failure)	-	-	-	✓	✓
Alginate Bicarbonate	Cardiovascular (heart failure)	-	✓	✓	-	-
Biphosphate	Cardiovascular (heart failure)	-	✓	✓	-	-
Citrate	Cardiovascular (heart failure)	-	✓	✓	-	-
Phosphate	Cardiovascular (heart failure)	-	✓	✓	-	-
Salicylate	Cardiovascular (heart failure)	-	✓	✓	-	-
Sulfate	Cardiovascular (heart failure)	-	✓	✓	-	-
Phenylpropanolamine hydrochloride	Cardiovascular (hypertension)	-	-	✓	-	-
Pseudoephedrine	Cardiovascular (hypertension)	-	-	✓	-	-
Diet pills	Cardiovascular (hypertension)	-	✓	✓	-	-
Amphetamines	Cardiovascular (hypertension)	-	✓	✓	-	-
AChEls*	Cardiovascular (syncope)	-	-	-	✓	✓

Beers Drug	Disease/Syndrome	1991	1997	2003	2012	2015
Doxazosin	Cardiovascular (syncope)	-	-	-	✓	✓
Prazosin	Cardiovascular (syncope)	-	-	-	✓	✓
Terazosin	Cardiovascular (syncope)	-	-	-	✓	✓
Tertiary TCAs*	Cardiovascular (syncope)	-	-	-	✓	✓
Chlorpromazine	Cardiovascular (syncope)	-	-	-	✓	✓
Thioridazine	Cardiovascular (syncope)	-	-	-	✓	✓
Olanzapine	Cardiovascular (syncope)	-	-	-	✓	✓
Beta Blockers	Cardiovascular (Peripheral vascular disease)	-	✓	-	-	-
Bupropion	CNS- Chronic seizures/epilepsy	-	-	✓	✓	✓
Chlorpromazine	CNS- Chronic seizures/epilepsy	-	-	✓	✓	✓
Chlorprothixene	CNS- Chronic seizures/epilepsy	-	✓	-	-	-
Clozapine	CNS- Chronic seizures/epilepsy	-	✓	✓	✓	✓
Maprotiline	CNS- Chronic seizures/epilepsy	-	-	-	✓	✓
Metoclopramide	CNS- Chronic seizures/epilepsy	-	✓	-	-	-
Olanzapine	CNS- Chronic seizures/epilepsy	-	-	-	✓	✓
Thioridazine	CNS- Chronic seizures/epilepsy	-	✓	✓	✓	✓
Thiothixene	CNS- Chronic seizures/epilepsy	-	-	✓	✓	✓
Thorazine	CNS- Chronic seizures/epilepsy	-	✓	-	-	-
Tramadol	CNS- Chronic seizures/epilepsy	-	-	-	✓	✓
Anticholinergics	CNS- Delirium	-	-	-	✓	✓
Antipsychotics	CNS- Delirium	-	-	-	✓	✓
Benzodiazepines	CNS- Delirium	-	-	-	✓	✓
Chlorpromazine	CNS- Delirium	-	-	-	✓	✓
Corticosteroids	CNS- Delirium	-	-	-	✓	✓
Cimetidine	CNS- Delirium	-	-	-	✓	✓
Famotidine	CNS- Delirium	-	-	-	✓	✓
Nizatidine	CNS- Delirium	-	-	-	✓	✓
Ranitidine	CNS- Delirium	-	-	-	✓	✓
Meperidine	CNS- Delirium	-	-	-	✓	✓
Sedative hypnotics	CNS- Delirium	-	-	-	✓	✓
Thioridazine	CNS- Delirium	-	-	-	✓	-
Anticholinergics	CNS- Dementia/Cognitive Impairment	-	-	-	✓	✓
Benzodiazepines	CNS- Dementia/Cognitive Impairment	-	-	-	✓	✓
H2-receptor antagonists	CNS- Dementia/Cognitive Impairment	-	-	-	✓	✓
Eszopiclone	CNS- Dementia/Cognitive Impairment	-	-	-	-	✓
Zolpidem	CNS- Dementia/Cognitive Impairment	-	-	-	✓	✓
Zaleplon	CNS- Dementia/Cognitive Impairment	-	-	-	-	✓
Antipsychotics, chronic & as needed	CNS- Dementia/Cognitive Impairment	-	-	-	✓	✓
Anticonvulsants	CNS- history of falls/fractures	-	-	-	✓	✓
Antipsychotics	CNS- history of falls/fractures	-	-	-	✓	✓
Benzodiazepines	CNS- history of falls/fractures	-	-	-	✓	✓

Beers Drug	Disease/Syndrome	1991	1997	2003	2012	2015
Eszopiclone	CNS- history of falls/fractures	-	-	-	✓	✓
Zolpidem	CNS- history of falls/fractures	-	-	-	✓	✓
Zaleplon	CNS- history of falls/fractures	-	-	-	✓	✓
TCAs	CNS- history of falls/fractures	-	-	-	✓	✓
SSRIs	CNS- history of falls/fractures	-	-	-	-	✓
Opiods	CNS- history of falls/fractures	-	-	-	-	✓
Pseudoephedrine	CNS- Insomnia	-	-	-	✓	✓
Phenylephrine	CNS- Insomnia	-	-	-	✓	✓
Amphetamine	CNS- Insomnia	-	-	✓	✓	✓
Armodafinil	CNS- Insomnia	-	-	-	-	✓
Methylphenidate	CNS- Insomnia	-	✓	✓	✓	✓
Modafinil	CNS- Insomnia	-	-	-	-	✓
Pemoline	CNS- Insomnia	-	-	-	✓	-
Theophylline	CNS- Insomnia	-	✓	✓	✓	✓
Caffeine	CNS- Insomnia	-	-	-	✓	✓
Beta agonists	CNS- Insomnia	-	✓	-	-	-
Decongestants	CNS- Insomnia	-	✓	✓	-	-
Monoamine oxidase inhibitors (MAOIs)	CNS- Insomnia	-	✓	✓	-	-
SSRIs	CNS- Insomnia	-	✓	-	-	-
Antipsychotics (except aripiprazole, quetiapine, clozapine)	CNS- Parkinson Disease	-	-	✓	✓	✓
Metoclopramide	CNS- Parkinson Disease	-	-	✓	✓	✓
Prochlorperazine	CNS- Parkinson Disease	-	-	-	✓	✓
Promethazine	CNS- Parkinson Disease	-	-	-	✓	✓
Tacrine	CNS- Parkinson Disease	-	-	✓	-	-
Barbiturates	Cognitive Impairment	-	-	✓	-	-
Anticholinergics	Cognitive Impairment	-	-	✓	-	-
Antispasmodics	Cognitive Impairment	-	-	✓	-	-
Muscle relaxants	Cognitive Impairment	-	-	✓	-	-
Dextroamphetamine	Cognitive Impairment	-	-	✓	-	-
Methylphenidate	Cognitive Impairment	-	-	✓	-	-
Methamphetamine	Cognitive Impairment	-	-	✓	-	-
Pemolin	Cognitive Impairment	-	-	✓	-	-
Beta Blockers	COPD	-	✓	-	-	-
Sedative hypnotics	COPD	-	✓	-	-	-
Chlordiazepoxide	COPD	-	-	✓	-	-
Chlordiazepoxide-amitriptyline	COPD	-	-	✓	-	-
Clidinium-chlordiazepoxide	COPD	-	-	✓	-	-
Diazepam	COPD	-	-	✓	-	-
Quazepam	COPD	-	-	✓	-	-
Halazepam	COPD	-	-	✓	-	-

Beers Drug	Disease/Syndrome	1991	1997	2003	2012	2015
Chlorazepate	COPD	-	-	✓	-	-
Propranolol	COPD	-	-	✓	-	-
Long-term benzodiazepine	Depression	-	-	✓	-	-
Methyldopa	Depression	-	-	✓	-	-
Reserpine	Depression	-	-	✓	-	-
Guanethidine	Depression	-	-	✓	-	-
Beta Blockers	Diabetes	-	✓	-	-	-
Corticosteroids	Diabetes	-	✓	-	-	-
Darifenacin	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Fesoterodine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Oxybutynin (oral)	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Solifenacin	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Tolterodine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Trospium	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Diltiazem	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Verapamil	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Brompheniramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Carbinoxamine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Chlorpheniramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Clemastine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Cyproheptadine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Dexbrompheniramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Dexchlorpheniramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Diphenhydramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Doxylamine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Hydroxyzine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Promethazine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Triprolidine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Anticholinergics	Gastrointestinal- Chronic constipation	-	✓	✓	-	-
Calcium channel blockers	Gastrointestinal- Chronic constipation	-	-	✓	-	-
Nartcotic drugs	Gastrointestinal- Chronic constipation	-	✓	-	-	-
Amitriptyline hydrochloride	Gastrointestinal- Chronic constipation	-	✓	✓	-	-
Doxepin hydrochloride	Gastrointestinal- Chronic constipation	-	✓	✓	-	-
Imipramine hydrochloride	Gastrointestinal- Chronic constipation	-	✓	✓	-	-
Antipsychotics	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Belladonna alkaloids	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Clidinium-chlordiazepoxide	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Dicyclomine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Hyoscyamine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Propantheline	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Scopolamine	Gastrointestinal- Chronic constipation	-	-	-	✓	-

Beers Drug	Disease/Syndrome	1991	1997	2003	2012	2015
Amitriptyline	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Clomipramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Doxepin	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Imipramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Trimipramine	Gastrointestinal- Chronic constipation	-	-	-	✓	-
Aspirin (>325 md/g)	Gastrointestinal- history of gastric/duodenal ulcers	-	✓	✓	✓	✓
Non-Cox-2 selective NSAIDs	Gastrointestinal- history of gastric/duodenal ulcers	-	✓	✓	✓	✓
Potassium supplements	Gastrointestinal- history of gastric/duodenal ulcers	-	✓	-	-	-
NSAIDs (non-Cox & COX-selective, oral & parenteral)	Kidney & urinary tract- chronic kidney disease stage IV or less	-	-	-	✓	✓
Triamterene	Kidney & urinary tract- chronic kidney disease stage IV or less	-	-	-	✓	-
Estrogen oral & transdermal (excludes intravaginal estrogen)	Kidney & urinary tract- urinary incontinence in women	-	-	-	✓	✓
Doxazosin	Kidney & urinary tract- urinary incontinence	-	✓	✓	✓	✓
Prazosin	Kidney & urinary tract- urinary incontinence	-	✓	✓	✓	✓
Terazosin	Kidney & urinary tract- urinary incontinence	-	✓	✓	✓	✓
Amitriptyline hydrochloride	Kidney & urinary tract- stress incontinence	-	-	✓	-	-
Doxepin hydrochloride	Kidney & urinary tract- stress incontinence	-	-	✓	-	-
Imipramine hydrochloride	Kidney & urinary tract- stress incontinence	-	-	✓	-	-
Long-acting benzodiazepine drugs	Kidney & urinary tract- stress incontinence	-	-	✓	-	-
Anticholinergics except Antimuscarinics	Kidney & urinary tract- lower urinary tract symptoms, benign prostatic hyperplasia	-	-	-	✓	✓
Inhaled anticholinergic agents	Kidney & urinary tract- lower urinary tract symptoms, benign prostatic hyperplasia	-	-	-	✓	-
Anticholinergics and antihistamines	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Gastrointestinal antispasmodics	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Muscle relaxants	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Oxybutynin	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Flavoxate	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Antidepressants	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Decongestants	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Tolterodine	Kidney & urinary tract- bladder outflow obstruction	-	-	✓	-	-
Dextroamphetamine	Malnutrition/Anorexia	-	-	✓	-	-
Methylphenidate	Malnutrition/Anorexia	-	-	✓	-	-
Methamphetamine	Malnutrition/Anorexia	-	-	✓	-	-
Pemolin	Malnutrition/Anorexia	-	-	✓	-	-
Fluoxetine	Malnutrition/Anorexia	-	-	✓	-	-
Olanzapine	Obesity	-	-	✓	-	-
Fluoxetine	SIADH/hyponatremia	-	-	✓	-	-
Citalopram	SIADH/hyponatremia	-	-	✓	-	-

Beers Drug	Disease/Syndrome	1991	1997	2003	2012	2015
Fluvoxamine	SIADH/hyponatremia	-	-	✓	-	-
Paroxetine	SIADH/hyponatremia	-	-	✓	-	-
Sertraline	SIADH/hyponatremia	-	-	✓	-	-
Beta Blockers	Syncope or Falls	-	✓	-	-	-
Long-acting benzodiazepine drugs	Syncope or Falls	-	✓	-	-	-
Short- to intermediate benzodiazepine drugs	Syncope or Falls	-	-	✓	-	-
Amitriptyline hydrochloride	Syncope or Falls	-	-	✓	-	-
Doxepin hydrochloride	Syncope or Falls	-	-	✓	-	-
Imipramine hydrochloride	Syncope or Falls	-	-	✓	-	-

Appendix L. PIMs to be used with caution in older adults represented in 2012 and 2015 Beers Criteria

Beers Drug	1991	1997	2003	2012	2015
Aspirin for primary prevention of cardiac events	-	-	-	✓	✓
Dabigatran	-	-	-	✓	✓
Prasugrel	-	-	-	✓	✓
Antipsychotics	-	-	-	✓	✓
Diuretics	-	-	-	-	✓
Carbamazepine	-	-	-	✓	✓
Carboplatin	-	-	-	✓	✓
Cyclophosphamide	-	-	-	-	✓
Cisplatin	-	-	-	✓	✓
Mirtazapine	-	-	-	✓	✓
Oxcarbazepine	-	-	-	-	✓
Serotonin norepinephrine reuptake inhibitor (SNRIs)	-	-	-	✓	✓
Selective serotonin reuptake inhibitor (SSRIs)	-	-	-	✓	✓
Tricyclic antidepressants (TCAs)	-	-	-	✓	✓
Vincristine	-	-	-	✓	✓
Vasodilators	-	-	-	✓	✓

Appendix M. Comprehensive list of variables included in the final dataset

Variable List		
#	**Variable**	**Label**
147	ADMS	# of hospital admissions
3	AGE	Age of Patient
41	Alpha_Agonist_Central_Dys	Beers Criteria Medication (Rx Days)
40	Alpha_Agonist_Central_Rx	Beers Criteria Medication (# Rx)
43	Alpha_Blocker_Dys	Beers Criteria Medication (Rx Days)
42	Alpha_Blocker_Rx	Beers Criteria Medication (# Rx)
123	Ambu	Frailty measure indicator
45	Antiarrhythmic_Dys	Beers Criteria Medication (Rx Days)
44	Antiarrhythmic_Rx	Beers Criteria Medication (# Rx)
47	Antiemetics_Dys	Beers Criteria Medication (Rx Days)
46	Antiemetics_Rx	Beers Criteria Medication (# Rx)
49	Antihistamine_1st_Gen_Dys	Beers Criteria Medication (Rx Days)
48	Antihistamine_1st_Gen_Rx	Beers Criteria Medication (# Rx)
51	Antihypertensive_Dys	Beers Criteria Medication (Rx Days)
50	Antihypertensive_Rx	Beers Criteria Medication (# Rx)
53	Antiinfective_Dys	Beers Criteria Medication (Rx Days)
52	Antiinfective_Rx	Beers Criteria Medication (# Rx)
55	Antiparkinson_agent_Dys	Beers Criteria Medication (Rx Days)
54	Antiparkinson_agent_Rx	Beers Criteria Medication (# Rx)
57	Antipsychotics_FirstGen_Dys	Beers Criteria Medication (Rx Days)
56	Antipsychotics_FirstGen_Rx	Beers Criteria Medication (# Rx)
59	Antipsychotics_SecondGen_Dys	Beers Criteria Medication (Rx Days)
58	Antipsychotics_SecondGen_Rx	Beers Criteria Medication (# Rx)
61	Antispasmodic_Dys	Beers Criteria Medication (Rx Days)
60	Antispasmodic_Rx	Beers Criteria Medication (# Rx)
63	Antithrombotic_Dys	Beers Criteria Medication (Rx Days)
62	Antithrombotic_Rx	Beers Criteria Medication (# Rx)
65	Anxiolytic_Dys	Beers Criteria Medication (Rx Days)
64	Anxiolytic_Rx	Beers Criteria Medication (# Rx)
151	AnyADM	Any hospital admission
102	AnyBeers	Use of any Beers Criteria Medication
15	Asthma	Elixhauser Comorbidity Indicator
67	Barbiturates_Dys	Beers Criteria Medication (Rx Days)
66	Barbiturates_Rx	Beers Criteria Medication (# Rx)
69	Benzodiazepines_Long_Acting_Dys	Beers Criteria Medication (Rx Days)
68	Benzodiazepines_Long_Acting_Rx	Beers Criteria Medication (# Rx)
71	Benzodiazepines_Short_Acting_Dys	Beers Criteria Medication (Rx Days)
70	Benzodiazepines_Short_Acting_Rx	Beers Criteria Medication (# Rx)
23	CF	Elixhauser Comorbidity Indicator
13	CHF	Elixhauser Comorbidity Indicator
14	COPD	Elixhauser Comorbidity Indicator

#	Variable	Label
17	CRF	Elixhauser Comorbidity Indicator
33	Carditis	Elixhauser Comorbidity Indicator
9	CharlsScore	Charlson Comorbidity Score
11	ConductHeart	Elixhauser Comorbidity Indicator
12	ConductHeartB	Elixhauser Comorbidity Indicator
146	Days	Days in hospital
19	Diab	Elixhauser Comorbidity Indicator
20	DiabComp	Elixhauser Comorbidity Indicator
73	Diuretic_Dys	Beers Criteria Medication (Rx Days)
72	Diuretic_Rx	Beers Criteria Medication (# Rx)
16	Divert	Elixhauser Comorbidity Indicator
5	EGEOLOC	Geographic Location Employee
1	ENROLID	Patient ID
29	Epil	Elixhauser Comorbidity Indicator
75	Ergoloid_Dys	Beers Criteria Medication (Rx Days)
74	Ergoloid_Rx	Beers Criteria Medication (# Rx)
129	Female	Gender of Patient
126	FrailCat	Frailty measure
137	FrailCat_0	Frailty measure (robust)
135	FrailCat_1	Frailty measure (pre-frail)
136	FrailCat_2	Frailty measure (frail)
125	FrailScore	Frailty Score
77	Gut_motility_stimulator_Dys	Beers Criteria Medication (Rx Days)
76	Gut_motility_stimulator_Rx	Beers Criteria Medication (# Rx)
121	HHBed	Frailty measure indicator
21	HIV	Elixhauser Comorbidity Indicator
22	Hep	Elixhauser Comorbidity Indicator
124	HomeO2	Frailty measure indicator
79	Hormones_Dys	Beers Criteria Medication (Rx Days)
78	Hormones_Rx	Beers Criteria Medication (# Rx)
127	HospitalAdm	Hospital admission
34	Hyp	Elixhauser Comorbidity Indicator
37	LateStroke	Elixhauser Comorbidity Indicator
99	Laxative_Dys	Beers Criteria Medication (Rx Days)
98	Laxative_Rx	Beers Criteria Medication (# Rx)
2	MEMDAYS	Member Days
28	MS	Elixhauser Comorbidity Indicator
6	MSA	Metropolitan Statistical Area
128	Male	Gender of Patient
81	NSAIDs_Dys	Beers Criteria Medication (Rx Days)
80	NSAIDs_Rx	Beers Criteria Medication (# Rx)
83	Narcotic_Dys	Beers Criteria Medication (Rx Days)
82	Narcotic_Rx	Beers Criteria Medication (# Rx)
85	NonCOX_NSAIDs_Dys	Beers Criteria Medication (Rx Days)

#	Variable	Label
84	NonCOX_NSAIDs_Rx	Beers Criteria Medication (# Rx)
87	Nonbarbiturate_sedative_hypn_Dys	Beers Criteria Medication (Rx Days)
86	Nonbarbiturate_sedative_hypn_Rx	Beers Criteria Medication (# Rx)
89	Nonbenzodiazepine_sedative_Dys	Beers Criteria Medication (Rx Days)
88	Nonbenzodiazepine_sedative_Rx	Beers Criteria Medication (# Rx)
30	Otitis	Elixhauser Comorbidity Indicator
39	Paral	Elixhauser Comorbidity Indicator
27	Parkin	Elixhauser Comorbidity Indicator
101	Phenothiazines_Dys	Beers Criteria Medication (Rx Days)
100	Phenothiazines_Rx	Beers Criteria Medication (# Rx)
10	PulmHeart	Elixhauser Comorbidity Indicator
18	RA	Elixhauser Comorbidity Indicator
7	REGION	Region
130	Region_1	Northeast
131	Region_2	North Central
132	Region_3	South
133	Region_4	West
134	Region_5	Unknown
4	SEX	Gender of Patient
35	SLE	Elixhauser Comorbidity Indicator
38	SUlcer	Elixhauser Comorbidity Indicator
26	Scizo	Elixhauser Comorbidity Indicator
25	Senile	Elixhauser Comorbidity Indicator
24	Sicle	Elixhauser Comorbidity Indicator
91	Skeletal_muscle_relaxants_Dys	Beers Criteria Medication (Rx Days)
90	Skeletal_muscle_relaxants_Rx	Beers Criteria Medication (# Rx)
148	Studycost	Total Cost (SumRx13+SumOP13+SumIP13)
93	Sulfonylureas_Dys	Beers Criteria Medication (Rx Days)
92	Sulfonylureas_Rx	Beers Criteria Medication (# Rx)
145	SumIP13	Sum of inpatient visit costs
144	SumOP13	Sum of outpatient visit costs
143	SumRx13	Sum of prescription drug costs
95	Tertiary_TCAs_Dys	Beers Criteria Medication (Rx Days)
94	Tertiary_TCAs_Rx	Beers Criteria Medication (# Rx)
32	Valve	Elixhauser Comorbidity Indicator
97	Vasodilator_Dys	Beers Criteria Medication (Rx Days)
96	Vasodilator_Rx	Beers Criteria Medication (# Rx)
31	Vertigo	Elixhauser Comorbidity Indicator
138	_LEVEL_	Response Value
140	_Lps	Logit of Propensity Score
141	_MATCHWGT_	Matched obs ATT weight
142	_MatchID	Matched ID number
150	adms_0	Hospital admission

#	Variable	Label
115	arthritis	Frailty measure indicator
103	bladder	Charlson Comorbidity Score variable
118	braininj	Charlson Comorbidity Score variable
107	cancer	Charlson Comorbidity Score variable
104	coagulopathy	Charlson Comorbidity Score variable
149	days_0	Days in hospital
106	dementia	Charlson Comorbidity Score variable
120	diabetes	Charlson Comorbidity Score variable
111	diffwalk	Frailty measure indicator
108	heartfail	Charlson Comorbidity Score variable
109	lipid	Charlson Comorbidity Score variable
105	paraplegic	Charlson Comorbidity Score variable
112	pd	Charlson Comorbidity Score variable
113	podiatry	Frailty measure indicator
139	pscore	Estimated Probability
110	psychiatric	Charlson Comorbidity Score variable
114	rehab	Frailty measure indicator
117	sepsis	Charlson Comorbidity Score variable
116	skinulcer	Charlson Comorbidity Score variable
119	weakness	Frailty measure indicator