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Risk of Medical Events for Falls, Fractures, Confusion, and Delirium for Patients with Filled Prescriptions for Drugs Listed on Beers Criteria Compared to Well-Matched Controls

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RISK OF MEDICAL EVENTS FOR FALLS, FRACTURES, CONFUSION, AND DELIRIUM FOR PATIENTS WITH FILLED PRESCRIPTIONS FOR DRUGS LISTED ON BEERS CRITERIA COMPARED TO WELL-MATCHED CONTROLS.

BY

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A doctoral project submitted to the faculty of the Medical University of South Carolina
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Using the 2013 edition of the Truven Marketscan ® Administrative Claims database, this study looks to link the expected side effects of Beers Criteria medications to logical hospital admissions. This study sets to examine hospital admissions and emergency department visits for community-dwelling elderly individuals 65 years or older specifically for falls and fracture as well as confusion and delirium admissions. These hospital admission types constitute a significant number of admissions the elderly experience due to the medication side effects which affect balance, gait, and cognition. Through the use of 2.6 million propensity-score matched patients, 1.297 million having been exposed to Beers Criteria medications and 1.297 million patients not exposed, this study was able to confirm the linkage between the expected side effects of the medication classes and their logical hospital admissions. Antipsychotics and benzodiazepines were the most frequent prescribed medications to both groups of admission and were also associated with the highest increase in risk of hospitalizations. Future research into medication specific research in regards to falls and fractures, and confusion and delirium in the elderly is warranted.

TABLE OF CONTENTS

List of Figures

List of Tables

Appendix

CHAPTER I INTRODUCTION

In the most recent report by the National Center for Health Statistics published in June 2019, it is estimated that the overall life expectancy of a person in the United States is 78.6 years for all races and sexes and this value has been on a steady increase since 1970 (Arias & Xu, 2019). There are several issues that a population who is not only aging and staying alive longer but a population who is also steadily increasing can cause; one of the most important and currently pressing issues is that of healthcare expenditures associated with aging. Many people may think the aging population "spend less money" as they are less able to travel, take part in recreational activities but this is not entirely true.

The question we struggle with is not completely clinical. To begin driving the total amount of healthcare expenditures in the United States down, we must first understand the absolute underlying causes of these expenditures and how to prevent them from occurring. Throughout much of the literature on healthcare expenditures in elderly populations there is a consistent trend present, what actions, both internal and external to the healthcare system, can we take to prevent the unplanned hospitalization of elderly patients? This question, while thoroughly researched, the true underlying question is not how we can prevent these unplanned admissions, but how can we predict future unplanned hospitalizations based on the medical and statistical information we currently have on the aging and elderly population.

It is consistently referenced through the literature on unplanned hospitalizations in elderly populations that the availability of a validated predictive model or integrated clinical decision support tool which can predict future hospitalizations would be the crucial first step in reducing the number of preventable readmissions (LaMantia et al., 2010; Parameswaran Nair, Chalmers, Peterson, et al., 2016). There have been several attempts to build such a model but the attempts

by Alassaad et al. (2015), Chang et al. (2005), LaMantia et al. (2010), and Parameswaran Nair, Chalmers, Connolly, et al. (2016) have only been able to build models with a concordance statistic, or c-statistic, of 0.73 at the greatest. While there is no published statistical rational, the c-statistic that is accepted in medical studies showing high discriminative power is 0.95 (Caetano et al., 2018).

One consequence of the growing elderly population in which we will focus on in this study is the concept of polypharmacy. While there is no standardized definition of "polypharmacy" across the literature, it is defined as the prescribing of multiple clinically indicated medications to one individual from one or more prescribers, to which these medications are unnecessary duplications of treatment, harmful to the patient, or whose effect could be synergistic or antagonistic when mixed with other medications (Dagli & Sharma, 2014; Endsley, 2018; Hammond & Wilson, 2013; Quinn & Shah, 2017; Sergi et al., 2011). In the United States, 61% of adults over the age of 65 have two or more chronic conditions, which further drives up the prevalence of polypharmacy from overprescribing practices and insufficient patient monitoring and follow-up (Quinn & Shah, 2017). Polypharmacy, adverse drug events (ADE), and drug related mortality are a few of the most burdensome affects from aging on the healthcare ecosystem today, which is why it is so very important to address this problem (Quinn & Shah, 2017).

A 2018 study by O'Neill Roldan aimed to measure healthcare resource utilization of elderly patients and the resulting healthcare costs associated with the use of potentially inappropriate medications. This study found that individuals whom were prescribed any Beers Criteria medication experienced a greater number of hospital admissions for a longer length of stay compared to a matched group of individuals not taking these medications (O'Neill Roldan,

2018). Multiple studies have already determined that a relationship exists between elderly patients taking medications on the Beers Criteria and unplanned hospitalizations. However, it is not known if these additional hospital admissions are logically related to the expected side effects of Beers drug used.

This study will use the O'Neill Roldan (2018) data set to identify the rate of readmissions that are logically linked to the Beers Criteria drugs. We will examine hospital admissions and emergency department visits (ED) for two key types of events associated with a broad array of medication classes listed on Beers Criteria:

1) Admissions for falls and/or fractures in patients taking medications on the Beers Criteria which are not recommended because of their effect on balance and gait, and
2) Admissions for confusion and/or delirium patients taking medications on the Beers Criteria which are not recommended because of their effect because on cognition and a persons' ability to live independently.

The population for this study will be secondary-use of the data set from an existing research study performed by O'Neill Roldan (2018) and colleagues at the Medical University of South Carolina. This dataset contains roughly 2.6 million patients extracted from the 2013 Truven Marketscan® Administrative Claims Database. The data are de-identified and the study meets the criteria for non-human research which requires no informed consent. Work on this patient cohort has been previously published in: **"**Simpson, K. N., Seamon, B. A., Hand, B. N., Roldan, C. O., Taber, D. J., Moran, W. P., & Simpson, A. N. (2018). Effect of frailty on resource use and cost for Medicare patients. *J Comp Eff Res*, 7(8), 817-825. https://doi.org/10.2217/cer-2018-0029".

CHAPTER II LITERATURE REVIEW

As previously discussed, there is extensive literature available in determining if an association present between Beers Criteria medications and an increased likelihood of a patient experiencing an unplanned hospitalization. Since that determination, researchers have sought to expand the domain and attempt to predict these unplanned hospitalizations, however, as of the time of this writing to our knowledge, there is still no validated tool available that can predict unplanned hospitalizations based solely on Beers Criteria and existing patient characteristics.

Clinically, elderly patients function and require different treatment and care provided in a manner different than your average adult. For example, elderly patients may have a decrease in kidney or liver function, metabolize and excrete medications at a faster or slower rate, an increased number of comorbid conditions, and an increased potential to experience an adverse drug event (ADE) (Berryman et al., 2012; Gokce Kutsal et al., 2009; LaMantia et al., 2010). Older patients are far more susceptible to adverse effects of pharmaceutical medications, yet studies have shown that high dose and very high doses of these inappropriate medications are still being used in the care and treatment of elderly patients. A study by Mitchell et al. (2017) found in two US academic medical centers in a 6-month period that 3,394 doses of potentially inappropriate medications were administered to 1,364 different patients. Mitchell et al. (2017) calls attention to the potentially unsafe use and higher than recommended dosing of potentially inappropriate medications being used in emergency departments.

2.1 American Geriatric Society Beers Criteria

The American Geriatrics Society (AGS), since 2011, has been the organization responsible for maintaining the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. First published in 1991, the Beers Criteria from the AGS is the oldest list of

medications that outside of extraordinary circumstances, should be avoided in the care and treatment of elderly individuals (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). The AGS publishes a revision to the Beers Criteria every three years by convening a panel of medical experts to review any newly published evidence and determine if any of the Beers Criteria recommendations should be removed or changed, or if there are new recommendations that should be added. There are five primary sections which make up the complete Beers Criteria list, potentially inappropriate medications for older adults, medications that should be avoided based on the patient's condition, medications that should be used with caution based on the patient's condition, medications with severe drug-drug interactions, and medications which require dose adjustment based on the patients renal function (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019).

In the 2019 revision of the Beers Criteria there were several notable changes made by the expert panel. Compared to the 2015 revision, the 2019 revision removed a number of medications the panel removed because "the drug-related problem was not sufficiently unique to older adults" and "they [the decisions] were made to help keep the AGS Beers Criteria® streamlined and focused on medications particularly problematic for older adults" (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). Overall the expert panel decided to remove 25 medications or classes of medications from the Beers Criteria and add new approved medications to the medications to use with caution, the drug-drug interaction, and the potentially inappropriate medications lists for 2019 (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). The AGS summarized their changes from the 2015 to 2019 revision of the Beers Criteria in table 10 of their publication and is presented below in Figure 1.

Figure 1: Medications/Criterion Modified Since 2015 American Geriatrics Society Beers Criteria®

Medication/Criterion	Modification
Independent of Diagnosis or Condition (Table 2)	
Peripheral α-1 blockers	For treatment of hypertension
Digoxin for atrial fibrillation and heart failure	Added wording to Drug column; modified rationale; QE for atrial fibrillation changed to Low
Estrogen with or without progestin	Added "recurrent" urinary tract infections
Sliding-scale insulin	Clarified definition of sliding-scale insulin
Metoclopramide	Added duration of use to recommendation
Meperidine	Removed caveat from recommendation
Considering Disease and Syndrome Interactions (Table 3)	
Heart failure	Reorganized recommendations; separated COX-2 inhibitors from other NSAIDs; added QE and SR for COX-2 inhibitors; changed recommendation for NSAIDs, COX-2 inhibitors, and thiazolidinediones to use with caution in asymptomatic heart failure and to avoid in symptomatic heart failure; modified rationale
Syncope	Specified "nonselective peripheral α-1 blockers"; separated rationales, QE, and SR for AChEIs and nonselective peripheral alpha-1 blockers; modified QE for ACHEIs and antipsychotics
Delirium	Changed "Sedative/hypnotics" to Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; changed QE of H2-receptor antagonists to low
History of fractures and falls	Changed SR of opioids to strong
Parkinson disease	Added rationale for quetiapine, clozapine, and pimavanserin
Chronic kidney disease and NSAIDs	Changed wording (minor) of criterion title
Use With Caution (Table 4)	
Aspirin as primary prevention	Modified age, indication, rationale, and QE
Dabigatran	Modified rationale and recommendation
Prasugrel	Modified rationale
Clinically Important Drug-Drug Interactions (Table 5)	
The table title	Dropped "Non–anti-infective"
ACEIs/ARBs and hyperkalemia	Changed to renin-angiotensin system inhibitors
Combination of three or more CNS agents (antidepressants, antiepileptics, antipsychotics, benzodiazepines, and opioids)	Replaced individual criteria with a single criterion
Medications That Should Be Avoided or Have Their Dosage Reduced With Decreased Kidney Function (Table 6)	
Apixaban, dabigatran, edoxaban, and rivaroxaban	Revised CrCl at which action is required, rationale and recommendations to reflect current labeling, and CrCl exclusion parameters in clinical trials

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AChEI, acetylcholinesterase inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; COX, cyclooxygenase; CrCl, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; QE, quality of evidence; SR, strength of recommendation.

For the purposes of this study, the 2012 edition of the Beers Criteria will be used as that was the most recent update of the Beers Criteria in tandem with the availability of the Truven Marketscan® dataset the O'Neill Roldan (2018) study used. The medications that comprise the 2012 Beers Criteria are available in Appendix A while the most recent version of the Beers Criteria, the 2019 revision, is available in Appendix B.

2.1.1 The Delphi Analysis Methodology

The AGS Beers Criteria, along with the other inappropriate medication lists discussed in section 2.2 Non-Beers Criteria Medication Guides, were all developed using the Delphi Method to reach a shared consensus among a group or panel of experts (McMillan et al., 2016). Developed in 1953 by the Rand Corporation, the Delphi Method uses multiple series of self-guided questionnaires that solicits individual feedback from the panel members or expert allowing for the confidentiality of their comments if the situation should require such (McMillan et al., 2016). The Delphi Method is a useful tool because it is intrinsically industry agnostic, meaning this methodology can be used and implemented outside of healthcare and health services research (McMillan et al., 2016; Powell, 2003). The Delphi Method is used when a specific research initiative needs to solicit, and eventually combine, the opinions and expertise of a group of subject matter experts (SMEs) when there is a general lack of agreement on a specific topic (Powell, 2003).

The advantage of using the Delphi Method for building guidelines and frameworks is the inclusion of a standard 3, 5, 7, or 9-point Likert scale rating for a quantitative evaluation as well as the ability for the participant to provide a free-text response to elaborate or justify their rating (McMillan et al., 2016). Once the first Delphi survey round is complete, the responses are collected and in turn used to develop the survey for the second Delphi round which contains the participants original rating and the groups median rating for each question, as well as a selection of the free-text responses to provide thought and insight from the other panel members (McMillan et al., 2016). The second round of the Delphi Method allows the participant to review the general rating as compared with their own and provides the opportunity for the participant to keep their previous rating or adjust it based on the information provided by the other participants

(McMillan et al., 2016). Because the second round of the Delphi Method is based on the results of the first round, Powell (2003) mentions this [second] round is when the researcher will either see, or begin to see, the opinions provided converge and become more uniform. Once the second round of surveying is complete, the researcher can then combine the participant's adjusted ratings and analyze the results.

According to McMillan et al. (2016), agreement on a topic is typically defined when the median score is greater than 77% of the maximum score for the Likert scale used in the survey. For example, if the survey used a 9-point Likert scale range, then agreement on a topic would be considered reached if the median score was greater than or equal to 7 (McMillan et al., 2016). Additionally, as described by McMillan et al. (2016), disagreement on a topic is considered when one-third of the number of respondents score the question or statement on the opposite end of the scale when compared to the other participants. This definition of agreement and disagreement on a topic is of course dependent upon the topic in which the Delphi Methodology is being used for. In a systematic review by Powell (2003), she found varying definitions of panel agreement and disagreement. In one study mentioned by Powell (2003), the outcome of the Delphi Method required 100% agreement between the participants, another only requiring 51% consensus, and others listed no specific threshold which was used.

With regards to the Delphi Method, while this methodology is well understood, researchers using this method have been called upon to explain and explicitly define the criteria their study is using for consensus among participants (Diamond et al., 2014). Various systematic reviews have revealed the criteria used to define agreement and overall consensus is both defined, and reported, poorly in published literature (Diamond et al., 2014; Toronto, 2017). Researchers using the Delphi Method should be specifically trained in the proper execution of

this tool due several caveats and complexities of the methodology itself. When used properly, the Delphi, or newer e-Delphi (electronic Delphi) methodology is an incredibly useful tool for collecting, aggregating, and eventually unifying the opinions of experts on a specific topic (Hasson et al., 2000; Toronto, 2017).

2.1.2 In regards to Potentially Inappropriate Medications

Beers Criteria is one of the many examples of potentially inappropriate medications lists published and in use today that recommend against use in the care and treatment of elderly individuals. Baldoni et al. (2014) published a study after interviewing 1,000 elderly Brazilian residents to identify not only the clinical, but the socioeconomic and demographic factors that may attribute PIM use in those elderly patients. This study also compared PIM usage using both the 2003 and the 2012 versions of the Beers Criteria and tested the agreement between the two versions directly. Baldoni et al. (2014) found was that the list of factors associated with PIM usage in their patients were the same between the 2003 and 2012 versions of Beers Criteria (female, self-medicates, use of OTCs, psychotropic medications, polypharmacy, and common ADE symptoms), there was a difference in the percentage of PIMs identified between the two versions of the criteria. The 2003 revision of Beers Criteria identified 48.0% of PIMs while the 2012 version identified 59.2% (Baldoni et al., 2014). Using the McNemar's test, Baldoni et al. (2014) determined that the difference in identification percentages between the two revisions was indeed significant. Outside of the analysis by Baldoni et al. (2014), the significant change in identification percentage may also have been due to the 2012 revision. The American Geriatric Society indicated that the 2012 revision of the Beers Criteria was one of the largest overhauls of the criteria as this was the first revision where the AGS was responsible for writing and publishing said update (American Geriatrics Society Beers Criteria Update Expert Panel, 2012).

There is a significant amount of literature available on Beers Criteria and the prevalence of potentially inappropriate medications in the elderly population. Research has shown the risk for unplanned hospitalizations increases as the number of active PIMs the patient is taking also increases (Gallagher et al., 2008; Price et al., 2014a, 2014b).

2.1.3 In regards to Drug Exposure and Unplanned Hospitalizations

As discussed earlier, one of the leading causes of unplanned hospitalizations in the elderly population is in fact from adverse drug events (Price et al., 2014b). Studies have shown that in elderly populations, an increase in polypharmacy has been correlated with an increased risk of the patient experiencing an adverse drug event, which has also been correlated with an significant increased risk of unplanned hospitalizations (Sarwar et al., 2018; Wimmer et al., 2014). Because of these, and other similar findings correlating the use of PIMs to unplanned hospitalizations, being able to predict future unplanned hospitalizations in this population.

A 2018 Pakistani study by Sarwar et al. found that in a population of 385 geriatric patients, 61% of participants were taking 5-9 prescription medications, and 56.4% of participants had an unplanned hospitalization that could be traced back to one of the PIMs they were taking. Sarwar et al. (2018) also found patients considered to have polypharmacy (5-9 medications) and excessive polypharmacy (10 or more medications) were 2.5 times and 38 times more likely to have an unplanned hospitalization, respectively (Sarwar et al., 2018).

2.2 Non-Beers Criteria Medication Guides

While the AGS Beers Criteria is a valuable tool for evaluating the pharmacologic care and treatment of an elderly patient, there are other generally accepted medication management criteria available as well. While there are others, two of the most common of these Beers alternatives of explicit or expert criteria is the Screening Tool to Alert Doctors to Right

Treatment (START)/Screening Tool for Older Persons' Prescriptions (STOPP) and the Fit fOR The Aged (EURO FORTA) listing.

2.2.1 START/STOPP Criteria

The START/STOPP criteria was first published in 2008 from an Irish study compiled using the Delphi consensus method, similar to Beers Criteria, and most recently updated in 2014 (Corsonello et al., 2012; Curtin et al., 2019). The START criteria consists of 34 prescribing indications for medications that have been either shown or are likely to provide a benefit to the patient while the STOPP criteria contains 80 inappropriate prescribing practices when caring for elderly patients (Corsonello et al., 2012; O'Mahony et al., 2015). While the STOPP criteria and the Beers Criteria have a similar purpose, there are a number of differences between the two that exist. First, the STOPP criteria is organized by body system making it easier for clinicians to navigate, while the Beers Criteria is organized by function as discussed earlier (Corsonello et al., 2012). Second, because drug approval and availability differ between the United States and most European countries, the two criteria primarily focus on the pharmaceuticals that are available for use in their geographic area. Next considering the pharmaceuticals that do overlap on both lists, there are a number of items that are present on the STOPP criteria that are not present on the Beers Criteria (Corsonello et al., 2012). This could be for a number of reasons, the specific evidence taken into consideration, scoring methods when evaluating the literature and evidence, or differences in validation methods (Corsonello et al., 2012). And lastly, the START/STOPP criteria have been used in various randomized clinical trials (RCT) and have shown evidence of a clinical benefit when used as an intervention tool; Beers Criteria has not (Curtin et al., 2019).

There has been a number of studies performed to access the head to head performance of START/STOPP and the Beers Criteria. A 2014 Spanish study by Hudhra et al. showed within a

population of 624 patients, Beers Criteria found 22.9% of PIMs while the STOPP criteria found 38.4% of PIMs. Their research also found that the number of PIMs increased with an increase in Charlson Index Score and the number of drugs prescribed to the specific patient (Hudhra et al., 2014). In another study by Salgueiro-Vázquez et al. (2016) found in a comparison between Beers Criteria and STOPP, that within a sample of 223 patients older than 65 years old and taking 10 or more medications per day, that 63.2% of patients met a Beers Criteria PIM and 73.9% of patients met a STOPP PIM. Additionally, a 2012 study from India echoes similar results as above; 19.8% PIP identification by START/STOPP while only 7.3% PIP identification by Beers Criteria (Karandikar et al., 2013).

An Irish study by Hamilton et al. (2011) found that ADEs in their patient sample were identified by STOPP criteria 2.54 times more often than with Beers Criteria and 67.7% of the time STOPP was involved with the identification of an avoidable ADE compared to Beers Criteria at 28.5%. Hamilton et al. (2011) presents that the use of STOPP criteria is more clinically relevant because of its ability to identify PIMs that would result in an ADE.

Studies have shown that there is a difference in sensitivity between Beers Criteria and using START/STOPP. A study by Brown et al. (2014) shows the inverse result from the studies discussed above. Brown et al. (2014) found that in a retrospective cohort of 174,275 patients, Beers Criteria was able to identify 34.1% of PIMs while STOPP was only able to identify 27.6%. Similarly in a 2015 Brazilian study, Oliveira et al. (2015) found that in a sample of 142 randomly selected patients, Beers Criteria was able to identify 51.8% of PIMs and STOPP was able to identify 33.8% of PIMs. A 2018 study by Sakr et al. with a group of 350 patient participants found that Beers Criteria was able to identify 20.4% of PIMs while STOPP was only able to identify 6.2% of PIMs. This study added an additional element, the Treatment Satisfaction

Questionnaire for Medications, or TSQM. The TSQM is a 14 item questionnaire aimed to evaluate the patient perceived success of the treatment provided to them (Sakr et al., 2018). This study also found that when either the Beers Criteria or STOPP criteria was actively being used in the experimental arm, the individual TSQM scores for patients with PIMs was significantly lower than for patients without PIMs (Sakr et al., 2018).

As discussed previously, the START/STOPP criteria was developed in Europe and contains medications that are not available for use in the United States and these medications do not appear on the Beers Criteria. When considering the international use of Beers Criteria, this needs to be taken into consideration as the two are not equally matched.

2.2.2 EURO FORTA

The Fit fOR The Aged, or FORTA, criteria was developed in Germany in 2008 and was later validated for use in 2012 (Curtin et al., 2019). Following FORTA's validation, in 2015 FORTA was updated to combine the six European medication management lists into one large, validated criteria, EURO FORTA (Curtin et al., 2019). The EURO FORTA criteria contains 264 medications and medication classes that are organized by clinical diagnosis or syndrome (Curtin et al., 2019). Within each clinical diagnosis, the EURO FORTA criteria assigns a letter grade, A-D, to each of the medications based on the safety and effectiveness in treating the particular diagnosis or syndrome (Curtin et al., 2019). The grading scheme would allow the clinician to ideally select the safest and most effective treatment while the medications that are harmful or should be avoided are indicated and EURO FORTA provides the clinician an alternative (Curtin et al., 2019). The EURO FORTA grading scheme is comprised of the following: "A, Absolutely, indispensable, clear-cut; B, Beneficial, proven benefit but limited extent of effect or safety concerns; C, Caution, questionable efficacy or safety profile, explore alternatives, and D, Don't,

avoid if possible, find alternative" (Curtin et al., 2019, p. 6). A significant downfall of the EURO FORTA criteria is, unlike the STOPP/START or Beers Criteria, EURO FORTA does not address any drug-drug or drug-disease interactions (Curtin et al., 2019).

There are a limited number of studies available which include EURO FORTA as a measurement tool. In a 2019 study by Awad and Hanna across 10 primary healthcare centers in Kuwait, they found that in a population of 420 participants, 53.1% of PIMs were identified by Beers Criteria, 55.7% by STOPP, and 44.3% by FORTA.

2.2.3 PRISCUS List

The PRISCUS list is a lesser known list of potentially inappropriate medications for use in elderly patients. Developed in 2010 by a group of German medical researchers after identifying the need for a PIM list based on the drugs and medications that were available for use within Germany and the differences in prescribing practices of its physicians (Holt et al., 2010). A study by Amann et al. (2012) found that in a retrospective study of medical care given in 2007 to 804,400 elderly German patients that 25% of these patients were receiving at least one PIM. Amann et al., (2012) discusses while further research and validation of the PRISCUS list was needed, developing a PIM list containing specific medications available in Germany was necessary. This PIM list was developed in a similar method as the other PIM listings discussed thus far using a two round Delphi method utilizing a group of 25 expert participants (Holt et al., 2010). After both Delphi evaluation rounds were complete, the expert panel agreed on the inclusion of 83 drugs from 18 different classes to the PRISCUS list (Holt et al., 2010). There was a subset of 46 of the 83 medications that the panel could not reach a clear decision of their appropriateness, and like Beers, the decision was made to include this subset of medications on a

separate list and if the PIM is absolutely necessary, recommendations for clinical adjustments are provided (Holt et al., 2010).

The number of studies published in English on the effectiveness PRISCUS list identifying PIMs are limited in comparison to the availability of studies for the other PIM lists. One study by Siebert et al. (2013) compared the effectiveness of PIM identification in 308 elderly patients at a geriatric rehabilitation facility using PRISCUS, STOPP/START, and Beers Criteria. The study found that the PRISCUS list found less than half as many PIMs as STOPP (0.5 vs. 1.2 PIMs) but identified slightly more PIMs as Beers (0.5 vs. 0.4 PIMs)

2.3 Falls and Fractures in the Elderly Population

It is well understood through the literature that falls and fractures in the elderly population, regardless of Beers Criteria medication exposure, are serious, yet unfortunately common occurrences. Published polypharmacy literature has found that 60% of elderly patients take 5 or more medications, while 20% of elderly patients take 10 or more medications (Scott et al., 2012). This study by Scott et al. (2012) found that elderly patients who experience hyper-polypharmacy, which is the concurrent use of 10 or more medications, are at a 6x increase of experiencing an injurious fall during their lifetime. Aside from physical effects, there are a number of psychological effects on the patient that also occur with falls – such as loss of confidence in walking, fear of an additional falls, or the fear of losing independent living (Chang et al., 2011; Dionyssiotis, 2012; Hester & Wei, 2013).

To begin to understand the relationship between falls and fractures and elderly populations, one of the pieces of early literature is a study by Weiner et al. (1998). This study was of particular importance because this was one of the few early studies that investigated and found a dose-response relationship between elderly patients using CNS-active medications and

their risk of falling. While this study had limitations bound to the convenience sample of 305 community-dwelling elderly male veterans, the risk of falls and fractures was still present following a dose-adjusted relationship of the CNS-acting medications the sample patients were taking.

Following the Weiner et al. (1998) study, a 2002 study by Neutel et al. found that elderly patients taking multiple drugs were at a higher risk of experiencing an injurious fall and investigated the presence of polypharmacy and hyperpolypharmacy in the elderly. This study found an unadjusted risk of patients who were exposed to some level of hyper-polypharmacy were at a 6 times higher risk of hospitalization than a patient taking less than 5 different medications (Neutel et al., 2002). A 2013 study by Hammond and Wilson further investigated polypharmacy and falls in the elderly after Neutel et al. (2002) and others. Hammond and Wilson (2013) found that polypharmacy can be independently linked as a risk factor to falls and hospitalizations in elderly individuals but a stronger link exists between the patient experiencing a fall and the specific type of medication that the patient is taking.

The study by Tinetti et al. 2006 focused on the healthcare expenditure of a single fall event and the burden than potentially preventable falls place on the United States healthcare system. Tinetti et al. (2006) found that the average healthcare expenditure for a single fall event was $24,330 while the overall healthcare burden caused by falls in patients over the age of 65 years old was in excess of $5.7 billion annually.

When examining the literature for studies that investigated the relationship between falls in the elderly and the presence of varying comorbidities yielded broad results. To my knowledge, none of the literature available focused on all 29 Elixhauser Comorbidity conditions as O'Neill Roldan (2018) and this study had. Chiu et al. (2015) considered patients with certain diagnoses

or comorbidities and their association with falls and fractures. This study found patients with an anxiety diagnosis were 4.7 times more likely to experience a fall than those without such a diagnosis. Chiu et al. (2015) considered different classes of medications in this study and found an increase in benzodiazepine use with the study group of patients. R. Gelbard et al. (2014) found 72.5% of elderly patients that experienced an injurious fall had at least one comorbidity. Gelbard's study was one of the very few I could find that specifically focused on non-ground level falls – which are a type of fall defined as beginning with both feet on the ground. Gelbard found that non-ground level falls are typically cause more injury and lead to a longer length of stay.

The study by Ambrose et al. (2015) found that falls account for more than 85% of fractures in the elderly. These fractures are commonly associated with impaired balance and gait, polypharmacy, and a prior history of falls and typically involve the fracture of an already osteoporotic bone. This study led to Allali et al. (2017) developing the GOOD initiative, "Gait, Cognition, & Decline" to study gait speed in relation to a patients quality of life. As predicted by the study's hypothesis, gait speed was significantly associated with an increased risk of falls in elderly individuals because the loss of balance and stability while walking.

2.3.1 Fall-Risk-Increasing Drugs (FRIDs)

In 2011, Kragh et al. coined the term "Fall-Risk Increasing Drugs", or FRIDs. This specific list is composed of six classes of medications identified from either previously published literature or classified by the World Health Organization as drugs that increase fall risk in elderly populations (Kragh et al., 2011). The specific medication classes are psychotropics, cardiovascular, anticholinergics, antiepileptics, antiparkinsonian, and opioids medications There are many medications which are routinely used in younger patients that are not safe for the

elderly for a variety of different reasons ranging from drug-drug or drug-disease interactions to physiological changes in the elderly as they age (Kragh et al., 2011).

2.3.2 Benzodiazepines

Benzodiazepine use in the elderly is common for a variety of reasons whether for sleep disorders, anxiety, or other psychological uses. This class of medications are known to sedative effects in regular adults and those sedative effects could be amplified in some cases in elderly individuals. Ray et al. (2000) considered this topic of the sedative effects in community-dwelling elderly individuals who still remained mobile and self-sufficient. Ray et al. (2000) echoes the already understood risk of increased sedative effects and falls in elderly patients using benzodiazepines but happened to be one of the earlier studies that considered falls and the actual timing of starting a new benzodiazepine prescription. This study found the greatest risk of falls in the elderly occur within the first seven days of beginning a new benzodiazepine prescription (OR = 2.96) but still remained elevated after as time continued.

The Neutel et al. (2002) study mentioned earlier also found patients who were starting a new benzodiazepine or antipsychotic prescription were at a very high risk of injurious fall. Through the use of a case-crossover study, Neutel et al. (2002) found that these patients starting a new course of benzodiazepine or antipsychotic medication treatment were at an 11 times higher risk of falling in comparison to their control. Bogunovic and Greenfield (2004) investigated benzodiazepine use in community-dwelling elderly who still operate motor vehicles. This study found because of the sedative properties of benzodiazepines, their usage in the elderly must be carefully monitored in those community-dwelling individuals still operating motor vehicles. Benzodiazepines can contribute to psychomotor impairment due to their sedative effects; and

while also increases the risk of falls in these individuals, may also increase the risk of automobile accidents with those who may still operate motor vehicles.

2.4 Polypharmacy

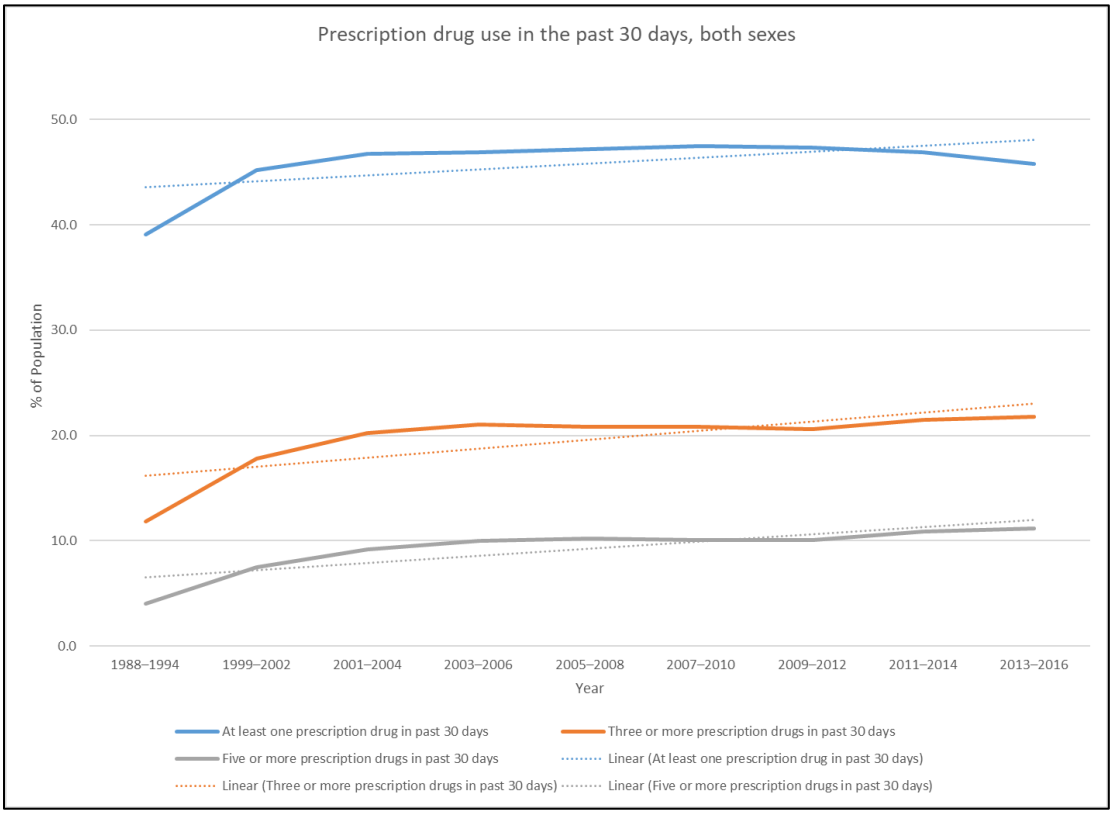
While there is no strict descriptive or quantitative definition of polypharmacy, it is generally described through the literature as the prescribing and administration of five or more medications that are clinically indicated for a patient but may be a duplication treatment or even unnecessary care for the individual (Dagli & Sharma, 2014; Endsley, 2018; Gokce Kutsal et al., 2009; Hosseini et al., 2018; Wimmer et al., 2014). In various systematic reviews of the literature, it was determined that the actual quantitative threshold for polypharmacy varied widely. Jokanovic et al. (2015) found that most studies in the review used 5 or more, 9, or 10 medications as the threshold for defining polypharmacy while Masnoon et al. (2017) found that the most common qualitative definition was 5 or more medications, but this also varied widely between two medications to 11 or more. One important distinction that Masnoon et al. (2017) makes in their literature review is that a pure numerical definition of polypharmacy should not be enough in making clinical decisions. Masnoon et al. (2017) argues that polypharmacy simply as an integer count does not take into consideration one important aspect, the pharmacology of the patients' medications along with the clinical needs of the patient. This argument for considering the actual clinical relevance of the medications and the patients' comorbidities is important according to Masnoon et al. (2017).

Considering this point by Masnoon et al. (2017), the definition of polypharmacy would only count the number of duplicate or harmful medications prescribed to the patient, not the medications that, while they might be listed as a PIM, are providing an overall positive clinical benefit to the patient. This is a valid point because the guidelines, Beers Criteria,

START/STOPP, and the others, are meant to provide high-level guidance for the clinician. Masnoon et al. (2017) presents the need for tools that consider polypharmacy, but also consider the patient as a whole to provide a more individualized approach to their medication management and eliminating harmful or unnecessary medications from their regimen.

In a recent report published by the Centers for Disease Control (CDC), the percentage of both males and females taking at least one, three or more, and five or more prescription medications has been steadily on the rise since 1988, see figure 2.3.1 (National Center for Health Statistics, 2019). Given prescription drug use across all genders and age brackets continues to rise, we can infer that the prevalence of adverse drug events, or ADEs, across all individuals also has the potential to increase.

Figure 2: Prescription drug use within 30 days, both sexes



(National Center for Health Statistics, 2019)

In a 2005 systematic review of the literature, Fulton and Allen studied polypharmacy as a general topic in the care and treatment of elderly patients. The outcomes of the Fulton and Allen (2005) study are an excellent summarization of the status of the literature on polypharmacy at that time but what is most beneficial are the areas for future research and the gaps in the literature that are noted. For example, Fulton and Allen (2005) notes that the utilization of computerized medication databases or electronic health record (EHR) systems as done in many European studies, removes the reliance on the patient to recall all of their prescriptions. Use of and EHR would also allow for the automation of different medication management tasks and would also allow physicians and hospitals to implement the different criteria sets into their clinical decision support systems (CDSS). Second, and most importantly, Fulton and Allen (2005) notes an important point in there is still no generally accepted definition on what constitutes polypharmacy. Fulton and Allen (2005) believes that the definition of polypharmacy should be based on clinical indication and whether or not the prescribed medication is appropriate for the patient, while other studies (Jokanovic et al., 2015; Olson et al., 2014) believe that the definition of polypharmacy should be quantitative in nature.

2.4.1 In regards to Potentially Inappropriate Medications

One of the most important considerations with polypharmacy and the aging and elderly population is polypharmacy with the involvement of potentially inappropriate medications, or PIMs. Beers Criteria, STOPP/START, EURO FORTA, and others all make attempts to reduce the number of PIMs prescribed to elderly patients.

A 2015 study of 124,051 Medicare beneficiaries by Lund et al. found that while interventions such as the ones noted above have displayed up to an 80% reduction in PIMs prescribed to elderly patients either at the point of care or through deprescribing, a significant

increase of PIM use in an in-patient setting was still displayed from admission to discharge. Lund et al. (2015) found that within their study population 7.7% of patients were prescribed a PIM on admission to the hospital and that number increased to 8.6% upon discharge.

In an Australian study by Price et al. (2014b), they examined the potential association between the exposure to PIMs on the Beers Criteria and unplanned hospitalizations in 251,305 elderly Western Australians. Price et al. (2014b) found that there was a direct correlation between overall PIM exposure and an elevated risk of unplanned hospitalizations. Price et al. (2014b) also found that the number of different PIMs taken and the quantity were also associated with an elevated risk of unplanned hospitalizations. In their study, 15% of unplanned hospitalizations of all patients in the study population has been due to PIM exposure and an ADE. The findings by Price et al. (2014b) support the theory of the number of PIM exposures a patient has, the greater their risk of an unplanned hospitalization.

2.4.2 In regards to Adverse Drug Reactions and Events

A serious consequence of polypharmacy are adverse drug reactions or events (ADR or ADE). The Institute of Medicine defines adverse drug events as an injury to a patient resulting from any medical intervention related to a drug while adverse drug reactions are defined as an event in which a patient experienced harm caused by a drug when taken at normal doses (Institute of Medicine, 2000). In a perfect world, medications designed to cure or alleviate diseases would do just that and not cause further harm or pain to the individual. Unfortunately, though, this is not the case. Every individual is different and unique in their own genetic way which means that every pharmaceutical has the potential to have a slightly different pharmacological action when taken.

Research has shown in an in-patient setting, ADEs comprise one-third of all hospital adverse events causing an average length of stay increase from 1.7 to 4.6 days, and accounts for more than 2 million hospital stays per year (US Department of Health and Human Services Office of Disease Prevention and Health Promotion, 2014). Additional research has also shown that in an out-patient setting, ADEs cause an estimated 1 million annual emergency department (ED) visits, 3.5 million physician or primary care office visits, and 125,000 hospital admissions annually (US Department of Health and Human Services Office of Disease Prevention and Health Promotion, 2014). Curtin et al. (2019) reports that ADEs contribute directly to 6-17% of all hospital admissions for older adults and are commonly overlooked in the elderly population. This is because ADEs commonly manifest themselves as common, nonspecific symptoms such as fatigue, constipation, confusion, and falls; all of which as generally prescribed to the aging process or "just getting old" (Curtin et al., 2019). Curtin et al. (2019, p. 2) made a feasible observation in their systematic review that "any new symptom in an older patient should be considered a drug side effect until proven otherwise."

Research in the area of polypharmacy and adverse drug events is very expansive in nature. A 2001 study by Hohl et al. found that in a population of 283 patients taking on average 4.2 medications per person, ADEs accounted for 10.6% of emergency department admissions within that patient sample. In an 11-year analysis by Bourgeois et al. (2010), they found that ADEs result in more than 100,000 hospital admissions annually with elderly patients being at the highest risk of hospitalization. In a 2012 British study by Calderón-Larrañaga et al. found that within a multicenter observational study of 79,089 patients polypharmacy was one of the risk factors [OR = 1.34] for an ADE and later subsequent hospital admission.

2.4.3 In regards to Long-Term Care Facilities

Consideration also needs to be given to elderly patients whom are no longer independent and reside in long term or assisted care facilities. These patients are more than likely to be taking more than one prescription medication, have decreased mobility increasing their susceptibility to falls and injuries, and may have cognitive impairment such as dementia (Jokanovic et al., 2015; Murray et al., 2004). The elderly and aging populations also pose unique clinical challenges when it comes to their treatment and care. For example, this group of patients typically also have physiological changes that cause different medications to absorb or excrete at different rates (Gokce Kutsal et al., 2009).

Research has also shown that the involvement of clinical pharmacists in a medication review or reconciliation process in long-term care facilities has decreased not only the overall number of prescriptions for a patient, but the number of inappropriately prescribed medications and adverse drug events, too (Thiruchelvam et al., 2017).

2.4.3.1 Complexity of medication regimens.

Jokanovic et al. (2015) presented administrative challenges in his study with regards to polypharmacy in long-term care facility patients and their medication regimens. Because of the additional number of medications that these patients require, there is a need for the appropriate number of employees in the workforce to support and care for their residents (Jokanovic et al., 2015). In 2009, Mitty performed an online survey of all members of the key assisted living professional organizations inquiring about their medication administration practices. She found that more than half of the “assisted living residences” (ALRs) administered medications to between 80 to 100% of their residents and that almost half of these ALRs use unlicensed assistive personnel, or medication aids, to administer said medications to their residents (Mitty,

2009). Through a policy review, Mitty (2009) also found that only 14 states require that a licensed nurse administer medications and 32 states permit these unlicensed assistive personnel to administer medications. Unlicensed assistive personnel do not have a deep level of clinical knowledge that should be required in administering medications, especially to a vulnerable population such as the elderly. This is worrisome due to the fact that fewer than 10 states require the reporting of a medication error or adverse drug event to the patients resident physician (Mitty, 2009).

This point is of specific discussion from an Australian study by Wimmer et al. (2014). This study took a specific look at an elderly patient's medication regimen on discharge and rated its complexity using the Medication Regimen Complexity Index (MRCI). Wimmer et al. (2014) found patients who had complex medication regimens upon discharge to their home or family had no association in future unplanned hospital admissions. Whereas patients with complex medication regimens who were discharged to a non-home or long-term care facility had a higher chance of an unplanned hospital admission based on the number of discharge medications and the presence of polypharmacy ($\geq$ 9 medications) (Wimmer et al., 2014).

On this topic, Mitty (2019) recommends that the medication aide or medication technician certification that only a few states offer to unlicensed ALR personnel should be regulated and required across the country. Not only would this provide an opportunity for training on proper medication administration and the identification of ADEs, but could also mimic the Medical Assistant certification and be one of the first stepping stones for individuals to possibly further their career or education.

2.4.4 The Prescribing Cascade Effect

A cause *and an* effect of polypharmacy is a concept called a prescribing cascade. A prescribing cascade is a clinical term that begins when healthcare providers misinterpret a newly presenting symptom or an ADE from interacting medications as an entirely new symptom of a disease and in turn, prescribes another medication to the patient (Kalisch et al., 2011; Piggott et al., 2020). The concept of prescribing cascades, their causes and effects, as well as their clinical implications have come under a new light with the growing problem of polypharmacy (Brath et al., 2018; McCarthy et al., 2019). The patients that are most at risk for prescribing cascades are those with multimorbid conditions and those reliant on others for their care and wellbeing, the elderly (Kalisch et al., 2011). Certain classes of medications either when mixed with other medications, or if certain conditions are present in the patient, the adverse effect of the added medications can become synergistic and amplified all while the physician was trying to provide relief to the patient from the first medication's side effect (Kalisch et al., 2011). For example, Brath et al. (2018) describes one of the most well-known prescribing cascades identified almost 30 years ago which linked nonsteroidal anti-inflammatory drugs (NSAIDs) to the development of hypertension and the later prescription of anti-hypertensive medications (Brath et al., 2018). Potentially not 30 years ago, but the identification of this cause, effect, and treatment could have saved the patient trips to their physician's office and lessened the amount of healthcare resources utilized.

Prescribing cascades are a serious consequence of polypharmacy, especially given the rate at which polypharmacy is seen in elderly, vulnerable populations (McCarthy et al., 2019). Kalisch et al. (2011) described a scenario where a more than common prescribing cascade took place; an elderly patient was recently prescribed an ACE-inhibitor developed a cough and was

later prescribed a codeine-based cough product, as the cough persisted the patient was then prescribed an antibiotic which in turn caused the patient to develop *Clostridium difficile* diarrhea, which later caused their hospitalization. This scenario caused an undue amount of harm to the patient, caused an unplanned and unnecessary hospitalization, which could have potentially led to the death of the patient. The most common medication classes that are typically found to be involved with prescribing cascades are drugs for dementia, antihypertensives, sedatives, opioids, NSAIDs, antiepileptics, antibiotics, and medicines for nausea (Brath et al., 2018; Kalisch et al., 2011). All these medication classes are coincidentally found on the Beers Criteria, STOPP/START, and other lists of potentially inappropriate medications. Strategies for interrupting prescribing cascades and polypharmacy are discussed later in this chapter.

2.4.5 Strategies for Reducing Polypharmacy

The primary strategy of reducing polypharmacy in not only elderly patients, but all patients, is called "deprescribing." Deprescribing is defined by Scott et al. (2015, p. 827) as "the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences." The goal of deprescribing is not to change treatment plans at will on a patient but to provide the patient the safest and most effective method of treatment for their condition. When performed appropriately for the drug or medication being deprescribed, as shown by a literature review by Scott et al. (2015), is a safe practice and often provides benefit to the patient in terms of reduced costs, medication burden, and decreased risk of various interactions or unplanned hospitalizations.

Scott et al. (2012) developed a 10-step conceptual framework for pharmacists and clinicians to accomplish two primary goals, first, to select the proper drug based on the patient and clinical indication, and second, reduce the number of inappropriate medications prescribed to the patient. Each step of the framework presented by Scott et al. (2012) was based on literature reviews and presented for use in a stepwise sequence. Shortly after in 2015, Scott et al. revised the framework into a condensed five steps:

- "(1) ascertain all drugs the patient is currently taking and the reasons for each one;
- (2) consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention;
- (3) assess each drug in regard to its current or future benefit potential compared with current or future harm or burden potential;
- (4) prioritize drugs for discontinuation that have the lowest benefit-harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes; and
- (5) implement a discontinuation regimen and monitor patients closely for improvement in outcomes or onset of adverse effects" (Scott et al., 2015, p. 829)

Using new and advanced technological measures discussed later in this chapter, the framework developed by Scott et al. (2012) could easily be streamlined into a useful clinical utility once the framework itself is validated for use.

Research in this area has shown with successful attempts at reducing polypharmacy and the number of medications prescribed to a patient. A 2010 study by Garfinkel and Mangin applied the Good Palliative-Geriatric Practice algorithm to a sample of 70 elderly patients in an attempt to reduce polypharmacy and the "medication burden" on these patients (Garfinkel & Mangin, 2010, p. 1648). Using this algorithm, Garfinkel and Mangin (2010) recommended the

discontinuation of 311 medications in 64 of the 70 participants, an overall 81% reduction in polypharmacy with no reported significant adverse drug events due to the discontinued medications.

Another strategy for decreasing polypharmacy was developed by Drenth-van Maanen et al. (2009) called the Prescribing Optimization Method or POM. The POM was designed to assist family and general medicine physicians reduce the amount of polypharmacy on their elderly patients through 6 guided questions:

- "Is undertreatment present and addition of medication indicated;
- Does the patient adhere to his/her medication schedule;
- Which drug(s) can be withdrawn or which drugs(s) is/are inappropriate for the patient;
- Which adverse effects are present;
- Which clinically relevant interactions are to be expected; and
- Should the dose, dose frequency and/or form of the drug be adjusted" (Drenth-van Maanen et al., 2009, pp. 690-691)

To test the efficiency of the newly designed POM tool, Drenth-van Maanen et al. (2009) first asked 45 physicians to review and deprescribe medications from two patients randomly selected from a pool of ten. Following this, the group of physicians were trained on the POM framework and optimization process then asked to perform the review and deprescribing process again on the same case. What Drenth-van Maanen et al. (2009) found was an increase in appropriate prescribing optimization from 34.7% pre-POM training to 48.1% post-training. Overall, the POM framework significantly increased valid deprescribing decisions in complex multimorbid elderly patients (Drenth-van Maanen et al., 2009).

2.4.5.1 ARMOR.

In 2009, Dr. Raza Haque, MD developed the ARMOR tool to address the growing problem of polypharmacy seen in long-term care facilities. The ARMOR tool has five components, Assess, Review, Minimize, Optimize, and Reassess, and when implemented and used properly will consider not only the patient's pharmaceutical profile, but their clinical history and their overall functional status (Haque, 2009). The first implementation of the ARMOR protocol was after its development by Haque (2009) in a long-term care facility using an interdisciplinary team of medical professionals to target geriatric admissions and those patients with frequent falls. This interdisciplinary team consisted of a medical director, director level nursing staff, occupational and recreational therapists, social workers, and pharmacists (Haque, 2009). The ARMOR process for managing polypharmacy begins with a regular review and analysis of the patient's charts to examine dosing as well as the presence of inappropriate medications (Haque, 2009). The team members would then report on their subjective and objective observations of the patient as well as any proposed changes to their current medication regimen (Haque, 2009). After a consensus was reached for each patient's profile, the facilities medical director would discuss the team's recommendations for modifications to the patient's care (Haque, 2009).

The ARMOR tool for reducing polypharmacy was effective in significantly reducing polypharmacy, the cost of care, and the number of hospitalizations from patients within the specific long-term care facility (Haque, 2009). Haque (2009) also found that the ARMOR tool reduced the number of falls and patient behaviors that may lead to self-harm. Given the results of ARMOR's first use, Haque (2009) expanded the scope of included patients to those receiving 9 or more medications and those admitted for rehabilitation. Haque (2009) found significant

improvement in the facilities quality indicators (QI) tracked by the facility in comparison to their state and national averages. In a follow-up study by Haque and Alavi (2019) found that utilizing ARMOR with an interdisciplinary team saw a significant reduction in the number of psychotropic medications prescribed to LTC patients within the study's facility. This finding is particularly important because psychotropic medications have been shown to have a significant association with falls in elderly patients (Huang et al., 2012). Studies have shown that falls are not only one of the leading causes of elderly hospitalizations and healthcare expenditures, but happen to also be one of the leading causes of morbidity and mortality in elderly patients with multiple co-morbidities (Rondi Gelbard et al., 2014; Huang et al., 2012).

2.4.5.2 The Brown Bag Method.

The brown bag method or brown bag approach is a well employed method for reducing polypharmacy in various clinical settings. The brown bag method is a medication review process where the patient collects all their medications including prescriptions, over-the-counter medications, vitamins, and herbal supplements together and brings them into their next provider appointment (Dovjak, 2012; Kim & Parish, 2017). The goal of the brown bag method is to review all of the patient's medications, identify medications that can be discontinued, medications or supplements that could be causing interactions, reconcile the patient's "brown bag" with the medications listed in their medical record, and to educate the patient on their use of their medications (Kim & Parish, 2017). Studies have shown this to be an effective method of not only reducing the number of medications the patient is taking, but reducing the number of potential adverse drug events as well.

In a 2015 study by O'Connell et al., found in a population of 85 patients in a convenience sampling from a senior center, that 40% of the patient's drug-related problems were due to

inappropriate drug selections on behalf of the prescriber, and 23% due to inappropriate doses being prescribed to the patent. The study found due to the patient's level of comfort with the brown bag review process begin able to talk and ask questions in a comfortable environment, 63% of the recommendations made by the clinical staff were implemented by the participants (O'Connell et al., 2015). Interestingly, a 2004 study by Williams et al. found that the patients who participated in a randomized control trial to receive a brown bag medication review that most patients who participated and received suggested changes to their medication regimens were hesitant to make such changes. Williams et al. (2004) cite one of the reasons why patients may have been resistant to the suggested changes because their primary physician was not directly involved in the medication review process. Williams et al. (2004) found that only 33% of the time, patients who were involved in the medication review process accepted the recommendations of the reviews *only* after they were told their primary physician was informed of and approved the recommended changes. In a similar type study by Garfinkel (2017) found that in some cases it's not the patient that is resistant to the change in regimen, it's the physician themselves.

2.4.6 Addressing Polypharmacy in the Primary Care Setting

One area lacking in the literature regarding polypharmacy is addressing the topic at one of the initial points of contact, the primary care setting. Especially in the elderly population, building a strong patient-physician relationship is crucial. Studies on the topic dating back to 1996 emphasize this point and the physician should lay the ground work starting with the initial meeting with the patient (McCormick et al., 1996). A 2015 literature review confirmed a known gap in the literature, the need for standardized strategies in addressing polypharmacy in the primary care setting and the effects of these interventions on patient outcomes. Nevertheless,

addressing polypharmacy in any way possible is important on behalf of the patient overall care and wellbeing.

2.5 Predicting Readmissions

We have shown there is an understanding of how Beers Criteria, different potentially inappropriate medications, adverse drug events, and unplanned hospitalization rates are all associated with each other through different studies in the literature. Researchers have begun to take the information they have learned and the data they have available to them in attempts to build a model able to predict a future hospital admission or indicate a patient may be at risk for a future hospitalization. There is a vast amount of literature on the topic of predicting readmissions but we have found that many published studies are focused on a specific disease state or chronic condition. For example, a 2016 study by Tandon et al. attempts to predict unplanned hospitalizations in patients with cirrhosis, a 2014 study by Manzano et al. attempts to determine patterns and predictors of unplanned hospitalizations in elderly patients with GI cancer, or a 2019 study by Rothenberg et al. attempting to predict unplanned admissions after elective outpatient surgery. There are very few pieces of published literature that use Beers Criteria medications, or other PIM lists, in an attempt to build a prediction model for unplanned hospitalizations.

A 2014 study by Louis et al. displays an attempt at building a risk of hospitalization prediction tool in 3,726,380 adults over the age of 18 in a specific region of Italy. While this study is not specific to elderly patients, the outcomes are substantial and should be discussed. The prediction model built by Louis et al. (2014) was able to predict hospitalizations in the cohort of patients with a c-statistic of 0.856 overall. This specific model took into consideration the patient's age, gender, demographics, healthcare utilization, cardiovascular disease, diabetes,

chronic renal failure, a history of cardiovascular medications, and the presence of polypharmacy; all variables used by Louis et al. (2014) are also available in the dataset for this study (Louis et al., 2014). Louis et al. (2014) also tested their 2012 prediction model built from 2011 data on data available from 2010 to build a 2011 prediction model. Louis et al. (2014) found between the two year's models built, there was only a slight change in c-statistic (2011 = 0.853, 2012 = 0.856). This indicated to Louis et al. (2014) the model build can be used on future data as it becomes available and provide reliable results.

A second readmission prediction tool, the 80+ Score, which takes into consideration patient demographics as well as their pharmacologic data as well (Alassaad et al., 2015). The 80+ score was built and internally validated against a sample of 368 elderly patients who were 80 years or older from a Swedish university medical center (Alassaad et al., 2015). The 80+ score and the study by Alassaad et al. (2015) is one of the first studies to include the patients' medication history as one of the potential indicators or causes for an unplanned hospital readmission. The final model for the 80+ score by Alassaad et al. (2015) included the following risk factors: eGFR separated into for levels of kidney function, social support (i.e. discharge location, nursing home vs. family home), presence of pulmonary diseases (asthma or COPD), presence of malignant diseases, use of prescription drugs for peptic ulcers or GERD, use of prescription opioids, and use of prescription non-TCA-antidepressants. The 80+ score is based on a point-scoring system and is presented in figure three. The 80+ score, to my knowledge at the time of this writing, is the only prediction model for unplanned hospitalizations that includes a patients prior pharmaceutical history with a c-statistic >0.7, at 0.72 (Alassaad et al., 2015). While the 80+ score is only internally validated, Schwab et al. (2019) make reference to the prediction model and the potential necessity to externally validate it for greater use.

Figure 3: Data used for the 80+ point scoring system

	Proportion of patients in each category	β	W and W_{ref} for each category	Regression unit for each category	Point score
eGFR*		−0.012			
>90 mL/min	0.014		105 mL/min=W_{ref}		0
60–89 mL/min	0.128		74.5 mL/min	0.397	1
30–59 mL/min	0.552		54.5 mL/min	0.787	2
<30 mL/min	0.307		17.5 mL/min	1.138	3
Social support					
Living alone or with spouse	0.818	0.481	0=W_{ref}	0	0
Nursing home	0.182		1	0.481	1
Pulmonary disease†		0.607			
No	0.878		0=W_{ref}	0	0
Yes	0.122		1	0.607	2
Malignant disease‡		0.506			
No	0.834		0=W_{ref}	0	0
Yes	0.166		1	0.506	1
Prescription of drug for peptic ulcer and GERD		0.362			
No	0.674		0=W_{ref}	0	0
Yes	0.326		1	0.362	1
Prescription of opioid drug		0.724			
No	0.821		0=W_{ref}	0	0
Yes	0.179		1	0.724	2
Prescription of non-TCA-antidepressant drug		−0.558			
No	0.791		0=W_{ref}	0	0
Yes	0.209		1	−0.558	−2
The average 1-year event-free rate=0.3215§					

Regression unit for each category=β(W−W_{ref}).
Point score=β(W−W_{ref})/B.
*Cockroft-Gault formula eGFR.
†Asthma or COPD.
‡Past or present.
§The Kaplan–Meier estimate of the event-free rate at the mean values of the risk factors.
COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; TCA, tricyclic antidepressant.

(Alassaad et al., 2015, p. 3)

An additional prediction model built by LaMantia et al. (2010) was able to produce a c-statistic of 0.73 when the model included age, triage score, heart rate, diastolic blood pressure, and the patient's chief complaint. This model is different than the goal of this study though, LaMantia et al. (2010) built a model in an attempt to streamline hospital admissions for elderly patients presenting directly to the ED, not to predict unplanned hospitalizations. LaMantia et al. (2010) attempted to further extrapolate their model attempting to predict another ED visit 30 days post-discharge in the same population of elderly patients, this modeling attempt also failed the c-statistic threshold. LaMantia et al. (2010) attributed the inability to build such a prediction model to the high rate of return in elderly patients to emergency departments ranging from their chronic medical conditions, to inadequate primary care availability, to the patient's social or psychological characteristics.

Other attempts at building prediction models for unplanned hospitalizations have not been as successful as the 80+ score by Alassaad et al. (2015). A study by Parameswaran Nair, Chalmers, Connolly, et al. (2016) attempted to build a prediction model they called the Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients, or PADR-EC. This model was built off a patient sample of 768 patients aged 65 years or older with admission to two specified Italian hospitals. Parameswaran Nair, Chalmers, Connolly, et al. (2016) found that even with 92.2% of the total admissions (n = 115), their model to predict hospitalization in these patients only yielded a ROC c-statistic of 0.70 which decreased to 0.67 in a later validation sample of patients.

2.5.1 In regards to Adverse Drug Events

In a 2015 German study by Henschel et al., they sought to understand the hospitalization rates for 647,073 patients aged 65 years or older as of the year 2010 and received a PIM as indicated by the German PRISCUS list of inappropriate medications. Henschel et al. (2015) used propensity score matching to build a control group of patients at an equivalent risk level but who did not receive any of the medications on the PRISCUS list. Despite using a different PIM criteria list local to Germany, the outcome of this study echoes what is seen already through the literature. Henschel et al. (2015) found patients in the PIM group experienced more ADEs and had a higher chance of hospitalization when compared to the non-PIM control group.

In a 2017 study by Shapiro et al. studying high-risk medications in 717 frail elderly patients in a long-term care facility, having more than more than four medications doubled the risk of readmission within 30-days of their initial discharge. The patients in the Shapiro et al. (2017) study though, have a much higher mean count of medications per person (14.1) and a

higher mean Charlson comorbidity index score (≥6) than seen in other published literature thus far.

CHAPTER III METHODOLOGY

As previously mentioned, the data used in this study is the dataset used by O'Neill Roldan's (2018) study, *Effect of Beers criteria on healthcare utilization and costs in community-dwelling elderly patients*. The initial patient sample was extracted from the 2013 edition of the Truven Health Marketscan® Commercial Claims and Encounters Database purchased by and housed at the Comparative Effectiveness & Data Analytics Research Resource (CEDAR) at the Medical University of South Carolina, Charleston, SC. All statistical analysis performed using SAS 9.4 (Cary, NC) at $\alpha = 0.05$.

3.1 Original Data Use by O'Neill Roldan (2018)

O'Neill Roldan's 2018 retrospective cohort study identified patients 65 years and older, who were community-dwelling patients, and were observed taking a medication present on the Beers Criteria during the selected baseline period of January 1, 2013 – March 31, 2013 (n= 3,512,540) from within the 2013 edition of the Marketscan® database. Once the initial patient sample was extracted, O'Neill Roldan grouped the patients based on those whom had taken at least one medication on the 2012 revision of the Beers Criteria and those who had not (n= 1,297,636 vs. 2,214,904), this step is crucial in the preparation of the propensity score matching process. Because the Marketscan® database contained commercial claims, the study was not limited to only the claims submitted to Medicare but was able to include those elderly patients that had commercial insurance to supplement their existing Medicare plan (O'Neill Roldan, 2018).

To select patients to place in the experimental, or Beers Criteria, arm of the study, O'Neill Roldan (2018) needed to translate the list of potentially inappropriate medications on the Beers Criteria into their individual National Drug Code (NDC), including secondary codes such

as packaging type or packaging quantity changes. The NDC is comprised of three components, first the labeler or manufacturer identifier, second the product code which identifies the strength, dosage form, and formulation, and third the package code to distinguish between different sizes and types (U.S. Food and Drug Administration, 2019). O'Neill Roldan (2018) reported that the 138 medications on the Beers Criteria were converted to a total of 73,644 NDC codes to identify the patients needing to be included in the experimental arm of the study. Inclusion into the control arm of O'Neill Roldan's study required the absence of any of the NDC codes identified as being a PIM on the Beers Criteria.

Once O'Neill Roldan (2018) constructed the two sample groups, the study then built a Charlson Comorbidity Index score and a frailty index score which was then subdivided into three dichotomous variables, robust, pre-frail, and frail. O'Neill Roldan (2018) also included a dichotomous variable to indicate if the patient had any type of hospital admission during the selected baseline period. O'Neill Roldan also used information from outpatient visits to construct an Elixhauser Comorbidity Index score as well as a dichotomous variable for 26 of the 29 Elixhauser conditions indicating their presence for each patient in the dataset, see table 3. As an extension from the Marketscan® database, O'Neill Roldan (2018) was also able to leverage the information contained within the Marketscan® database to calculate the patient's total inpatient, outpatient, and prescription medications costs as well. Because the Marketscan® database included prescription drug data and claim information, this was one of the primary reasons O'Neill Roldan (2018) selected this data source.

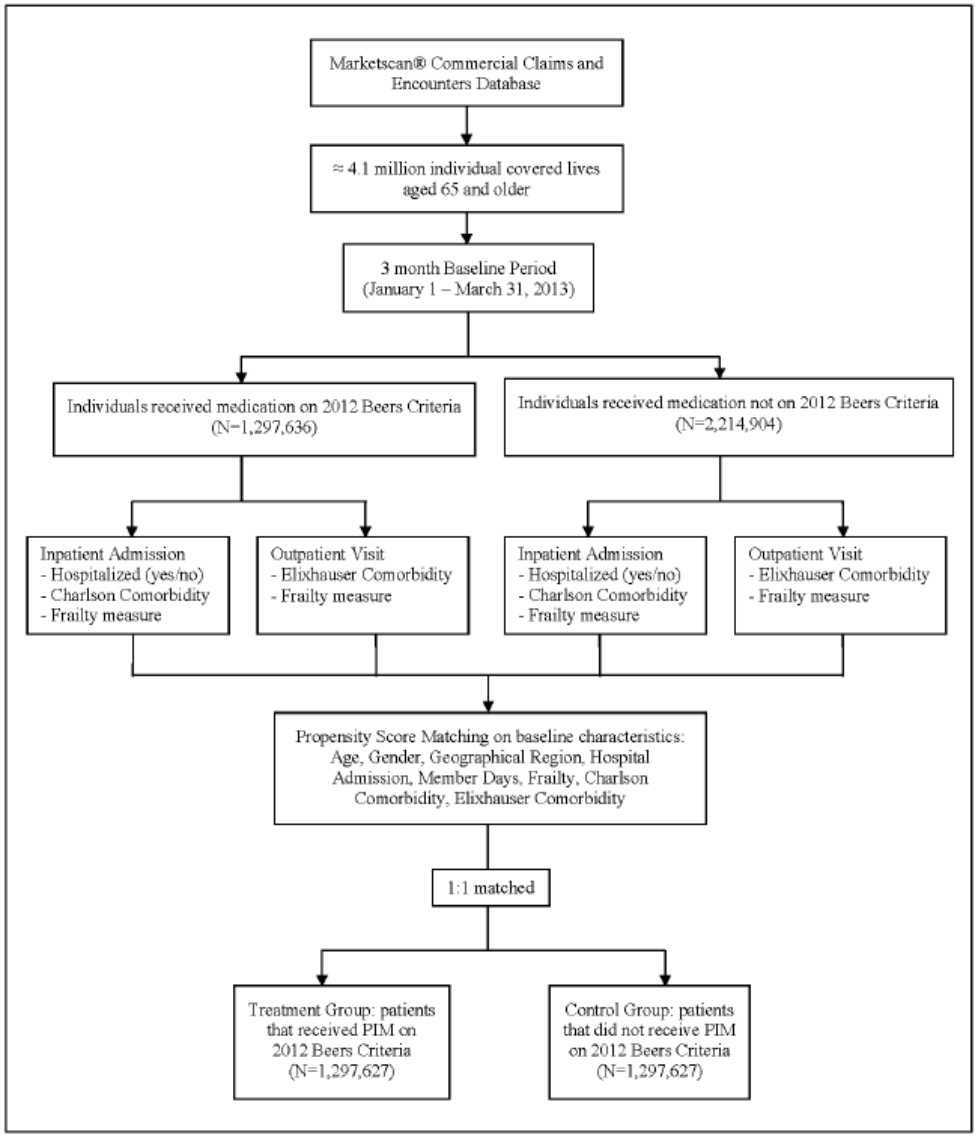
Table 1
Elixhauser Comorbidity conditions included and excluded

Included	Excluded
Asthma	Chronic Ulcers of the Skin
Cardiac Dysrhythmias	Late Stroke
Chronic Obstructive Pulmonary Disease	Paralysis
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	
Vertigo	

(O'Neill Roldan, 2018)

The treatment and control sampling methodology from O'Neill Roldan (2018) is presented in figure 3.1.1 below.

Figure 4: Treatment and Control Sample Design



(O'Neill Roldan, 2018)

With the selection and grouping of the patient sample based on the presence of any Beers Criteria medications, O'Neill Roldan (2018) could then begin the propensity score matching process between the two patient groups. Propensity score matching is the process of assigning a score to a subject in an observational or retrospective study equaling the conditional probability of that subject being included in the treatment arm of the study (Austin, 2011; Gant & Crowland, 2017). Propensity score matching allows researchers to reduce confounding between variables

and allows for observational or retrospective types of studies to mimic the structure of a randomized control trial (Gant & Crowland, 2017). O'Neill Roldan (2018, p. 81) used the following variables to match patients in both arms of the study: "age, gender, geographic region, hospital admission, member days [days insured], frailty, Charlson Comorbidity Index, and the 26 Elixhauser Comorbidity Indicators." Through the use of these matching variables, O'Neill Roldan (2018) was able to complete a 1:1 propensity score match between all 1.297 million patients in the Beers arm of the study to 1.297 million patients in the control arm. Those patients in the control arm of the study were removed from the data set if they were not matched to a patient in the experimental arm of the study.

A data dictionary containing the variables and descriptions from the data used by O'Neill Roldan (2018) is available in Table 18.

3.1.1 Propensity Score Matching

Many studies that examine the relationship between PIMs and unplanned hospitalizations utilize a statistical method called propensity score matching. Propensity score matching is the process in which a study is able to mimic randomization between a control and experimental group when using retrospective data or if the study has already begun without randomization taking place (Henschel et al., 2015). The propensity score matching process allows researchers to directly compare the effect of an intervention on two groups of participants in the matched sample (Austin, 2011).

3.2 Research Design and Secondary Use of Data Set

Our study is a retrospective cohort study using propensity-score matched patients in a Beers Criteria medication exposed and non-exposed group. The Beers Criteria classification and propensity-score matching was performed by O'Neill Roland (2018) and augmentations of that

dataset would be necessary to fit the purposed of this study. The first set of data augmentations needed required the extraction of data for hospital admissions and emergency department visits for the specific ICD-9 codes for falls and fractures, and confusion and delirium. To achieve this, the patients ENROLID was matched back to the original MarketScan® data set and the primary ICD-9 code for the admission was identified. The presence of an ICD-9 code for falls present in Table 2 was indicated in the dataset as (falls=1) and the presence of an ICD-9 code for confusion and delirium admissions present in Table 3 was indicated in the dataset as (dill=1). These dichotomous variables were set to "0" if the primary ICD-9 code for the admission was not present in the inclusion list.

Within the augmented dataset was created drug sub-group specifications for the specific medication classes associated with falls, delirium, and confusion and a residual group named "Other Beers Drugs" to capture the use of any other Beers Criteria medication not specific to a named medication class. These Beers Criteria indicator variables are discussed in more detail in section 3.2.2 below. The final dataset contained roughly 2.6 million patients and through the propensity score matching by O'Neill Roldan (2018), this dataset had 1,297,627 patients who took any Beers Criteria medications during January – March 2013 and an equal amount of patients who took no Beers Criteria medications in January – March 2013.

3.2.1 Indicator Variables

To identify and construct indicator variables for falls and fractures, this study selected ICD-9 "E" codes – "E" for external causes of injuries and poisonings. Listed in Table 2, the selected ICD-9 codes for falls and fractures ranged from accidental falls from stairs or steps, slipping, tripping or stumbling, to fractures. The same procedure was performed for confusion

and delirium admissions. Listed in Table 3, this study considered drug-induced delirium, subacute delirium, reactive confusion, psychoses, hallucinations, and altered mental status.

Table 2
List of ICD-9-CM codes for identification of falls

E Code	Code Description
E880	Accidental fall on or from stairs or steps
E881	Accidental fall on or from ladders or scaffolding
E882	Accidental fall from or out of building or other structure
E883	Accidental fall into hole or other opening in surface
E884	Other accidental falls from one level to another
E885	Accidental fall on same level from slipping tripping or stumbling
E886	Fall on same level from collision, pushing, or shoving, by or with other person
E887	Fracture, cause unspecified
E888	Other and unspecified fall

Table 3
List of ICD-9-CM codes for identification of delirium

ICD-9 Code	Code Description
292.81	Drug-induced delirium
293.0	Delirium due to conditions classified elsewhere
293.1	Subacute delirium
298.2	Reactive confusion
298.9	Unspecified psychosis
780.1	Hallucinations
780.97	Altered mental status

The presence of either a fall or fracture ICD-9 “E” code, or a confusion or delirium ICD-9 code was indicated in the dataset using the “Falls” or “Dill” indicator variable. The value of 1 indicated the presence and the value of 0 indicated the absence.

3.2.2 Selected Beers Criteria Medication Classes

Following the creation of the falls and delirium admission indicator variables, two categorical variables were created to indicate the Beers Medication class present for the patient.

Table 4 indicates the Beers Criteria medication classes selected for falls and fractures and Table 5 indicates the Beers Criteria medication classes selected for confusion and delirium.

Table 4
Selected Beers Medication classes for falls and fractures

Medication Class	Label
Antipsychotics	APsyco
Barbiturates	Barbit
Benzodiazepines	Benzo
Sedatives	Sedativ
Tricyclic antidepressants	TCA

Table 5
Selected Beers Medication classes for confusion and delirium

Medication Class	Label
Antihistamines	AHist
Antipsychotics	APsycho
Benzodiazepines	Benzo
Narcotics	Narcoti

All other Beers Criteria medication classes were indicated using an "OtherBeers" category. If the patient was not exposed to any Beers Criteria medications, they were indicated using the "NoBeers" category.

3.3 Statistical Analysis

To begin the statistical analysis of this dataset, we will begin by determining the frequency of the categorical variables and the means and standard deviations of the continuous variables to build a patient descriptive characteristics table grouped by the Beers Criteria medication indicator *(AnyBeers)*. Significant differences between the two groups will be determined using Pearson Chi-square tests for categorical variables and either Nonparametric

methods, such as the Mann-Whitney U two-sample test, or using independent-samples t-tests for non-normally and normally distributed continuous data, respectively.

Once the most frequent conditions are identified in the dataset, we will then be able to study the association between various Beers Criteria medication classes these patients are taking and the presence of hospital admissions. Significance between these categorical variables will be determined using the Pearson Chi-square test, Elixhauser conditions that show significant differences between the two patient sample groups will be identified and used as a starting point for further analysis. Based on the specific Elixhauser conditions that are selected to build models for, we will construct sub-tables to show the specific patient demographics for the selected Elixhauser conditions.

Once associations are determined and ranked based on statistical significance, we then used a multiple regression model to control for the variables to determine which in our dataset would contribute significantly to a model. The regression models will consider the 26/29 Elixhauser conditions, patient demographics, frailty measures, and the patient's calculated Charlson Comorbidity Index score. A gamma log-linked regression model will be used to determine costs for each of the selected Beers medication classes for inpatient, outpatient, and pharmacy Rx specific costs as well as an estimated total study cost as compared to the NoBeers baseline costs.

3.4 Protection of Human Subjects

This study is exempt from the MUSC Institutional Review Board processes as the data analyzed does not meet the criteria for human subjects as per the definition contained in the MUSC Human Research Protection Program guide, section 1.3 Definition of Terms, page 12, item 106 Human Subject. The data used in this study is deidentified to meet the criteria listed in

MUSC Human Research Protection Program guide, section 1.3 Definition of Terms, page 7, item 53, part B, containing none of the 18 personal identifiers.

CHAPTER IV RESULTS

The patient sample in this study (n = 2,595,254) was first analyzed following the same grouping methodology as used by O'Neill Roldan (2018) using the AnyBeers variable to group patients based on their use of Beers Criteria medications during the study period. This structuring of the dataset retains the propensity score matching as completed by the original study. Through this analysis it was determined that the study population for both Beers and non-Beers use was predominately female and were roughly 74 years of age. Patients in the Beers versus non-Beers categories were more frail (0.451 vs. 0.353, $p < 0.0001$), had a higher mean Charlson score (0.09 vs. 0.07, $p < 0.0001$), and had a significantly larger number of delirium (43,117 vs. 25,727, $p < 0.0001$) and falls (32,725 vs. 26,255, $p < 0.0001$) admissions than the non-beers group. It was determined there was a statistically significant difference in total treatment cost between the two groups as well. Patients in the Beers group had a total mean treatment cost of almost $15,000, which is roughly $6,400 dollars more than the non-Beers group ($14,987 vs. 8,580, $p < 0.0001$). Patients exposed to Beers medications also experienced a significantly larger number of hospitalizations for any reason as compared to the non-Beers patients (213,106 vs. 130,489, $p < 0.001$). Additionally, when comparing the average length of stay between the Beers and non-Beers patients, it was determined that the additional one-half day difference in length of stay was significant between the Beers and non-Beers patients (6.63 vs. 6.11, $p < 0.0001$).

Table 6
Descriptive statistics for all patients by Beers Criteria medication status

Characteristic	Patients receiving no Beers Medications (n = 1,297,627)	Patients receiving ≥1 Beers Medications (n = 1,297,627)	*p*-value
Age, years	74.06 ± 6.9	73.93 ± 6.8	<.0001
Hospital Admissions/person	1.197 ± 0.6	1.263 ± 0.7	<.0001
Patients with Any Hospital Admission	130,489 (10.1%)	213,106 (16.4%)	<.0001
Charlson Score	0.07 ± 0.5	0.09 ± 0.6	<.0001
Length of Stay, days	6.11 ± 9.4	6.63 ± 9.8	<.0001
Delirium Admissions	25,727 (2.0%)	43,117 (3.3%)	<.0001
Falls Admissions	26,255 (2.0%)	32,725 (2.5%)	<.0001
Female	750,416 (57.8%)	757,171 (58.3%)	<.0001
Frailty Category			<.0001
Frailty Cat 0 (Robust)	949,620 (73.2%)	930,800 (71.7%)	
Frailty Cat 1 (Pre-frail)	300,759 (23.2%)	311,359 (24.0)	
Frailty Cat 2 (Frail)	47,248 (3.6%)	55,468 (4.3%)	
Frailty Score	0.35 ± 2.2	0.45 ± 2.4	<.0001
Insured Days (Member Days)	355 ± 41.8	355 ± 43.5	<.0001
Geographical Region			<.0001
Region 1 (Northeast)	293,690 (22.6%)	291,603 (22.5%)	
Region 2 (North Central)	356,401 (27.5%)	359,885 (27.7%)	
Region 3 (South)	372,216 (28.7%)	378,048 (29.1%)	
Region 4 (West)	263,344 (20.3%)	257,402 (19.8%)	
Region 5 (Unknown)	11,976 (0.9%)	10,689 (0.8%)	
Total Treatment Cost	$ 8,580 ± 30,962	$ 14,987 ± 36,033	<.0001
Inpatient Cost	$ 2,566 ± 16,055	$ 4,760 ± 23,238	<.0001
Outpatient Cost	$ 4,912 ± 23,962	$ 7,492 ± 21,909	<.0001
Pharmacy (Rx) Cost	$ 1,102 ± 3,633	$ 2,734 ± 5,590	<.0001

*Data expressed as mean ± standard deviation (SD) or otherwise indicated as Number (%), and compared by *t*-test or by Mann-Whitney *U*-test.

4.1 Falls and Fractures

When considering the patient population (n = 2,595,254) in regards to falls and fractures admissions, the analysis determined between the falls patients (n = 58,980) and non-falls patients (n = 2,536,274) had a larger gap in age (77.52 vs. 73.91, $p < 0.0001$) and both groups again being predominately female (65.8% vs. 57.9%, $p < 0.0001$). The patients who experienced a fall/fracture admission, similarly to the Beers exposure grouping discussed in the last section, the

falls patients had a significantly higher Charlson score (0.19 vs. 0.08, $p < 0.0001$) and frailty score (1.78 vs. 0.37, $p < 0.0001$) as compared to patients without a fall or fracture admission. The falls patients in the study population also experienced a significantly longer average length of stay (7.84 vs. 6.32, $p < 0.0001$) and a significantly higher mean number of hospital admissions per person (1.354 vs. 1.23, $p < 0.0001$). Interestingly, patients without falls admissions, 49.9% of these patients were taking at least one Beers Criteria medication. Geographically the analysis determined the majority of the falls and fractures patients were located in the North Central region while the majority of non-falls patients were located in the South region. Lastly, there is a $15,820 dollar difference in total treatment cost between the patients with falls admissions and those without ($27,244 vs. $11,424, $p < 0.0001$).

Table 7
Descriptive statistics for all patients by falls admission

Characteristic	Patients with no falls admissions (n = 2,536,274)	Patients with falls admissions (n = 58,980)	*p*-value
Age, years	73.91 ± 6.8	77.52 ± 7.1	<.0001
Hospital Admissions/person	1.23 ± 0.6	1.354 ± 0.8	<.0001
Patients with Any Hospital Admission	318,748 (12.3%)	24,847 (1.0%)	<.0001
Patients taking Any Beers Medications	1,264,902 (49.9%)	32,725 (55.5%)	<.0001
Falls Admissions/person	---	2.6 ± 3.5	
Fall Drug Days	0.86 ± 21.7	2.82 ± 37.7	<.001
Charlson Score	0.08 ± 0.6	0.19 ± 0.8	<.0001
Length of Stay, days	6.32 ± 9.6	7.84 ± 10.7	<.0001
Female	1,468,759 (57.9%)	38,828 (65.8%)	<.0001
Frailty Category			<.0001
Frailty Cat 0 (Robust)	1,851,882 (73.0%)	28,538 (48.4%)	
Frailty Cat 1 (Pre-frail)	590,096 (23.3%)	22,022 (37.5%)	
Frailty Cat 2 (Frail)	94,296 (3.7%)	8,420 (14.3%)	
Frailty Score	0.37 ± 2.3	1.78 ± 3.5	<.0001
Insured Days (Member Days)	355 ± 42.8	357 ± 33.3	<.0001
Geographical Region			<.0001
Region 1 (Northeast)	572,041 (22.6%)	12,892 (21.9%)	
Region 2 (North Central)	697,119 (27.5%)	19,167 (32.5%)	
Region 3 (South)	736,512 (29.1%)	13,752 (23.3%)	
Region 4 (West)	508,093 (20.0%)	12,653 (21.4%)	
Region 5 (Unknown)	22,149 (0.9%)	516 (0.9%)	
Total Treatment Cost	$ 11,424 ± 33,350	$ 27,244 ± 45,144	<.0001
Inpatient Cost	$ 3,499 ± 19,677	$ 10,742 ± 30,069	<.0001
Outpatient Cost	$ 6,018 ± 22,897	$ 14,115 ± 25,644	<.0001
Pharmacy (Rx) Cost	$ 1,907 ± 4,705	$ 2,387 ± 7,420	<.0001

*Data expressed as mean ± standard deviation (SD) or otherwise indicated as Number (%), and compared by *t*-test or by Mann-Whitney *U*-test.

4.1.1 Medication Class Frequency Analysis

Utilizing the Beers Criteria medication classes selected as ones causing disruptions in balance and gait which could lead to an injurious fall, a frequency analysis on the prevalence of each medication class by falls and non-falls patients was performed. For the purposes of this portion of the analysis, the Beers Criteria medication classes selected were: antipsychotics, barbiturates, benzodiazepines, sedatives, and tricyclic antidepressants. It was determined that in

the study population the most commonly used medication class in patients with falls admissions were benzodiazepines (n = 10,598), followed by antipsychotics, sedatives, tricyclic antidepressants, and lastly barbiturates (n = 4,008; 2,040; 898; and 231 patients respectively). For the non-falls patients, it was determined the most frequently used medication class was also benzodiazepines (n = 354,080), but was followed by sedatives (n = 94,429), not antipsychotics as with the falls patients. Following sedative use with the non-falls patients were antipsychotics, tricyclic antidepressants, and lastly barbiturates (n = 58,753; 33,999; and 9,878 patients respectively). A lower overall percentage of falls patients were found to be taking a medication in any other Beers Criteria medication class or no Beers medications at all as compared to the non-falls patients (Other Beers: 25.4% vs. 28.2%; No Beers: 44.5% vs. 50.1%, $p < 0.0001$).

Table 8
Incidence of falls admissions by Beers Medications categories

	Patients with no fall admissions (n = 2,536,274)	Patients with ≥1 fall admission (n = 58,980)	*p*-value
Beers Criteria Grouping			<.0001
Antipsychotics[a]	58,753 (2.3%)	4,008 (6.8%)	
Barbiturates	9,878 (0.4%)	231 (0.4%)	
Benzodiazepines[b]	354,080 (14.0%)	10,598 (18.0%)	
Sedatives[c]	94,429 (3.6%)	2,040 (3.5%)	
TCA[d]	33,999 (1.3%)	898 (1.5%)	
Other Medication Classes[e]	715,763 (28.2%)	14,950 (25.4%)	
No Beers Medications Present	1,271,372 (50.1%)	26,255 (44.5%)	

a Includes first- and second-generation antipsychotics
b Includes short- and long-acting benzodiazepines
c Includes Nonbarbiturate and nonbenzodiazepine sedatives hypnotics
d Includes tertiary tricyclic antidepressants
e Includes any other classification of Beers Criteria medications

4.1.2 Logistic Regression Results

A logistic regression analysis was performed to determine if there is an increase in risk of hospitalization from falls between patients taking each of the specified Beers potential fall risk medication classes listed in section 4.1.1 compared to those taking no Beers medications. The

five medication classes, along with an “Other Beers Medication” categorical variable was compared against a baseline of the “No Beers Medications” category. The analysis determined antipsychotics posed the highest risk of an injurious fall or fracture by 1.93 times (95% CI: 1.865, 2.007), benzodiazepines increased hospitalization due to fall risk by 1.37 times (95% CI: 1.341, 1.405), tricyclic antidepressants by 1.34 times (95% CI: 1.245, 1.427), and lastly, barbiturates increased this risk by 1.3 times (95% CI: 1.13, 1.472). Sedatives only increased the risk of hospitalization by 1.18 times (95% CI: 1.13, 1.427) while patients taking any other medications present on the Beers Criteria were found to have only a very slight risk increase of 1.07 times (95% CI: 1.051, 1.095).

In addition to the specific Beers Criteria medication classes this study analyzed, it is worth noting other patient characteristics in the final logistic regression model that also had a significant increase in risk of a fall or fracture admission. One of these characteristics most notably is the changes in frailty category. Using a robust patient as the baseline (frailcat_0), patients who moved into the pre-frail category had a 1.8 times (95% CI: 1.777, 1.847) increase in hospitalization risk while patients who moved into the frail category had a 2.7 times (95% CI: 2.595, 2.778) increase in risk. This study was able to control for a significant number of Elixhauser Comorbidity and frailty indicators and through these additional controlling variables, the regression analysis found patients diagnosed with Cystic Fibrosis had a 2.43 times (95% CI: 1.175, 5.06) increase in risk of hospitalization and patients with Multiple Sclerosis were at a 2.0 times increase in risk (95% CI: 1.766, 2.283).

Table 9
Logistic regression results for falls

Variable	β	Odds Ratio (=e^{β})	OR 95% C.I.	*p*-value
Intercept	-9.6497			<.0001
BeersCat - APsyco vs No Beers	0.4089	1.935	[1.865, 2.007]	<.0001
BeersCat - Barbit vs No Beers	0.00342	1.290	[1.13, 1.472]	0.953
BeersCat - Benzos vs No Beers	0.0655	1.372	[1.341, 1.405]	<.0001
BeersCat - OtherRx vs No Beers	-0.1807	1.073	[1.051, 1.095]	<.0001
BeersCat - Sedativ vs No Beers	-0.0824	1.184	[1.13, 1.239]	0.0002
BeersCat - TCA vs No Beers	0.0364	1.333	[1.245, 1.427]	0.2426
AGE	0.055	1.057	[1.055, 1.058]	<.0001
MEMDAYS	0.00381	1.004	[1.004, 1.004]	<.0001
Male	-0.3325	0.717	[0.705, 0.73]	<.0001
Region_2	0.1849	1.203	[1.176, 1.231]	<.0001
Region_3	-0.1166	0.89	[0.868, 0.912]	<.0001
Region_4	0.1278	1.136	[1.108, 1.165]	<.0001
Region_5	0.3346	1.397	[1.277, 1.53]	<.0001
HospitalAdm	0.1159	1.123	[1.061, 1.188]	<.0001
CharlsScore	0.00338	1.003	[0.985, 1.023]	0.7268
FrailCat_1	0.5944	1.812	[1.777, 1.847]	<.0001
FrailCat_2	0.9877	2.685	[2.595, 2.778]	<.0001
PulmHeart	0.1131	1.12	[1.054, 1.19]	0.0003
ConductHeart	0.1853	1.204	[1.136, 1.275]	<.0001
CHF	0.00184	1.002	[0.969, 1.036]	0.9143
COPD	0.1909	1.21	[1.179, 1.242]	<.0001
Asthma	0.1631	1.177	[1.13, 1.226]	<.0001
Divert	0.1009	1.106	[1.05, 1.165]	0.0001
CRF	0.2337	1.263	[1.223, 1.305]	<.0001
RA	0.1367	1.146	[1.086, 1.21]	<.0001
SLE	0.1002	1.105	[0.996, 1.227]	0.0592
ConductHeartB	0.0587	1.06	[1, 1.125]	0.0516
Diab	0.1544	1.167	[1.142, 1.193]	<.0001
DiabComp	0.2438	1.276	[1.241, 1.312]	<.0001
HIV	0.2558	1.291	[0.883, 1.889]	0.1877
Hep	0.4527	1.572	[1.382, 1.789]	<.0001
CF	0.8914	2.438	[1.175, 5.06]	0.0167
Sicle	-0.0733	0.929	[0.377, 2.289]	0.8733
Senile	0.2706	1.311	[1.268, 1.355]	<.0001
Scizo	-0.0366	0.964	[0.812, 1.145]	0.6765
Parkin	0.4776	1.612	[1.532, 1.697]	<.0001

(continued)

Variable	β	Odds Ratio (=e^{β})	OR 95% C.I.	*p*-value
MS	0.6971	2.008	[1.766, 2.283]	<.0001
Epil	0.533	1.704	[1.604, 1.81]	<.0001
Otitis	0.1354	1.145	[1.064, 1.233]	0.0003
Vertigo	0.3814	1.464	[1.409, 1.522]	<.0001
Valve	0.0374	1.038	[1.003, 1.074]	0.0317
Carditis	-0.0437	0.957	[0.905, 1.012]	0.1249
Hyp	0.2648	1.303	[1.28, 1.326]	<.0001

*c-statistic: 0.725

4.2 Delirium and Confusion

The last patient group this study considered were those with confusion and delirium admissions. In our entire patient sample (n = 2,595,254), the analysis found differences between the delirium patients (n = 68,844) and non-delirium patients (n = 2,526,410) in age (78.34 vs. 73.87, $p < 0.0001$) female sex (58.1% vs. 56.8%, $p < 0.0001$). The patients who experienced a confusion or delirium admission, similarly to the Beers exposure grouping discussed at the beginning of this chapter, the delirium patients had a significantly higher Charlson score (0.34 vs. 0.08, $p < 0.0001$) and frailty score (2.91 vs. 0.33, $p < 0.0001$) as compared to patients without a confusion or delirium admission. The delirium patients in the study experienced a significantly longer average length of stay (9.86 vs. 5.86 days, $p < 0.0001$) and a significantly higher mean number of hospital admissions per person (1.44 vs. 1.20, $p < 0.0001$).

Also similar to the falls and fracture finding, 49.7% of the patients without a delirium admissions were taking at least one Beers Criteria medication. The delirium patients had the highest prevalence of any beers medications out of all three groupings with 62.2% of patients receiving at least one Beers medication. One of the most noticeable differences when comparing any stratification of study patients analyzed in this study, is the difference in the total treatment cost. The patients with a delirium admission were found to have a higher unadjusted mean treatment cost of $45,380 compared to the non-delirium patients having a mean treatment cost of

only $10,868, a difference of $34,512 ($p < 0.0001$) over the follow-up period of April – December 2013. Geographically, the analysis similarly determined the majority of delirium patients were located in the North Central region while the majority of non-delirium patients were located in the South.

Table 10
Descriptive statistics for all patients by delirium admission

Characteristic	Patients with no delirium admissions (n = 2,526,410)	Patients with delirium admissions (n = 68,844)	*p*-value
Age, years	73.87 ± 6.8	78.34 ± 6.9	<.0001
Hospital Admissions/person	1.20 ± 0.57	1.44 ± 0.93	<.0001
Patients with Any Hospital Admission	294,398 (11.6%)	49,197 (71.5%)	<.0001
Patients taking Any Beers Medications	1,254,510 (49.7%)	43,117 (62.6%)	<.0001
Charlson Score	0.08 ± 0.5	0.34 ± 1.1	<.0001
Length of Stay, days	5.86 ± 8.5	9.86 ± 14.4	<.0001
Female	1,468,454 (58.1%)	39,133 (56.8%)	<.0001
Frailty Category			<.0001
Frailty Cat 0 (Robust)	1,853,562 (73.4%)	26,858 (39.0%)	
Frailty Cat 1 (Pre-frail)	585,931 (23.2%)	26,187 (38.0%)	
Frailty Cat 2 (Frail)	86,917 (3.4%)	15,799 (22.9%)	
Frailty Score	0.33 ± 2.2	2.91 ± 4.3	<.0001
Insured Days (Member Days)	355 ± 42.3	344 ± 52.3	<.0001
Geographical Region			<.0001
Region 1 (Northeast)	569,998 (22.6%)	15,295 (22.2%)	
Region 2 (North Central)	693,772 (27.5%)	22,514 (32.7%)	
Region 3 (South)	730,201 (28.9%)	20,063 (29.1%)	
Region 4 (West)	510,282 (20.2%)	10,464 (15.2%)	
Region 5 (Unknown)	22,157 (0.9%)	508 (0.7%)	
Total Treatment Cost	$ 10,868 ± 31,546	$ 45,380 ± 72,459	<.0001
Inpatient Cost	$ 3,154 ± 17,903	$ 22,342 ± 54,417	<.0001
Outpatient Cost	$ 5,819 ± 22,347	$ 20,240 ± 37,459	<.0001
Pharmacy (Rx) Cost	$ 1,894 ± 4,754	$ 2,798 ± 5,735	<.0001

*Data expressed as mean ± standard deviation (SD) or otherwise indicated as Number (%), and compared by *t*-test or by Mann-Whitney *U*-test.

4.2.1 Medication Class Frequency Analysis

When considering Beers Criteria medication classes that cause disruptions in cognition and decreases in cognitive ability, a frequency analysis was again performed for each medication

class by delirium and the non-delirium patients. For the purposes of this portion of the analysis, the Beers Criteria medication classes selected for analysis were: antihistamines, antipsychotics, benzodiazepines, and narcotics. Through this frequency analysis it was determined the most commonly used medication class in patients with delirium admissions were benzodiazepines (n = 13,308), followed by antipsychotics, antihistamines, and lastly narcotics (n = 10,574; 1,237; and 27 respectively). The non-delirium patients followed the same distribution frequency as the delirium patients (n = 351,640; 52,187; 49,907; and 1,514 respectively) A lower overall percentage of delirium patients were found to be taking a medication in any other Beers Criteria medication class or no Beers medications at all as compared to the non-delirium patients (Other Beers: 26.5% vs. 31.8%; No Beers: 37.4% vs. 50.3%, $p < 0.0001$).

Table 11
Incidence of delirium admissions by Beers Medications categories

Characteristic	Patients with no delirium admissions (n=2,526,410)	Patients with ≥1 delirium admission (n=68,844)	*p*-value
Beers Criteria Grouping			<.0001
Antihistamines	45,907 (1.8%)	1,231 (1.8%)	
Antipsychotics[a]	52,187 (2.1%)	10,574 (15.4%)	
Benzodiazepines[b]	351,640 (13.9%)	13,038 (18.9%)	
Narcotics	1,514 (0.1%)	27 (0.04%)	
Other Medication Classes[c]	803,262 (31.8%)	18,247 (26.5%)	
No Beers Medications Present	1,271,900 (50.3%)	25,727 (37.4%)	

a Includes first- and second-generation antipsychotics
b Includes short- and long-acting benzodiazepines
c Includes any other classification of Beers Criteria medications

4.2.2 Logistic Regression Results

Ensuring statistical consistency, the same logistic regression analysis was performed on the delirium and non-delirium patients to determine the increase in risk of hospitalization when taking one of the specified confusion and delirium Beers medication classes listed in section 4.2.1. The four medication classes, and the "Other Beers Medication" categorical variable was

compared against the “No Beers Medications” baseline category. The analysis determined antipsychotics posed the highest risk for a confusion or delirium admission with 5.12 times increase in risk (95% CI: 4.985, 4.263), benzodiazepines with 1.8 times increase (95% CI: 1.762, 1.841), and antihistamines increased risk by 1.42 times (95% CI: 1.335, 1.503). Narcotics only marginally increased the risk of hospitalization by 1.05 times (95% CI: 0.714, 1.544) while patients taking any other medications present on the Beers Criteria were found to have risk increase of 1.22 times (95% CI: 1.197, 1.245).

Like the falls and fracture regression analysis, one of the patient characteristics outside of Beers Criteria medication use found to increase the risk of a confusion or delirium admission was again frailty category. Using a robust patient as the baseline (frailcat_0), patients who moved into the pre-frail category had 2.1 times (95% CI: 1.974, 2.051) increase in hospitalization risk while patients in the frail category had 3.7 times (95% CI: 3.592, 3.809) increase in risk in hospitalization. As performed in the falls and fracture regression, the Elixhauser Comorbidity and frailty indicators were included as additional controlling variables. The regression analysis found patients diagnosed with Sickle Cell Anemia had 2.7 times increase (95% CI: 1.564, 4.732) in risk of hospitalization and patients with Multiple Sclerosis or Epilepsy both saw 2.4 times increase (95% CI: 2.126, 2.693; 95% CI: 2.33, 2.57) in risk.

Table 12
Logistic regression results for delirium

Variable	β	Odds Ratio (=e^{β})	OR 95% C.I.	*p*-value
Intercept	-8.954			<.0001
DillBeersCat2 - AHist vs No Beers	-0.1218	1.416	[1.335, 1.503]	0.003
DillBeersCat2 - APsyco vs No Beers	1.1638	5.122	[4.985, 5.263]	<.0001
DillBeersCat2 - Benzos vs No Beers	0.1186	1.801	[1.762, 1.841]	0.0005
DillBeersCat2 - Narcoti vs No Beers	-0.4206	1.05	[0.714, 1.544]	0.0103
DillBeersCat2 - OtherRx vs No Beers	-0.2703	1.221	[1.197, 1.245]	<.0001
AGE	0.0646	1.067	[1.065, 1.068]	<.0001
MEMDAYS	-0.00038	1	[0.999, 1]	<.0001
Male	0.0685	1.071	[1.054, 1.088]	<.0001
Region_2	0.1771	1.194	[1.168, 1.22]	<.0001
Region_3	0.1179	1.125	[1.1, 1.15]	<.0001
Region_4	-0.226	0.798	[0.777, 0.819]	<.0001
Region_5	0.2264	1.254	[1.143, 1.375]	<.0001
HospitalAdm	0.3492	1.418	[1.357, 1.481]	<.0001
CharlsScore	0.0354	1.036	[1.022, 1.05]	<.0001
FrailCat_1	0.6992	2.012	[1.974, 2.051]	<.0001
FrailCat_2	1.3081	3.699	[3.592, 3.809]	<.0001
PulmHeart	0.0524	1.054	[0.996, 1.115]	0.068
ConductHeart	0.1353	1.145	[1.086, 1.207]	<.0001
CHF	0.0648	1.067	[1.037, 1.098]	<.0001
COPD	0.1806	1.198	[1.17, 1.227]	<.0001
Asthma	-0.0608	0.941	[0.902, 0.982]	0.0053
Divert	-0.0163	0.984	[0.934, 1.037]	0.5421
CRF	0.3868	1.472	[1.431, 1.514]	<.0001
RA	0.024	1.024	[0.969, 1.082]	0.3947
SLE	-0.0481	0.953	[0.852, 1.067]	0.402
ConductHeartB	0.0241	1.024	[0.97, 1.082]	0.384
Diab	0.2471	1.28	[1.255, 1.307]	<.0001
DiabComp	0.3605	1.434	[1.399, 1.47]	<.0001
HIV	0.2242	1.251	[0.887, 1.765]	0.2011
Hep	0.5379	1.712	[1.524, 1.925]	<.0001
CF	-0.6296	0.533	[0.161, 1.759]	0.3015
Sicle	1.0008	2.721	[1.564, 4.732]	0.0004
Senile	0.547	1.728	[1.682, 1.775]	<.0001
Scizo	0.1281	1.137	[1.006, 1.284]	0.0396
Parkin	0.3221	1.38	[1.319, 1.444]	<.0001
MS	0.8725	2.393	[2.126, 2.693]	<.0001

(continued)

Variable	β	Odds Ratio (=e^{β})	OR 95% C.I.	*p*-value
Epil	0.8949	2.447	[2.33, 2.57]	<.0001
Otitis	-0.0397	0.961	[0.889, 1.04]	0.3221
Vertigo	0.3154	1.371	[1.319, 1.424]	<.0001
Valve	-0.00934	0.991	[0.959, 1.023]	0.574
Carditis	-0.0461	0.955	[0.909, 1.003]	0.0659
Hyp	0.1125	1.119	[1.1, 1.138]	<.0001

* c-statistic = 0.80

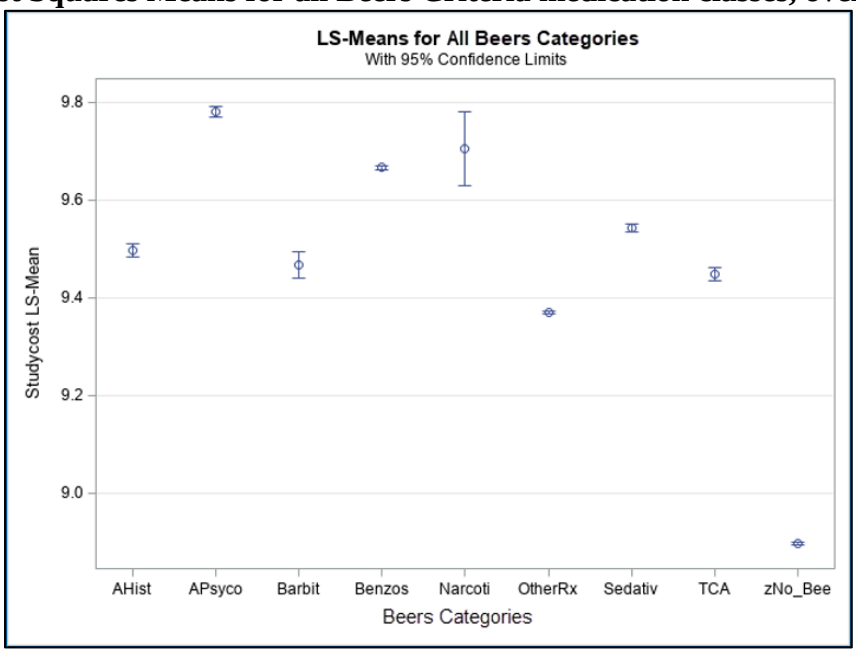
4.3 Gamma Log-Linked Regression for Study Cost

The final component of this study was the effect of the different Beers Criteria medication classes on the overall study or treatment cost. Using a gamma log-linked regression, we found that all 7 medication classes, including the "OtherRx" category, all significantly increased the total study or treatment costs from the non-Beers exposed control group over a follow-up period of April – December 2013. As shown in Table 13, the largest effect on study cost was patients using antipsychotics at $17,692 (95% CI: 17,500, 17,886) followed by narcotic use at $16,393 (95% CI: 15,201, 17,679). It is worth noting the results for the barbiturates and tricyclic antidepressant categories are specific for the falls and fracture admissions while the narcotic category is specific for the confusion and delirium admissions.

Table 13
Gamma log-link regression results for overall study cost

Variable	Label	β Est.	β 95% C.I.	Exponentiated (=e^{β})	e^{β} 95% C.I.	*p*-value
AHist	Antihistamines	9.4961	[9.4828, 9.5094]	$13,308	[13132, 13487]	<.0001
APsyco	Antipsychotics	9.7809	[9.7699, 9.7918]	$17,692	[17500, 17886]	<.0001
Barbit	Barbiturates	9.467	[9.4402, 9.4937]	$12,926	[12584, 13276]	<.0001
Benzos	Benzodiazepines	9.6666	[9.6621, 9.6711]	$15,782	[15712, 15853]	<.0001
Narcoti	Narcotics	9.7046	[9.6291, 9.7801]	$16,393	[15201, 17679]	<.0001
Sedativ	Sedatives	9.5438	[9.535, 9.5525]	$13,957	[13836, 14080]	<.0001
TCA	Tricyclic Antidepressants	9.4485	[9.4341, 9.463]	$12,690	[12508, 12874]	<.0001
OtherRx	Other Beers Rx	9.3696	[9.3663, 9.3728]	$11,726	[11688, 11765]	<.0001
zNo_Bee	No Beers Rx	8.8971	[8.8947, 8.8995]	$ 7,311	[7293, 7328]	<.0001

Figure 5: Least Squares Means for all Beers Criteria medication classes, overall study cost



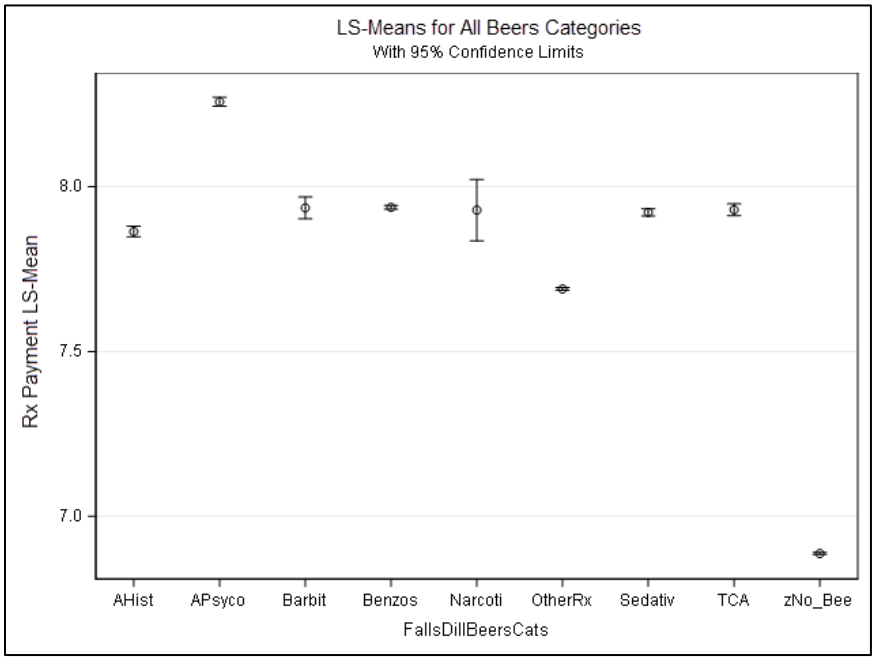
When the same gamma log-linked regression model was run specifically on the pharmacy Rx cost variable similar to the overall study cost model, we found that antipsychotic use was the largest contributing factor to the change in direct pharmacy costs by $3,858 (95% CI = 3,806, 3,911). Following antipsychotics, benzodiazepines, barbiturates, narcotics, and tricyclic antidepressants all very similarly contributed to the overall change in pharmacy costs.

Table 14

Gamma log-link regression results for pharmacy Rx cost

Variable	Label	β Est.	β 95% C.I.	Exponentiated (=eβ)	e^{β} 95% C.I.	p- value
AHist	Antihistamines	7.8643	[7.8478, 7.8807]	$2,602	[2560, 2655]	<.0001
APsyco	Antipsychotics	8.2579	[8.2443, 8.2715]	$3,858	[3806, 3911]	<.0001
Barbit	Barbiturates	7.9361	[7.9031, 7.9691]	$2,796	[2706, 298]	<.0001
Benzos	Benzodiazepines	7.9377	[7.9322, 7.9432]	$2,801	[2785, 2816]	<.0001
Narcoti	Narcotics	7.9294	[7.8364, 8.0224]	$2,778	[2531, 3048]	<.0001
Sedativ	Sedatives	7.9225	[7.9117, 7.9333]	$2,759	[2729, 2789]	<.0001
TCA	Tricyclic Antidepressants	7.9306	[7.9128, 7.9483]	$2,781	[2732, 2831]	<.0001
OtherRx	Other Beers Rx	7.6901	[7.6860, 7.6941]	$2,186	[2178, 2195]	<.0001
zNo_Bee	No Beers Rx	6.8869	[6.8840, 6.8899]	$ 979	[977, 982]	<.0001

Figure 6: Least Squares Means for all Beers Criteria medication classes, Rx payment costs

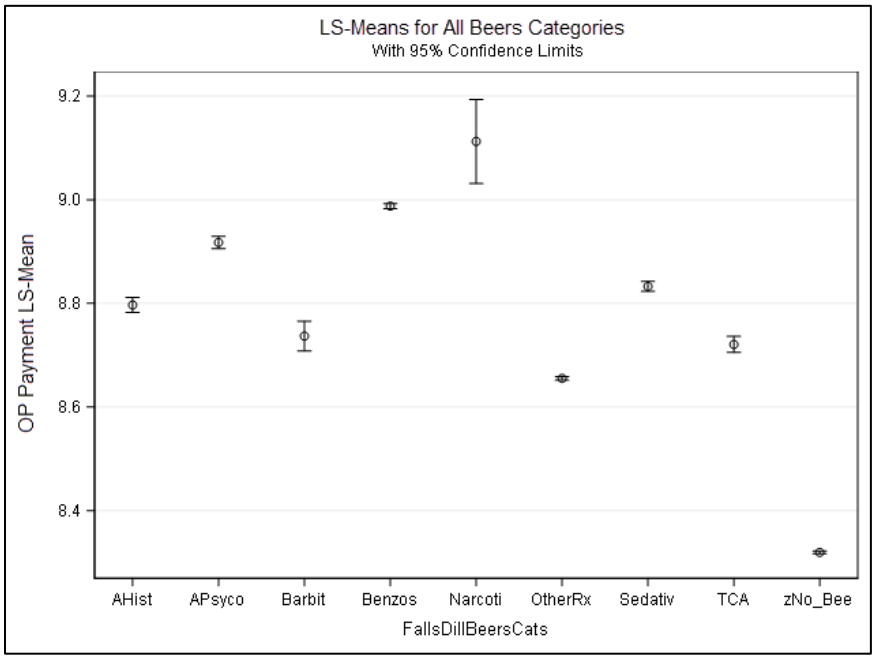


The gamma log-linked regression results when considering the effect of the Beers Criteria medication classes on the outpatient costs yielded a different result than the previous two models. In this model, the highest contributing factor to outpatient costs was the presence of narcotics with an average annual outpatient cost of $9,068 (95% CI: 8,631, 9,835). Following narcotic use, the second largest contributor to outpatient costs were benzodiazepines, followed by antipsychotics, tricyclic antidepressants, antihistamines, barbiturates, and lastly, sedatives.

Table 15
Gamma log-link regression results for outpatient costs

Variable	Label	β Est.	β 95% C.I.	Exponentiated (=eβ)	e^{β} 95% C.I.	p- value
AHist	Antihistamines	8.7968	[8.7825, 8.8111]	$6,613	[6519, 6708]	<.0001
APsyco	Antipsychotics	8.9174	[8.9056, 8.9292]	$7,461	[7373, 7549]	<.0001
Barbit	Barbiturates	8.7369	[8.7081, 8.7657]	$6,228	[6052, 6410]	<.0001
Benzos	Benzodiazepines	8.9877	[8.9829, 8.9925]	$8,004	[7966, 8043]	<.0001
Narcoti	Narcotics	9.1125	[9.0313, 9.1937]	$9,068	[8631, 9835]	<.0001
Sedativ	Sedatives	8.8327	[8.7052, 8.7362]	$6,855	[6034, 6224]	<.0001
TCA	Tricyclic Antidepressants	8.7207	[8.6518, 8.6588]	$6,129	[5721, 5761]	<.0001
OtherRx	Other Beers Rx	8.6553	[8.8233, 8.8422]	$5,741	[6791, 6920]	<.0001
zNo_Bee	No Beers Rx	8.3194	[8.3168, 8.3219]	$4,102	[4092, 4113]	<.0001

Figure 7: Least Squares Means for all Beers Criteria medication classes, outpatient costs



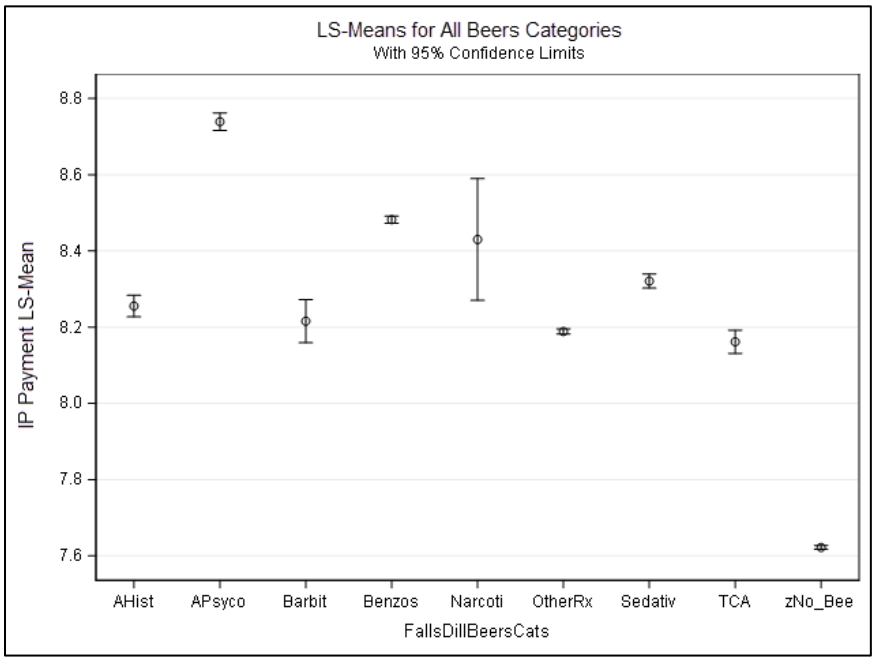
The last gamma log-linked regression analysis performed examined the effect of the Beers Criteria categories on the inpatient costs. In this model, the antipsychotic medication class had the largest inpatient costs at $6,240 (95% CI: 6098, 6385). The inpatient model followed the generalized model and the pharmacy Rx costs model with benzodiazepines having the second

largest effect. Narcotics, sedatives, antihistamines, barbiturates, and tricyclic antidepressants followed benzodiazepines in order from next largest effect to smallest.

Table 16
Gamma log-linked regression results for inpatient costs

Variable	Label	β Est.	β 95% C.I.	Exponentiated (=e^{β})	e^{β} 95% C.I.	p- value
AHist	Antihistamines	8.2552	[8.2271, 8.2834]	$3,848	[3741, 3958]	<.0001
APsyco	Antipsychotics	8.7388	[8.7158, 8.7618]	$6,240	[6098, 6385]	<.0001
Barbit	Barbiturates	8.2155	[8.1589, 8.2721]	$3,698	[3494, 3913]	<.0001
Benzos	Benzodiazepines	8.4820	[8.4725, 8.4914]	$4,827	[4781, 4873]	<.0001
Narcoti	Narcotics	8.4298	[8.2701, 8.5894]	$4,581	[3905, 5375]	<.0001
Sedativ	Sedatives	8.3208	[8.3022, 8.3393]	$4,108	[4033, 4185]	<.0001
TCA	Tricyclic Antidepressants	8.1615	[8.1310, 8.1920]	$3,503	[3398, 3612]	<.0001
OtherRx	Other Beers Rx	8.1884	[8.1815, 8.1953]	$3,599	[3574, 3624]	<.0001
zNo_Bee	No Beers Rx	7.6219	[7.6169, 7.6269]	$2,042	[2032, 2053]	<.0001

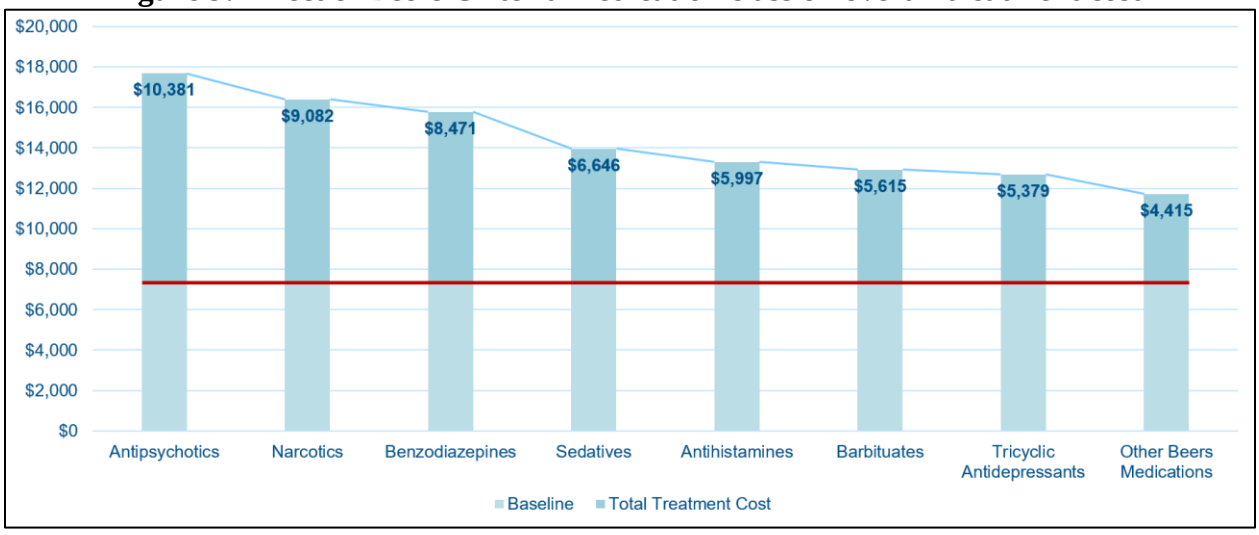
Figure 8: Least Squares Means results for all Beers Criteria medication classes, inpatient costs



CHAPTER V DISCUSSION

Overall, patients in both experimental groups were older, had a longer length of stay, and a higher Charlson Score than their well-matched control groups. Antipsychotics and benzodiazepines were consistently the most frequent prescribed class of Beers Criteria medications to both groups of patients who experienced a fall or fracture, or delirium or confusion admission. Antipsychotics and benzodiazepines were also associated with the greatest increase in risk of admission both the falls and fractures, and the delirium and confusion groups. Antipsychotics were associated with the highest overall expected cost of admission and benzodiazepines third, when considering admission type independently. Narcotics, specifically considered for the delirium patients, was the second highest contributor to the expected cost of admission. Figure 9 shows all Beers Criteria medication classes analyzed in this study for the overall treatment costs for all patients. The baseline total treatment costs for the control groups in the absence of Beers Criteria medications (NoBeers) was $7,311 and is indicated by the red line in the figure. The increase in total treatment cost is shown in the bar above the red baseline relative to the magnitude of the increase by the Beers Criteria medication class.

Figure 9: Effect of Beers Criteria medication class on overall treatment cost



When specifically considering the patients who experiences a fall or fracture admission, we found benzodiazepines and antipsychotics as the most frequent Beers Criteria classes involved with these types of admissions. We also saw an increased risk of a falls and fracture admission of 1.9 times with antipsychotics, and 1.4 times with benzodiazepines.

Patients with delirium or confusion admissions we again saw benzodiazepines and antipsychotics as the most frequently involved Beers Criteria classes. We saw an increased risk of a confusion and delirium admission of 5.1 times with antipsychotic use, 1.8 times with the use of benzodiazepines, and 1.4 times with the use of antihistamines.

These findings show validation of the logical linkage between the use of certain Beers Criteria medications and their expected hospital admissions.

5.1 Limitations

As with any study there are limitations we encountered, some could be managed while others could not due to the design of our study. First, as identified by the O'Neill Roldan (2018) study during the creation of the study design and dataset, the inclusion of only community-dwelling individuals ≥65 years old would exclude those who are institutionalized in nursing homes, long-term assisted living, or short-term rehabilitation facilities. This exclusion of a large segment of the elderly population could skew the actual cost burden placed on the patient, payer, and healthcare system as the costs data excluded costs relating to skilled nursing, long-term, palliative, or hospice care.

Second, the use of Truven Marketscan® Administrative Claims data contains its own logical limitations. The Marketscan® database is a convenience, not a randomized, sample. Because of this, there are analytical cases where the extracted data may contain unintended biases which can diminish generalizability to larger populations. This was taken into

consideration in the initial construction of the data source by O'Neill Roldan (2018) and this effect and limitation is minimized by our population sample size. Additionally, given the frequencies calculated for Beers Criteria medication use and general population characteristics, we in this study found that these proportions are in alignment with already existing literature and are confident generalizations from our data are accurate.

Marketscan® data is aggregated from data sources which are intended for billing and not specifically research. Therefore, the accuracy in coding of billing data within the dataset, while unlikely, could be incorrect causing the unintended exclusion of patients from the original dataset. While the various Marketscan® databases are touted for their high-quality and comprehensive coding, the potential for this error could equally affect both groups, so the effect from this limitation is minimized. Lastly, Marketscan® data only captures encounters data for which a claim was actually captured. This unintended bias, similar to coding errors, may cause certain comorbidities, procedures, or medications to not be included in the data set and patients could be unintentionally excluded.

5.2 Future Research

Due to time constraints, there areas of research planned in this study that could not be completed. First, future researchers should consider examining different popular combinations of drug classes and their effects on falls, fractures, delirium, and confusion on community-dwelling individuals. Second, the examination and investigation of the impact of specific medications versus an entire class on these types of admissions. Lastly, examining risks of falls, fractures, confusion, and delirium outside of community-dwelling individuals as this study did, for example, short-term rehab facilities, long-term care, and skilled nursing facilities. This suggestion for future research was also considered in O'Neill Roldan (2018).

5.3 Conclusions

Our study found that patients using antipsychotics are at twice the risk for a fall or fracture hospitalization than their well-matched controls. Second, our study found patients using antipsychotics are at more than a five times risk for a delirium or delirium-related hospitalization than their well-matched controls. We saw with all patients that antipsychotics use was associated with a $10,381 dollar increase in cost and benzodiazepines use was associated with an $8,471 dollar increase over their well-matched non-Beers baselines. We also found specifically with the delirium patients, narcotic use was associated with a $9,082 dollar increase in treatment costs over their well-matched non-Beers baseline.

Through our study we found and can confirm that additional hospital admissions are logically linked to the expected side effects of certain classes of Beers Criteria medications in regards to falls and fracture admissions for medications effecting balance and gait; and delirium and confusion admissions for those medications effecting cognition in the elderly. Future research and investigation into specific medication-level research and medication class combinations with regards to falls and fractures, and confusion and delirium in the elderly is warranted.

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Appendix A: 2012 Beers List Medications

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)	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.	Avoid	Hydroxyzine and promethazine: high;	Strong
Brompheniramine	Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate		All others: moderate	
Carbinoxamine				
Chlorpheniramine				
Clemastine				
Cyproheptadine				
Dexbrompheniramine				
Dexchlorpheniramine				
Diphenhydramine (oral)				
Doxylamine				
Hydroxyzine				
Promethazine				
Triprolidine				
Antiparkinson agents	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more-effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Benztropine (oral)				
Trihexyphenidyl				
Antispasmodics	Highly anticholinergic, uncertain effectiveness	Avoid except in short-term palliative care to decrease oral secretions	Moderate	Strong
Belladonna alkaloids				
Clidinium-chlordiazepoxide				
Dicyclomine				
Hyoscyamine				
Propantheline				

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Scopolamine				
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	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
Doxazosin				
Prazosin				
Terazosin				
Alpha agonists, central	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.	Low	Strong
Clonidine	Avoid others as listed			
Guanabenz *				
Guanfacine *				
Methyldopa *				
Reserpine (> 0.1 mg/d) *				
Antiarrhythmic drugs (Class Ia, Ic, III)	Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults.	Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation	High	Strong
Amiodarone				

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Dofetilide				
Dronedarone	Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders, and QT-interval prolongation			
Flecainide				
Ibutilide				
Procainamide				
Propafenone				
Quinidine				
Sotalol				
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:	Highly anticholinergic,	Avoid	High	Strong

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
	sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≥ 6 mg/d) is comparable with that of placebo			
Amitriptyline				
Chlordiazepoxide-amitriptyline				
Clomipramine				
Doxepin > 6 mg/d				
Imipramine				
Perphenazine-amitriptyline				
Trimipramine				
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	Highly anticholinergic and risk of QT-interval prolongation	Avoid	Moderate	Strong
Mesoridazine				
Barbiturates	High rate of physical dependence; tolerance to sleep benefits; risk of overdose at low dosages	Avoid	High	Strong
Amobarbital *				
Butabarbital *				
Butalbital				
Mephobarbital *				
Pentobarbital *				
Phenobarbital				
Secobarbital *				
Benzodiazepines	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	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium	High	Strong
Short and intermediate acting:				

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Alprazolam				
Estazolam				
Lorazepam				
Oxazepam				
Temazepam				
Triazolam				
Long acting:	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			
Clorazepate				
Chlordiazepoxide				
Chlordiazepoxide-amitriptyline				
Clidinium-chlordiazepoxide				
Clonazepam				
Diazepam				
Flurazepam				
Quazepam				
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	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
Eszopiclone				
Zolpidem				
Zaleplon				
Ergot mesylates *	Lack of efficacy	Avoid	High	Strong
Isoxsuprine *				
Endocrine				

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Androgens	Potential for cardiac problems and contraindicated in men with prostate cancer	Avoid unless indicated for moderate to severe hypogonadism	Moderate	Weak
Methyltestosterone *				
Testosterone				
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	Avoid oral and topical patch.	Oral and patch: high	Oral and patch: strong
	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	Topical vaginal cream: acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms	Topical: moderate	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
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: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion.	Avoid	High	Strong
Chlorpropamide	Glyburide: greater risk of severe prolonged hypoglycemia in older adults			
Glyburide				

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
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	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
Aspirin > 325 mg/d				
Diclofenac				
Diflunisal				
Etodolac				
Fenoprofen				
Ibuprofen				
Ketoprofen				
Meclofenamate				
Mefenamic acid				

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Meloxicam				
Nabumetone				
Naproxen				
Oxaprozin				
Piroxicam				
Sulindac				
Tolmetin				
Indomethacin	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	Strong
Ketorolac, includes parenteral			Ketorolac: high	
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	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
Carisoprodo				
Chlorzoxazone				
Cyclobenzaprine				
Metaxalone				
Methocarbamol				
Orphenadrine				

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.

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.

* Infrequently used drugs.

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

Drug	Rationale	Recommendation	Quality of lation 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	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
Carbamazepine				
Carboplatin				
Cisplatin				
Mirtazapine				
Serotonin norepinephrine reuptake inhibitor				
Selective serotonin reuptake inhibitor				
Tricyclic antidepressants				
Vincristine				
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 2012 Beers Criteria Update Expert Panel (2012). American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *60*(4), 616–631. https://doi.org/10.1111/j.1532-5415.2012.03923.x

Appendix B: 2012 Beers Criteria Medications Added and Removed

Medications Added Since 2003 Beers Criteria

	Considering Diagnoses	
Independent of Diagnoses Medication	**Corresponding Diagnosis or Syndrome**	
Aspirin for primary prevention of cardiac events	Acetylcholinesterase inhibitors	Syncope
Antiarrhythmic drugs, Class 1a, 1c, III	Anticonvulsants	History of falls or fractures
Belladonna alkaloids	H_1 and H_2 antihistamines	Delirium
Benztropine (oral)	Aspirin >325 mg	History of gastric or duodenal ulcers
Brompheniramine	Brompheniramine	Chronic constipation
Carbinoxamine	Caffeine	Insomnia
Chloral hydrate	Carbamazepine	SIADH or hyponatremia
Clemastine	Carbinoxamine	Chronic constipationa
Clomipramine	Carboplatin	SIADH or hyponatremia
Clonazepam	Clemastine (various)	Chronic constipation
Dabigatran	Clozapine	Chronic seizures or epilepsy
Desiccated thyroid	Cisplatin	SIADH or hyponatremia
Dexbrompheniramine	Cyclooxygenase-2 inhibitors	Heart failure
Doxylamine	Darifenacin	Chronic constipation
Dronedarone	Desipramine	Falls and fractures
Estazolam	Dexbrompheniramine	Chronic constipation
Eszopiclone	Dexchlorpheniramine	Chronic constipation
First- and second-generation antipsychotics	Doxylamine	Chronic constipation
Flurazepam	Estrogen, transdermal	Urinary incontinence (all types) in women
Glyburide	Eszopiclone	History of falls or fractures
Growth hormone	Fesoterodine	Chronic constipation
Guanabenz	Inhaled anticholinergics	Lower urinary tract symptoms and benign prostatic hyperplasia
Guanfacine	Maprotiline	Chronic seizures or epilepsy
Insulin, sliding scale	Mirtazapine	SIADH or hyponatremia
Megestrol	Nondihydropyridine calcium channel blockers	Heart failure
Metoclopramide	Nortriptyline	Falls and fractures
Oral doxepin >6 mg/d	Pioglitazone	Heart failure
Phenobarbital	Prochlorperazine	Parkinson disease
Prasugrel	Rosiglitazone	Heart failure
Prazosin	Scopolamine	Chronic constipation
Scopolamine	Serotonin-norepinephrine reuptake inhibitors	SIADH or hyponatremia
Spironolactone	Solifenacin	Chronic constipation
Testosterone	Thiothixene	Chronic seizures or epilepsy
Trihexyphenidyl	Thioridazine	Syncope
Trimipramine	Triamterene	Chronic kidney disease Stages IV and V
Triprolidine	Triprolidine	Chronic constipation

	Considering Diagnoses	
Independent of Diagnoses Medication	**Corresponding Diagnosis or Syndrome**	
Zaleplon	Trospium	Chronic constipation
Zolpidem	Vincristine	SIADH or hyponatremia
	Zaleplon	History of falls or fractures
	Zolpidem	Dementia and cognitive impairment

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Medications Removed Since 2003 Beers Criteria

Independent of Diagnoses	Considering Diagnoses
Cimetidine (H_2 antihistamines added as a class; see Table 7)	Antispasmodics and muscle relaxants; CNS stimulants: dextroamphetamine, methylphenidate, methamphetamine, pemoline, with cognitive impairment
Cyclandelate	CNS stimulants: dextroamphetamine, methylphenidate, methamphetamine, pemoline, and fluoxetine with anorexia and malnutrition
Daily fluoxetine	Clopidogrel with blood clotting disorders or receiving anticoagulant therapy
Ferrous sulfate <325 mg/d	Guanethidine with depression
Guanadrel	High-sodium content drugs with heart failure
Guanethidine	Monoamine oxidase inhibitors with insomnia
Halazepam	Oxybutynin and tolterodine with bladder outlet obstruction
Long-term use of stimulant laxatives: bisacodyl, cascara sagrada, and neoloid except in the presence of opiate analgesic use	Pseudoephedrine and diet pills with hypertension
Mesoridazine	Tacrine with Parkinson's disease
Propoxyphene and combination products	
Tripelennamine	

CNS = central nervous system.

Source: American Geriatrics Society 2012 Beers Criteria Update Expert Panel (2012). American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *60*(4), 616–631. https://doi.org/10.1111/j.1532-5415.2012.03923.x

Appendix C: 2015 Beers Criteria Medications Added and Removed

Table 9. Medications Removed Since 2012 Beers Criteria

Independent of Diagnoses or Condition (Table 2)	Considering Disease and Syndrome Interactions (Table 3)
Antiarrhythmic drugs (Class 1a, 1c, III except amiodarone) as first-line treatment for atrial fibrillation	Chronic constipation—entire criterion
Trimethobenzamide	Lower urinary tract—inhaled anticholinergic drugs
Mesoridazine—no longer marketed in United States	
Chloral hydrate—no longer marketed in United States	

Table 10. Medications Added Since 2012 Beers Criteria

Independent of Diagnoses or Condition (Table 2)	Considering Disease and Syndrome Interactions (Table 3)
Proton-pump inhibitors	Falls and fractures—opioids
Desmopressin	Insomnia—armodafinil and modafinil
Anticholinergics, first-generation antihistamines—meclizine	Dementia or cognitive impairment—eszopiclone and zaleplon
	Delirium—antipsychotics

Source: By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel (2015). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*, *63*(11), 2227–2246. https://doi.org/10.1111/jgs.13702

Table 2. 2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults[a]

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics[b]				
First-generation antihistamines Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Dimenhydrinate Diphenhydramine (oral) Doxylamine Hydroxyzine Meclizine Promethazine Pyrilamine 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 or treatment 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 Homatropine (excludes opthalmic) Hyoscyamine Methscopolamine 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; IV form acceptable for use in cardiac stress testing	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	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers for treatment of hypertension Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Central alpha-agonists		Avoid as first-line antihypertensive	Low	Strong

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Clonidine for first-line treatment of hypertension Other CNS alpha-agonists Guanabenz Guanfacine Methyldopa Reserpine (>0.1 mg/day)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid other CNS alpha-agonists as listed	Low	Strong
Disopyramide	May induce heart failure in older adults because of potent negative inotropic action; 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 for first-line treatment of atrial fibrillation or of heart failure	Use in atrial fibrillation: should not be used as a first-line agent in atrial fibrillation, because there are safer and more effective alternatives for rate control supported by high-quality evidence. Use in heart failure: evidence for benefits and harms of digoxin is conflicting and of lower quality; most but not all of the evidence concerns use in HFrEF. There is strong evidence for other agents as first-line therapy to reduce hospitalizations and mortality in adults with HFrEF. In heart failure, higher dosages are not associated with additional benefit and may increase risk of toxicity. Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in those with stage 4 or 5 chronic kidney disease.	Avoid this rate control agent as first-line therapy for atrial fibrillation Avoid as first-line therapy for heart failure If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day	Atrial fibrillation: low Heart failure: low Dosage >0.125 mg/day: moderate	Atrial fibrillation: strong Heart failure: strong Dosage >0.125 mg/day: strong
Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; 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 as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	High	Strong
Central nervous system				
Antidepressants, alone or in combination Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/day Imipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable to that of placebo	Avoid	High	Strong

(Continued)

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Nortriptyline Paroxetine Protriptyline Trimipramine				
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 (eg, behavioral interventions) have failed or are not possible *and* the older adult is threatening substantial harm to self or others	Avoid, except in schizophrenia or bipolar disorder, or for 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 *Long acting:* Chlordiazepoxide (alone or in combination with amitriptyline or clidinium) Clonazepam Clorazepate Diazepam Flurazepam Quazepam	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 May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia	Avoid	Moderate	Strong
Meprobamate	High rate of physical dependence; sedating	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs") Eszopiclone Zaleplon Zolpidem	Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/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				

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
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	Avoid systemic estrogen (eg, oral and topical patch)	Oral and patch: high	Oral and patch: strong
	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 risks and benefits of low-dose vaginal estrogen (dosages of estradiol <25 µg twice weekly) with their healthcare provider	Vaginal cream or vaginal tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, recurrent lower urinary tract infections, and other vaginal symptoms	Vaginal cream or vaginal tablets: moderate	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 for patients rigorously diagnosed by evidence-based criteria with growth hormone deficiency due to an established etiology	High	Strong
Insulin, sliding scale (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. Avoid insulin regimens that include only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin. This recommendation does not apply to regimens that contain basal insulin or long-acting 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 acting Chlorpropamide Glimepiride Glyburide (also known as glibenclamide)	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glimepiride and glyburide: higher risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong
Gastrointestinal				
Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	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 (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, because of failure of drug discontinuation trial or H2-receptor antagonists)	High	Strong

(Continued)

Organ System, Therapeutic Category, Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Pain medications				
Meperidine	Oral analgesic not effective in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid	Moderate	Strong
Non–cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/day 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 >75 years 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 ~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. Also can increase blood pressure and induce kidney injury. Risks are dose related.	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	Increased risk of gastrointestinal bleeding/peptic ulcer disease and acute kidney injury in older adults 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
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

Abbreviations: CNS, central nervous system; HFrEF, heart failure with reduced ejection fraction; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

[a]The primary target audience is the practicing clinician. The intentions of the criteria include (1) improving the selection of prescription drugs by clinicians and patients; (2) evaluating patterns of drug use within populations; (3) educating clinicians and patients on proper drug usage; and (4) evaluating health-outcome, quality-of-care, cost, and utilization data.

[b]See also criterion on highly anticholinergic antidepressants.

Source: American Geriatrics Society Beers Criteria® Update Expert Panel. (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*, *67*(4), 674-694. https://doi.org/10.1111/jgs.15767

Appendix E: 2019 Beers Criteria Medications Added and Removed

Table 8. Medications/Criteria Removed Since 2015 American Geriatrics Society Beers Criteria®

Medication/Criterion	Reason for Removal
Independent of Diagnosis or Condition (Table 2)	
Ticlopidine	No longer on US market; low use
Pentazocine	Oral no longer on US market
Considering Disease and Syndrome Interactions (Table 3)	
Chronic seizures or epilepsy Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Not unique to older adults
Dementia H2-receptor antagonists	Weak evidence and to avoid overly restricting therapeutic options for older adults with dementia who have gastroesophageal reflux or similar issues (given a coexisting criterion advising against chronic use of PPIs except in specific circumstances)
Insomnia *Oral decongestants* Phenylephrine Pseudoephedrine *Stimulants* Amphetamine Armodafinil Methylphenidate Modafinil *Theobromines* Theophylline Caffeine	Not unique to older adults
Parkinson disease Aripiprazole	Removed as a preferred antipsychotic in older adults with Parkinson disease because of safety and efficacy concerns
Use With Caution (Table 4)	
SIADH/hyponatremia Carboplatin Cyclophosphamide Cisplatin Vincristine	Highly specialized drugs that fell outside the scope of the criteria
Syncope Vasodilators	Not unique to older adults

Abbreviations: PPI, proton-pump inhibitor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 9. Medications/Criteria Added Since 2015 American Geriatrics Society Beers Criteria®

Medication/Criterion	Reason for Addition
Independent of Diagnosis or Condition (Table 2)	
Glimepiride	Severe, prolonged hypoglycemia in older adults
Methscopolamine Pyrilamine	Strong anticholinergic
Considering Disease and Syndrome Interactions (Table 3)	
History of falls or fractures SNRI	Associated with increased risk in older adults
Parkinson disease Pimavanserin	Unlike most other antipsychotics, the revised criteria consider pimavanserin acceptable for treatment of psychosis in Parkinson disease
Use With Caution (Table 4)	
Rivaroxaban	Emerging evidence of increased risk of serious bleeding compared with other anticoagulant options
Tramadol	Risk of SIADH/hyponatremia
Dextromethorphan/quinidine	Limited efficacy in treating patients with dementia symptoms disorder in absence of pseudobulbar affect while potentially increasing risk of falls and drug-drug interactions
TMP-SMX	Increased risk of hyperkalemia in combination with ACEIs and ARBs in patients with reduced kidney function
Clinically Important Drug-Drug Interactions (Table 5)	
Opioids + benzodiazepines	Increased risk of overdose
Opioids + gabapentin/pregabalin	Increased risk of overdose
Phenytoin + TMP-SMX	Increased risk of phenytoin toxicity
Theophylline + ciprofloxacin	Increased risk of theophylline toxicity
Warfarin + ciprofloxacin	Increased risk of bleeding
Warfarin + macrolides (excluding azithromycin)	Increased risk of bleeding
Warfarin + TMP-SMX	Increased risk of bleeding
Medications That Should Be Avoided or Have Their Dosage Reduced With Decreased Kidney Function (Table 6)	
Ciprofloxacin	Increased risk of CNS effects
TMP-SMX	Increased risk of worsening of renal function and hyperkalemia

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNS, central nervous system; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNRI, serotonin-norepinephrine reuptake inhibitor; TMP-SMX, trimethoprim-sulfamethoxazole.

Source: American Geriatrics Society Beers Criteria® Update Expert Panel. (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society, 67*(4), 674-694. https://doi.org/10.1111/jgs.15767

Table 17
List of dataset variables for Saber (2020)

Col#	Variable	Label
144	ADMS	# of Hospital Admissions
147	adms_0	# of Hospital Admissions
3	AGE	Age of Patient
39	Alpha_Agonist_Central_Dys	Beers Criteria Medication Class, Rx Days
159	Alpha_Agonist_Central_IND	Beers Criteria Medication Class, Binary Indicator
38	Alpha_Agonist_Central_Rx	Beers Criteria Medication Class, # Rx
41	Alpha_Blocker_Dys	Beers Criteria Medication Class, Rx Days
160	Alpha_Blocker_IND	Beers Criteria Medication Class, Binary Indicator
40	Alpha_Blocker_Rx	Beers Criteria Medication Class, # Rx
120	Ambu	Frailty Measure Indicator
43	Antiarrhythmic_Dys	Beers Criteria Medication Class, Rx Days
161	Antiarrhythmic_IND	Beers Criteria Medication Class, Binary Indicator
42	Antiarrhythmic_Rx	Beers Criteria Medication Class, # Rx
45	Antiemetics_Dys	Beers Criteria Medication Class, Rx Days
162	Antiemetics_IND	Beers Criteria Medication Class, Binary Indicator
44	Antiemetics_Rx	Beers Criteria Medication Class, # Rx
47	Antihistamine_1st_Gen_Dys	Beers Criteria Medication Class, Rx Days
163	Antihistamine_1st_Gen_IND	Beers Criteria Medication Class, Binary Indicator
46	Antihistamine_1st_Gen_Rx	Beers Criteria Medication Class, # Rx
49	Antihypertensive_Dys	Beers Criteria Medication Class, Rx Days
164	Antihypertensive_IND	Beers Criteria Medication Class, Binary Indicator
48	Antihypertensive_Rx	Beers Criteria Medication Class, # Rx
51	Antiinfective_Dys	Beers Criteria Medication Class, Rx Days
165	Antiinfective_IND	Beers Criteria Medication Class, Binary Indicator
50	Antiinfective_Rx	Beers Criteria Medication Class, # Rx
53	Antiparkinson_agent_Dys	Beers Criteria Medication Class, Rx Days
166	Antiparkinson_agent_IND	Beers Criteria Medication Class, Binary Indicator
52	Antiparkinson_agent_Rx	Beers Criteria Medication Class, # Rx
55	Antipsychotics_FirstGen_Dys	Beers Criteria Medication Class, Rx Days
167	Antipsychotics_FirstGen_IND	Beers Criteria Medication Class, Binary Indicator
54	Antipsychotics_FirstGen_Rx	Beers Criteria Medication Class, # Rx
57	Antipsychotics_SecondGen_Dys	Beers Criteria Medication Class, Rx Days
168	Antipsychotics_SecondGen_IND	Beers Criteria Medication Class, Binary Indicator
56	Antipsychotics_SecondGen_Rx	Beers Criteria Medication Class, # Rx
59	Antispasmodic_Dys	Beers Criteria Medication Class, Rx Days
169	Antispasmodic_IND	Beers Criteria Medication Class, Binary Indicator
58	Antispasmodic_Rx	Beers Criteria Medication Class, # Rx

(continued)

Col#	Variable	Label
61	Antithrombotic_Dys	Beers Criteria Medication Class, Rx Days
170	Antithrombotic_IND	Beers Criteria Medication Class, Binary Indicator
60	Antithrombotic_Rx	Beers Criteria Medication Class, # Rx
63	Anxiolytic_Dys	Beers Criteria Medication Class, Rx Days
171	Anxiolytic_IND	Beers Criteria Medication Class, Binary Indicator
62	Anxiolytic_Rx	Beers Criteria Medication Class, # Rx
148	AnyADM	Any Hospital Admission, Binary Indicator
100	AnyBeers	Any Beers Medication Present, Binary Indicator
113	arthritis	Frailty Measure Indicator
14	Asthma	Elixhauser Comorbidity Indicator
65	Barbiturates_Dys	Beers Criteria Medication Class, Rx Days
172	Barbiturates_IND	Beers Criteria Medication Class, Binary Indicator
64	Barbiturates_Rx	Beers Criteria Medication Class, # Rx
158	BeersCat	Beers Criteria Medication Class, Categorical, Study-based
67	Benzodiazepines_Long_Acting_Dys	Beers Criteria Medication Class, Rx Days
173	Benzodiazepines_Long_Acting_IND	Beers Criteria Medication Class, Binary Indicator
66	Benzodiazepines_Long_Acting_Rx	Beers Criteria Medication Class, # Rx
69	Benzodiazepines_Short_Acting_Dys	Beers Criteria Medication Class, Rx Days
174	Benzodiazepines_Short_Acting_IND	Beers Criteria Medication Class, Binary Indicator
68	Benzodiazepines_Short_Acting_Rx	Beers Criteria Medication Class, # Rx
101	bladder	Charlson Comorbidity Score Indicator
116	braininj	Charlson Comorbidity Score Indicator
105	cancer	Charlson Comorbidity Score Indicator
32	Carditis	Elixhauser Comorbidity Indicator
22	CF	Elixhauser Comorbidity Indicator
8	CharlsScore	Charlson Score
12	CHF	Elixhauser Comorbidity Indicator
102	coagulopathy	Charlson Comorbidity Score Indicator
10	ConductHeart	Elixhauser Comorbidity Indicator
11	ConductHeartB	Elixhauser Comorbidity Indicator
13	COPD	Elixhauser Comorbidity Indicator
16	CRF	Elixhauser Comorbidity Indicator
143	Days	Length of Stay, # of Days
146	days_0	Length of Stay, # of Days
104	dementia	Charlson Comorbidity Score Indicator
18	Diab	Elixhauser Comorbidity Indicator
19	DiabComp	Elixhauser Comorbidity Indicator
118	diabetes	Charlson Comorbidity Score Indicator
109	diffwalk	Frailty Measure Indicator
155	Dill	Delirium Admission, Binary Indicator

(continued)

Col#	Variable	Label
193	DillBeersCat	Delirium Beers Medication Class, Categorical
194	DillBeersCat2	Delirium Beers Medication Class, Categorical
156	DillNum	# of Hospital Admissions, Delirium Specific
71	Diuretic_Dys	Beers Criteria Medication Class, Rx Days
175	Diuretic_IND	Beers Criteria Medication Class, Binary Indicator
70	Diuretic_Rx	Beers Criteria Medication Class, # Rx
15	Divert	Elixhauser Comorbidity Indicator
5	EGEOLOC	Geographic Location Employee
1	ENROLID	Enrollee ID
28	Epil	Elixhauser Comorbidity Indicator
73	Ergoloid_Dys	Beers Criteria Medication Class, Rx Days
176	Ergoloid_IND	Beers Criteria Medication Class, Binary Indicator
72	Ergoloid_Rx	Beers Criteria Medication Class, # Rx
153	FallDrug	Fall Beers Medication Class, Binary Indicator
151	FallDrugDays	# of Rx Days for Combined Fall Drug Medication Classes
152	FallDrugMos	# of Rx Mos for Combined Fall Drug Medication Classes
150	FallNum	# of Hospital Admissions, Falls Specific
149	Falls	Falls Admission, Binary Indicator
192	FallsBeersCat	Fall Beers Medication Class, Categorical
195	FallsDillBeersCats	Fall and Delirium Beers Medication Classes, Categorical
126	Female	Gender, Female
123	FrailCat	Frailty Category, Categorical
134	FrailCat_0	Frailty Indicator, Pre-Frail, Binary Indicator
132	FrailCat_1	Frailty Indicator, Frail, Binary Indicator
133	FrailCat_2	Frailty Indicator, Robust, Binary Indicator
122	FrailScore	Calculated Frailty Score
75	Gut_motility_stimulator_Dys	Beers Criteria Medication Class, Rx Days
177	Gut_motility_stimulator_IND	Beers Criteria Medication Class, Binary Indicator
74	Gut_motility_stimulator_Rx	Beers Criteria Medication Class, # Rx
106	heartfail	Charlson Comorbidity Score Indicator
21	Hep	Elixhauser Comorbidity Indicator
119	HHBed	Frailty Measure Indicator
20	HIV	Elixhauser Comorbidity Indicator
121	HomeO2	Frailty Measure Indicator
77	Hormones_Dys	Beers Criteria Medication Class, Rx Days
178	Hormones_IND	Beers Criteria Medication Class, Binary Indicator
76	Hormones_Rx	Beers Criteria Medication Class, # Rx
124	HospitalAdm	Hospital Admissions, Binary Indicator
33	Hyp	Elixhauser Comorbidity Indicator
35	LateStroke	Elixhauser Comorbidity Indicator

(continued)

Col#	Variable	Label
97	Laxative_Dys	Beers Criteria Medication Class, Rx Days
179	Laxative_IND	Beers Criteria Medication Class, Binary Indicator
96	Laxative_Rx	Beers Criteria Medication Class, # Rx
107	lipid	Charlson Comorbidity Score Indicator
125	Male	Gender, Male
2	MEMDAYS	Member Days
27	MS	Elixhauser Comorbidity Indicator
6	MSA	Metropolitan Statistical Area
157	Narcotic	Narcotic, Binary Indicator
81	Narcotic_Dys	Beers Criteria Medication Class, Rx Days
180	Narcotic_IND	Beers Criteria Medication Class, Binary Indicator
80	Narcotic_Rx	Beers Criteria Medication Class, # Rx
191	NoBeersRx_IND	No Beers Medications Taken, Binary Indicator
85	Nonbarbiturate_sedative_hypn_Dys	Beers Criteria Medication Class, Rx Days
181	Nonbarbiturate_sedative_hypn_IND	Beers Criteria Medication Class, Binary Indicator
84	Nonbarbiturate_sedative_hypn_Rx	Beers Criteria Medication Class, # Rx
87	Nonbenzodiazepine_sedative_Dys	Beers Criteria Medication Class, Rx Days
182	Nonbenzodiazepine_sedative_IND	Beers Criteria Medication Class, Binary Indicator
86	Nonbenzodiazepine_sedative_Rx	Beers Criteria Medication Class, # Rx
83	NonCOX_NSAIDs_Dys	Beers Criteria Medication Class, Rx Days
183	NonCOX_NSAIDs_IND	Beers Criteria Medication Class, Binary Indicator
82	NonCOX_NSAIDs_Rx	Beers Criteria Medication Class, # Rx
79	NSAIDs_Dys	Beers Criteria Medication Class, Rx Days
184	NSAIDs_IND	Beers Criteria Medication Class, Binary Indicator
78	NSAIDs_Rx	Beers Criteria Medication Class, # Rx
154	OtherBeers	Other Beers Medication Class, Categorical, Study Specific
190	OtherRx_IND	Other Beers Medication Class, Binary Indicator, Study Specific
29	Otitis	Elixhauser Comorbidity Indicator
37	Paral	Elixhauser Comorbidity Indicator
103	paraplegic	Charlson Comorbidity Score Indicator
26	Parkin	Elixhauser Comorbidity Indicator
110	pd	Charlson Comorbidity Score Indicator
99	Phenothiazines_Dys	Beers Criteria Medication Class, Rx Days
185	Phenothiazines_IND	Beers Criteria Medication Class, Binary Indicator
98	Phenothiazines_Rx	Beers Criteria Medication Class, # Rx
111	podiatry	Frailty Measure Indicator
136	pscore	Estimated Probability
108	psychiatric	Charlson Comorbidity Score Indicator
9	PulmHeart	Elixhauser Comorbidity Indicator
17	RA	Elixhauser Comorbidity Indicator

(continued)

Col#	Variable	Label
7	REGION	Region, Categorical
127	Region_1	Region, Northeast, Binary Indicator
128	Region_2	Region, North Central, Binary Indicator
129	Region_3	Region, South, Binary Indicator
130	Region_4	Region, West, Binary Indicator
131	Region_5	Region, Unknown, Binary Indicator
112	rehab	Frailty Measure Indicator
25	Scizo	Elixhauser Comorbidity Indicator
24	Senile	Elixhauser Comorbidity Indicator
115	sepsis	Charlson Comorbidity Score Indicator
4	SEX	Gender of Patient
23	Sicle	Elixhauser Comorbidity Indicator
89	Skeletal_muscle_relaxants_Dys	Beers Criteria Medication Class, Rx Days
186	Skeletal_muscle_relaxants_IND	Beers Criteria Medication Class, Binary Indicator
88	Skeletal_muscle_relaxants_Rx	Beers Criteria Medication Class, # Rx
114	skinulcer	Charlson Comorbidity Score Indicator
34	SLE	Elixhauser Comorbidity Indicator
145	Studycost	Total Cost, Inpatient+Outpatient+Rx
36	SUlcer	Elixhauser Comorbidity Indicator
91	Sulfonylureas_Dys	Beers Criteria Medication Class, Rx Days
187	Sulfonylureas_IND	Beers Criteria Medication Class, Binary Indicator
90	Sulfonylureas_Rx	Beers Criteria Medication Class, # Rx
142	SumIP13	Total Cost, Inpatient
141	SumOP13	Total Cost, Outpatient
140	SumRx13	Total Cost, Rx
93	Tertiary_TCAs_Dys	Beers Criteria Medication Class, Rx Days
188	Tertiary_TCAs_IND	Beers Criteria Medication Class, Binary Indicator
92	Tertiary_TCAs_Rx	Beers Criteria Medication Class, # Rx
31	Valve	Elixhauser Comorbidity Indicator
95	Vasodilator_Dys	Beers Criteria Medication Class, Rx Days
189	Vasodilator_IND	Beers Criteria Medication Class, Binary Indicator
94	Vasodilator_Rx	Beers Criteria Medication Class, # Rx
30	Vertigo	Elixhauser Comorbidity Indicator
117	weakness	Frailty Measure Indicator
135	_LEVEL_	Response Value
137	_Lps	Logit of Propensity Score
139	_MatchID	Matched ID number
138	_MATCHWGT_	Matched obs ATT weight

Table 18
List of dataset variables from O'Neill Roldan (2018)

Col#	Variable	Label
144	ADMS	# of Hospital Admissions
147	adms_0	# of Hospital Admissions
3	AGE	Age of Patient
39	Alpha_Agonist_Central_Dys	Beers Criteria Medication Class, Rx Days
38	Alpha_Agonist_Central_Rx	Beers Criteria Medication Class, # Rx
41	Alpha_Blocker_Dys	Beers Criteria Medication Class, Rx Days
40	Alpha_Blocker_Rx	Beers Criteria Medication Class, # Rx
120	Ambu	Frailty Measure Indicator
43	Antiarrhythmic_Dys	Beers Criteria Medication Class, Rx Days
42	Antiarrhythmic_Rx	Beers Criteria Medication Class, # Rx
45	Antiemetics_Dys	Beers Criteria Medication Class, Rx Days
44	Antiemetics_Rx	Beers Criteria Medication Class, # Rx
47	Antihistamine_1st_Gen_Dys	Beers Criteria Medication Class, Rx Days
46	Antihistamine_1st_Gen_Rx	Beers Criteria Medication Class, # Rx
49	Antihypertensive_Dys	Beers Criteria Medication Class, Rx Days
48	Antihypertensive_Rx	Beers Criteria Medication Class, # Rx
51	Antiinfective_Dys	Beers Criteria Medication Class, Rx Days
50	Antiinfective_Rx	Beers Criteria Medication Class, # Rx
53	Antiparkinson_agent_Dys	Beers Criteria Medication Class, Rx Days
52	Antiparkinson_agent_Rx	Beers Criteria Medication Class, # Rx
55	Antipsychotics_FirstGen_Dys	Beers Criteria Medication Class, Rx Days
54	Antipsychotics_FirstGen_Rx	Beers Criteria Medication Class, # Rx
57	Antipsychotics_SecondGen_Dys	Beers Criteria Medication Class, Rx Days
56	Antipsychotics_SecondGen_Rx	Beers Criteria Medication Class, # Rx
59	Antispasmodic_Dys	Beers Criteria Medication Class, Rx Days
58	Antispasmodic_Rx	Beers Criteria Medication Class, # Rx
61	Antithrombotic_Dys	Beers Criteria Medication Class, Rx Days
60	Antithrombotic_Rx	Beers Criteria Medication Class, # Rx
63	Anxiolytic_Dys	Beers Criteria Medication Class, Rx Days
62	Anxiolytic_Rx	Beers Criteria Medication Class, # Rx
148	AnyADM	Any Hospital Admission, Binary Indicator
100	AnyBeers	Any Beers Medication Present, Binary Indicator
113	arthritis	Frailty Measure Indicator
14	Asthma	Elixhauser Comorbidity Indicator
65	Barbiturates_Dys	Beers Criteria Medication Class, Rx Days
64	Barbiturates_Rx	Beers Criteria Medication Class, # Rx
158	BeersCat	Beers Criteria Medication Class, Categorical, Study-based
67	Benzodiazepines_Long_Acting_Dys	Beers Criteria Medication Class, Rx Days

(continued)

Col#	Variable	Label
66	Benzodiazepines_Long_Acting_Rx	Beers Criteria Medication Class, # Rx
69	Benzodiazepines_Short_Acting_Dys	Beers Criteria Medication Class, Rx Days
68	Benzodiazepines_Short_Acting_Rx	Beers Criteria Medication Class, # Rx
101	bladder	Charlson Comorbidity Score Indicator
116	braininj	Charlson Comorbidity Score Indicator
105	cancer	Charlson Comorbidity Score Indicator
32	Carditis	Elixhauser Comorbidity Indicator
22	CF	Elixhauser Comorbidity Indicator
8	CharlsScore	Charlson Score
12	CHF	Elixhauser Comorbidity Indicator
102	coagulopathy	Charlson Comorbidity Score Indicator
10	ConductHeart	Elixhauser Comorbidity Indicator
11	ConductHeartB	Elixhauser Comorbidity Indicator
13	COPD	Elixhauser Comorbidity Indicator
16	CRF	Elixhauser Comorbidity Indicator
143	Days	Length of Stay, # of Days
146	days_0	Length of Stay, # of Days
104	dementia	Charlson Comorbidity Score Indicator
18	Diab	Elixhauser Comorbidity Indicator
19	DiabComp	Elixhauser Comorbidity Indicator
118	diabetes	Charlson Comorbidity Score Indicator
109	diffwalk	Frailty Measure Indicator
71	Diuretic_Dys	Beers Criteria Medication Class, Rx Days
70	Diuretic_Rx	Beers Criteria Medication Class, # Rx
15	Divert	Elixhauser Comorbidity Indicator
5	EGEOLOC	Geographic Location Employee
1	ENROLID	Enrollee ID
28	Epil	Elixhauser Comorbidity Indicator
73	Ergoloid_Dys	Beers Criteria Medication Class, Rx Days
72	Ergoloid_Rx	Beers Criteria Medication Class, # Rx
126	Female	Gender, Female
123	FrailCat	Frailty Category, Categorical
134	FrailCat_0	Frailty Indicator, Pre-Frail, Binary Indicator
132	FrailCat_1	Frailty Indicator, Frail, Binary Indicator
133	FrailCat_2	Frailty Indicator, Robust, Binary Indicator
122	FrailScore	Calculated Frailty Score
75	Gut_motility_stimulator_Dys	Beers Criteria Medication Class, Rx Days
74	Gut_motility_stimulator_Rx	Beers Criteria Medication Class, # Rx
106	heartfail	Charlson Comorbidity Score Indicator
21	Hep	Elixhauser Comorbidity Indicator

(continued)

Col#	Variable	Label
119	HHBed	Frailty Measure Indicator
20	HIV	Elixhauser Comorbidity Indicator
121	HomeO2	Frailty Measure Indicator
77	Hormones_Dys	Beers Criteria Medication Class, Rx Days
76	Hormones_Rx	Beers Criteria Medication Class, # Rx
124	HospitalAdm	Hospital Admissions, Binary Indicator
33	Hyp	Elixhauser Comorbidity Indicator
35	LateStroke	Elixhauser Comorbidity Indicator
97	Laxative_Dys	Beers Criteria Medication Class, Rx Days
96	Laxative_Rx	Beers Criteria Medication Class, # Rx
107	lipid	Charlson Comorbidity Score Indicator
125	Male	Gender, Male
2	MEMDAYS	Member Days
27	MS	Elixhauser Comorbidity Indicator
6	MSA	Metropolitan Statistical Area
157	Narcotic	Narcotic, Binary Indicator
81	Narcotic_Dys	Beers Criteria Medication Class, Rx Days
80	Narcotic_Rx	Beers Criteria Medication Class, # Rx
85	Nonbarbiturate_sedative_hypn_Dys	Beers Criteria Medication Class, Rx Days
84	Nonbarbiturate_sedative_hypn_Rx	Beers Criteria Medication Class, # Rx
87	Nonbenzodiazepine_sedative_Dys	Beers Criteria Medication Class, Rx Days
86	Nonbenzodiazepine_sedative_Rx	Beers Criteria Medication Class, # Rx
83	NonCOX_NSAIDs_Dys	Beers Criteria Medication Class, Rx Days
82	NonCOX_NSAIDs_Rx	Beers Criteria Medication Class, # Rx
79	NSAIDs_Dys	Beers Criteria Medication Class, Rx Days
78	NSAIDs_Rx	Beers Criteria Medication Class, # Rx
154	OtherBeers	Other Beers Medication Class, Categorical, Study Specific
29	Otitis	Elixhauser Comorbidity Indicator
37	Paral	Elixhauser Comorbidity Indicator
103	paraplegic	Charlson Comorbidity Score Indicator
26	Parkin	Elixhauser Comorbidity Indicator
110	pd	Charlson Comorbidity Score Indicator
99	Phenothiazines_Dys	Beers Criteria Medication Class, Rx Days
98	Phenothiazines_Rx	Beers Criteria Medication Class, # Rx
111	podiatry	Frailty Measure Indicator
136	pscore	Estimated Probability
108	psychiatric	Charlson Comorbidity Score Indicator
9	PulmHeart	Elixhauser Comorbidity Indicator
17	RA	Elixhauser Comorbidity Indicator
7	REGION	Region, Categorical

(continued)

Col#	Variable	Label
127	Region_1	Region, Northeast, Binary Indicator
128	Region_2	Region, North Central, Binary Indicator
129	Region_3	Region, South, Binary Indicator
130	Region_4	Region, West, Binary Indicator
131	Region_5	Region, Unknown, Binary Indicator
112	rehab	Frailty Measure Indicator
25	Scizo	Elixhauser Comorbidity Indicator
24	Senile	Elixhauser Comorbidity Indicator
115	sepsis	Charlson Comorbidity Score Indicator
4	SEX	Gender of Patient
23	Sicle	Elixhauser Comorbidity Indicator
89	Skeletal_muscle_relaxants_Dys	Beers Criteria Medication Class, Rx Days
88	Skeletal_muscle_relaxants_Rx	Beers Criteria Medication Class, # Rx
114	skinulcer	Charlson Comorbidity Score Indicator
34	SLE	Elixhauser Comorbidity Indicator
145	Studycost	Total Cost, Inpatient+Outpatient+Rx
36	SUlcer	Elixhauser Comorbidity Indicator
91	Sulfonylureas_Dys	Beers Criteria Medication Class, Rx Days
90	Sulfonylureas_Rx	Beers Criteria Medication Class, # Rx
142	SumIP13	Total Cost, Inpatient
141	SumOP13	Total Cost, Outpatient
140	SumRx13	Total Cost, Rx
93	Tertiary_TCAs_Dys	Beers Criteria Medication Class, Rx Days
92	Tertiary_TCAs_Rx	Beers Criteria Medication Class, # Rx
31	Valve	Elixhauser Comorbidity Indicator
95	Vasodilator_Dys	Beers Criteria Medication Class, Rx Days
94	Vasodilator_Rx	Beers Criteria Medication Class, # Rx
30	Vertigo	Elixhauser Comorbidity Indicator
117	weakness	Frailty Measure Indicator
135	_LEVEL_	Response Value
137	_Lps	Logit of Propensity Score
139	_MatchID	Matched ID number
138	_MATCHWGT_	Matched obs ATT weight

Table 19

List of ICD-9 codes for Charlson Score Index indicator variables

Charlson Comorbidity Condition	ICD-9 Code Range/Values
AIDS/HIV	042.x - 044.x
Any malignancy, except malignant neoplasm of skin	140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6
Cerebrovascular disease	362.34, 430.x - 438.x
Chronic pulmonary disease	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x
Dementia	290.x, 294.1, 331.2
Diabetes with chronic complication	250.4 - 250.7
Diabetes without chronic complication	250.0 - 250.3, 250.8, 250.9
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9
Metastatic solid tumour	196.x - 199.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Moderate or severe liver disease	456.0 - 456.2, 572.2- 572.8
Myocardial infarction	410.x, 412.x
Peptic ulcer disease	531.x - 534.x
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Rheumatic disease	446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x

Source: (Quan et al., 2005)

Table 20
List of ICD-9 codes for Elixhauser Comorbidity Index indicator variables

Elixhauser Condition	ICD-9 Code Range/Values
AIDS/HIV	042.x - 044.x
Alcohol abuse	265.2, 291.1 - 291.3, 291.5 - 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0 - 571.3, 980.x, V11.3
Blood loss anemia	280.0
Cardiac arrhythmias	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0 - 427.4, 427.6 - 427.9, 785.0, 996.01, 996.04, V45.0, V53.3
Chronic pulmonary disease	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8
Coagulopathy	286.x, 287.1, 287.3 - 287.5
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x
Deficiency anemia	280.1 - 280.9, 281.x
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311
Diabetes, complicated	250.4 - 250.9
Diabetes, uncomplicated	250.0 - 250.3
Drug abuse	292.x, 304.x, 305.2 - 305.9, V65.42
Fluid and electrolyte disorders	253.6, 276.x
Hypertension, complicated	402.x - 405.x
Hypertension, uncomplicated	401.x
Hypothyroidism	240.9, 243.x, 244.x, 246.1, 246.8
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0 - 456.2, 570.x, 571.x, 572.2 - 572.8, 573.3, 573.4, 573.8, 573.9, V42.7
Lymphoma	200.x - 202.x, 203.0, 238.6
Metastatic cancer	196.x - 199.x
Obesity	278.0
Other neurological disorders	331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x - 335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3
Paralysis	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9
Peptic ulcer disease, excluding bleeding	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9
Peripheral vascular disorders	093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4
Psychoses	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Pulmonary circulation disorders	415.0, 415.1, 416.x, 417.0, 417.8, 417.9
Renal failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Rheumatoid arthritis	446.x, 701.0, 710.0 - 710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30
Solid tumor without metastasis	140.x - 172.x, 174.x - 195.x
Valvular disease	093.2, 394.x - 397.x, 424.x, 746.3 - 746.6, V42.2, V43.3
Weight loss	260.x - 263.x, 783.2, 799.4

Source: (Quan et al., 2005)