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Meaningful Measurement Matters: Defining Potentially Inappropriate Medication Use to Target Cognitive Outcomes

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MEANINGFUL MEASUREMENT MATTERS: DEFINING POTENTIALLY INAPPROPRIATE MEDICATION USE TO TARGET COGNITIVE OUTCOMES

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Pharmacy
at the University of Kentucky

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ABSTRACT OF DISSERTATION

MEANINGFUL MEASUREMENT MATTERS: DEFINING POTENTIALLY INAPPROPRIATE MEDICATION USE TO TARGET COGNITIVE OUTCOMES

Preventable and unintended consequences of medication use occur in more than 25% of ambulatory and hospitalized patients, and nearly half of long-term care patients.[1] Unfortunately, many medications used to treat common health conditions in older adults (such as anxiety, behavioral disturbances, incontinence, insomnia, depression, and pain) have also been linked to cognitive impairment and decline. Recently, substantial efforts to investigate medications and medication classes that may be associated with cognitive impairment and decline in older adults have been undertaken. Unfortunately, studies have used a wide variety of different tools to define “potentially inappropriate medication” (PIM) use, and no published literature has consistently associated a particular medication appropriateness tool with cognitive outcomes, leaving clinicians and patients without a much-needed approach to deprescribing for preservation of cognitive function. Given the national focus on prevention of cognitive decline, the vast pool of available PIM measurement tools, and the variety of ways in which to consider exposure to PIMs, there is a need to determine which tool (if any) identifies PIMs most strongly associated with cognitive decline. Without widespread consensus as to what measure of PIM use is the best to use when studying the aptitude of medications to cause cognitive decline, clinicians will not have the tools they need to improve outcomes for their patients. As the world awaits further developments that may one day produce an effective treatment (or even cure) for the terrible brain-destroying disease of dementia, we can take steps today to improve medication therapy that may dampen its horrific impact on the lives of older adults and their loved ones.

In this work, we set out to examine the issue of measuring medication appropriateness to target cognitive outcomes with the intent of informing future research and clinical practice. While the gold-standard in evidence generation remains randomized placebo-controlled clinical trials, we have seen that even the most rigorously performed trials are not useful to generate evidence if there is not a consistent meaning to "inappropriate medication." Groundwork must laid to provide crucial validation and consensus to the measurement of medication appropriateness in light of cognition, and then it must be applied to numerous prospective research endeavors in order to provide a synthesized evidence-base for how medications should be managed to ensure appropriate use in older adults wishing to preserve cognition.

In this first section, we have provided a historical context for the importance of medication management, described the current state of affairs in the US and around the world, and provided an overview of the available tools that have been used to measure medication appropriateness with a perspective toward cognition.

Section two will utilize a number of these tools to estimate prevalence of potentially inappropriate medication use in various populations of American older adults.

The next section will use various methodological techniques and data sources to explore how some of these tools may or may not be associated with cognitive decline in older adults. We will define both PIM use and cognitive decline in a variety of ways to determine the effect varying definitions may have on new evidence generation.

Finally, we will explore how the findings provided in this work may be applied to clinical practice, future research endeavors, and governmental policies.

KEYWORDS: dementia, potentially inappropriate medication, measurement validation, cognitive decline, deprescribing

Ashley Irene Martinez

May 14, 2020
Date

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DEDICATION

This work is dedicated to my grandparents, Londa and Larry Jeppesen, who are champions battling the demon dementia everyday, and to all caregivers and those afflicted with this terrible disease. You inspire me to work harder.

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1 INTRODUCTION

1.1 Changing Healthcare, Changing Priorities

The year is 1900, and the United States of America (US) had finally established itself as a world power: successful agricultural ventures, transcontinental railroads, and the world's largest steel production meant life in America was good.[1] The average US newborn could expect to live approximately 47 years, and the top three causes of death were pneumonia, tuberculosis, and gastrointestinal infections.[2] Only one in twenty Americans were over the age of 65.

Medicine was rapidly adapting to the new "germ theory" of disease, and the success of antibiotics and other public health interventions meant that by the mid-20th century, life expectancy had risen nearly 20 years and the leading causes of death shifted to chronic conditions.[3] With this shift came the increasing importance of medication therapy in lives of all Americans, but especially for older adults. As studies of the causes of chronic diseases expanded more focus was drawn to prevention of long-term consequences of chronic disease, including treatment of such conditions as hypertension and hyperlipidemia.[4] By the beginning of the 21st century, one in six Americans was at least 65 years old, and multimorbidity had become the normal state for older adults.[5] In fact, 15% of adults aged 65 years and older have four or more common chronic conditions.[6]

The changes in healthcare and its delivery over the last century have led to a landscape in which heart disease and cancer have taken over as the leading causes of death in America, and providers have needed to adapt into a more specialty-driven model. Just as medical doctors branched out into specialized subdivisions of internal medicine to treat specific diseases,[7] so did pharmacists begin to play a larger role in the clinical management of medications.[8] While medication management is important in all disease states for patients of all ages, the burden of multimorbidity in older adults as well as biological changes leading to pharmacokinetic and pharmacodynamic peculiarities makes managing their multiple treatments especially important.

1.2 Medication Management in Older Adults

The older adult population represents a unique challenge to optimization of medication appropriateness. Although many in this population suffer from life-limiting diseases, the course from diagnosis and initial medication therapy is neither short nor linear. The vast variability in health status amongst older adults – known as aged heterogeneity[9] – creates a complex situation wherein healthcare providers must take generalized guidelines and apply them to individuals who range functionally from fit to frail. Thus, it becomes of essential importance for healthcare providers to consider their patients' desires and choices while medical priorities continue to change. A survey of physicians found that some of the most important barriers to optimizing medication use in older adults include "inadequate guidelines, incomplete medical histories, lack of time, avoidance of negative consequences, established beliefs in the benefits and harms of medication use and others."[10]

Evidence-based medicine dictates that healthcare providers should use clinical practice guidelines (CPGs) to direct treatment regimens for all patients. While multiple medication therapies can often be effective, and many CPGs recommend them, many fail to consider the impact these guidelines can have on older adults with multimorbidity. While appropriate use of multiple medications in older adults is common and often beneficial, strict adherence to CPGs can result in polypharmacy (the receipt of *too many* medications), which increases the potential for adverse drug reactions (ADRs) and drug-drug interactions (DDIs).[11] ADRs and DDIs can be especially troublesome because they can be difficult to distinguish from other medical conditions, often resulting in the prescribing of more medications to treat symptoms caused initially by a DDI or ADR. This phenomenon is known as a "prescribing cascade"[12] (see Figure 1.6.1).

Today, polypharmacy is so common that it was considered a priority medication safety concern by the US government in 1990,[13] and has been consistently associated with numerous adverse health outcomes.[14] As the tide ebbs and flows, the field has come to realize that assessing medication appropriateness is not as simple as merely counting the number of medications

one receives.[15] Even in cases where significant polypharmacy is present, investigators and clinical providers alike realize that there is more nuance to appropriateness than ADRs and DDIs. In a recent systematic review with an expert panel, clinicians identified 16 additional indicators that guide decisions into whether polypharmacy is appropriate.[16] Nearly all of these indicators revolve around patient-specific factors that can transform an otherwise appropriate medication into an inappropriate therapy. Another review found 138 different definitions for polypharmacy, with 65 different studies defining polypharmacy as either ≥4 or ≥5 total medications.[17] Other definitions consider varying extents of polypharmacy, such as *hyperpolypharmacy*, or the use of ≥10 medications.

Despite its vast range of definitions, there is a general perception by researchers, policymakers, and clinicians alike that polypharmacy is always inappropriate. While many studies have found associations between polypharmacy and multiple health outcomes including mortality, ADEs, and hospitalization,[18–20] more recent publications have advocated shifting toward using the term “appropriate polypharmacy” to encourage providers to focus on patient-specific context that may be more clinically relevant than a count of medications.[15]

These concerns have not gone unnoticed in the medical community. Recognizing that specialized guidance may help ameliorate the problem of complex treatment decisions in multimorbid older adults, researchers and clinicians have undertaken to provide such recommendations. The "CRIteria to assess appropriate Medication use among Elderly complex patients" (CRIME) project provided recommendations for treating five common comorbidities in older adults.[21] These recommendations are based on taking a systematic approach to ensuring optimal therapy, which can be broken down into 8 steps[22] (Figure 1.6.2). Further complicating prescribing decisions in older adults is the fact that often medication effectiveness and safety are in conflict, as are costs and patient choice (see Figure 1.6.3).

Governments throughout the world have begun to recognize this problem and take action. A stellar example of proactive emphasis on this problem can be found in Australia. The Australian government has been emphasizing the

importance of “quality use of medicines” since 1999, and most recently has published recommendations for a national strategy to reduce PIM use in older adults.[23] Similarly, the European Union has taken steps to improve awareness and research into both polypharmacy and PIM use with their Stimulating Innovation Management of Polypharmacy and Adherence in THe ElderlY (SIMPATHY) project.[24] Collaboration with ten institutions across eight European countries aims to spur research into medicine use in older adults, with a focus on evidence-based polypharmacy interventions.

While the US does not have a national strategy to improve appropriate medication use, the Centers for Medicare and Medicaid Services requires Part D plan sponsors to establish quality assurance measures “to reduce medication errors and adverse drug interactions and improve medication use.”[25] At a minimum, these measures must include both concurrent and retrospective drug utilization review (DUR) systems. Concurrent DURs must screen for therapeutic duplication, age and gender-related contraindications, over- and under-utilization, drug-drug interactions, incorrect dosage and duration of therapy, and drug-allergy contraindications. Additionally, Part D plan sponsors are required to offer Medication Therapy Management (MTM) programs to beneficiaries with multiple chronic diseases and who are using multiple medications in order to “optimize therapeutic outcomes through improved medication use.”[25] Both DUR and MTM program requirements are codified in regulations found at 42 CFR § 423.153.13. While neither of these programs are targeted specifically at improving appropriate prescribing or reducing potentially inappropriate medication use, the population served by Medicare Part D prescription drug plans could benefit greatly from targeted programs.

1.2.1 Cognition as a Driver of Medication Management

One particular health outcome of extreme importance in today’s society is cognitive decline. Alzheimer’s Disease and related-dementias are now the fifth-leading cause of death globally;[26] in the US at least 1 in 9 people over 45 years of age experience subjective cognitive decline.[27] In addition to cognitive decline being an

extremely prevalent condition, subjects with dementia or cognitive impairment have as many comorbidities as similar cognitively-intact persons, and take on average at least five medications daily.[28] Despite having a similar burden of comorbidity, people living with dementia more commonly use certain medication classes such as antidepressants and antipsychotics[28] that have been shown to worsen cognitive decline. While older adults in general are more susceptible to ADRs than their younger counterparts due to pharmacokinetic changes,[29,30] older adults with dementia may be even more sensitive to cognitive adverse events than similar cognitively-intact older adults due to changes in the permeability of the blood-brain barrier.[31,32] For some individual medications or medication classes, there is ample enough evidence to support their link to cognition that deprescribing guidelines have been developed. These include proton-pump inhibitors,[33,34] benzodiazepines,[35] and certain psychotropic medications.[36]

These facts highlight the importance of appropriate medication management in older adults at risk for and living with cognitive impairment. Access to medication appropriateness tools that have been externally validated and shown to be associated with cognitive decline is an invaluable tool for healthcare providers when making important medication therapy optimizations.

1.2.2 Measuring Medication Appropriateness

While medication management is an essential component in the medical care of older adults (including those with or at risk for cognitive impairment), simply understanding the importance of medication management is not enough to be able to implement it consistently and effectively in both clinical practice and research. Indeed, the first step to implementing assessment of medication appropriateness into all necessary aspects of clinical care is to accurately and specifically define exactly what one is measuring when assessing "appropriateness."

In general, to measure appropriate prescribing, one must consider not only the avoidance of inappropriate medications, but also the appropriate use of indicated medications, monitoring for adverse events, avoidance of drug-drug interactions, and ensuring that the care provided optimizes the patient's choice.[37]

Fortunately, researchers have developed tools that aim to facilitate the identification of both appropriate and potentially inappropriate medications (PIMs) in an effort to optimize medication therapy. These tools range from long lists of explicit criteria that define PIMs to calculated formulas that give scores based on risks. Some tools require extensive clinical judgement, while others are easily automated and require little patient-specific information. Each tool addresses different appropriateness indicators, ranging from patient adherence, ADRs, DDIs, contraindications, alternative therapies, clinical efficacy, medication regimen complexity, cost-effectiveness, dosage, duplication, indication, under-prescribing, specific safety issues, and other inappropriate prescribing. The plethora of tools available to clinicians to guide prescribing decisions can be overwhelming, so efforts are being undertaken to validate these tools. Unfortunately, some have been more extensively researched than others.

Measurements for prescribing appropriateness can be either explicit or implicit. Explicit measures of prescribing appropriateness generally consist of lists of criteria that should be considered “inappropriate” and are the most commonly used, with one study finding that almost 62% of prescribing appropriateness assessment tools were criteria-based.[38] These measures are generally developed using expert opinions or consensus techniques, as there is a dearth of evidence on important treatment decisions in geriatrics.[39]

While explicit measures are easily applied in practice as they require no in-depth clinical reasoning, they also do not generally address patient preferences or the nuances of multi-morbidity. Conversely, implicit measures require practitioners to use patient-specific information to guide decisions about prescribing. In this sense, implicit measures tend to be more patient-centric, rather than medication-centric. Additionally, implicit measures commonly include scoring systems to aid healthcare providers in decision making. Despite the importance and potential benefits of using these types of measures, they are time-consuming and difficult to apply in practice.

Both explicit criteria and implicit guides are utilized by healthcare providers working with older adults, but it can be difficult to determine which measure best

meets the provider and patient's needs. One recent systematic review identified 42 prescribing appropriateness tools, which varied not only in their format (explicit vs. implicit), but also in their focus on stopping inappropriate and starting appropriate medications, suggesting alternative treatment strategies, and whether dosing was considered.[38]

As noted previously, determining whether a medication or medication regimen is appropriate is a nuanced process, involving consideration of more than 20 distinct clinical providers.[16] Determining how to measure the appropriateness of medication(s) in research is no less complicated. Each of the more than 40 different medication appropriateness tools has been used in a variety of manners and combinations to assess medication appropriateness in research studies. A recent systematic review found that nearly one-third of studies that assessed medication appropriateness used multiple tools to do so, and almost 90% did not use the complete clinical tool, but a version of it.[40]

While much research has been dedicated to developing measures of prescribing appropriateness, few of these measures have been externally validated and correlated with patient outcomes. There has certainly been progress in this arena, evidenced by a systematic review published in 2007 finding only 18 studies that linked various prescribing appropriateness measures to health outcomes, while another published in 2018 found 53 separate studies.[37,38] Still, only about one-third of available tools have ever been investigated for association with any patient outcome,[38] highlighting the need for more patient-centered prescribing appropriateness measures.

1.3 Cognitively Targeted Medication Appropriateness Assessment Tools

Though there are many tools available to both researchers and clinicians, only six of them have ever been investigated with regards to their relationship to cognitive outcomes. Here, we present a brief description of each of these tools, including their development and relevant external validation studies. They are presented in order of their initial publication. A summary of these tools can be found in Table

1.6.1, while a summary of studies investigating the tools' association with cognitive decline is detailed in Table 1.6.2.

1.3.1 Beers Criteria

What is now known as the Beers criteria began as a list of 30 therapeutic classes and medications that should be avoided in older adults residing in nursing homes. Compiled by geriatrician Mark Beers and a consensus panel of experts and published in 1991, the Beers criteria was one of the first sets of explicit criteria to identify PIM use.[28] The Beers criteria were subsequently updated in 1997 and 2003, followed by a major reformation in 2012 to more closely follow evidence-based medicine guidelines. Over time, the Beers criteria have evolved to be applicable to all older adults, and the 2015 and 2019 versions of Beers criteria now include five different types of criteria including: potentially inappropriate medications in most older adults, medications that should be avoided only in certain health conditions (DZIs), medications that should be used with caution, drug-drug interactions (DDIs), and recommended dose adjustments based on kidney function.[42,43]

The Beers criteria are thus intended for use by clinicians treating adults aged 65 years or older in all ambulatory, acute, and institutionalized settings, and its creators urge that the criteria "not be applied in a punitive manner", but rather as an opportunity for education and quality improvement.[43] Being the most commonly used tool to assess medication appropriateness assessment tool in the literature,[40] the Beers criteria have been extensively studied for their relationship with a number of health outcomes, but only a few studies have considered cognitive outcomes. In one large database study with over 70,000 subjects, Beers "high-severity" (BHS) anticholinergics were not associated with delirium or hallucinations after one year, but BHS narcotics were. In another database study investigating drug-related problems (DRPs) as defined by ICD-9 codes, 1.45% of PIM users experienced "any cognitive impairment" (definition not specified) compared to 0.51% of non-PIM users (OR [95% CI] 2.88 [2.05-4.04]).[44]

Neither study used the 2015 Beers criteria, and no studies have been published using the updated criteria that were released in January 2019. For the 2019 criteria, two medications no longer on the US market were removed and a number of medications to be used with caution in older adults with certain conditions were also removed because they are not uniquely inappropriate to older adults. Specific for our population of interest, histamine-2 receptor antagonists were removed from the list of medications to be avoided in older adults with dementia due to weak evidence and to avoid overly restricting therapeutic options given the strong evidence against use of proton pump inhibitors[33]; aripiprazole was also removed as a preferred agent in Parkinson disease due to both safety and efficacy concerns.

The 2019 update also added 3 PIMs, 4 medications to be used with caution, 2 DZIs, and 7 DDIs. The added DZIs and DDIs are significant because these categories of PIMs make Beers criteria the only among the six tools studied for cognitive outcome associations that has any patient-specific recommendations.

1.3.2 Anticholinergic Drug Scale

The investigators who developed the Anticholinergic Drug Scale (ADS) did so with the recognition that the relationship between delirium and anticholinergic medications was wrought with poor measurement of anticholinergic exposure, but using serum anticholinergic activity was too cumbersome to be done routinely. In a prospective cohort study published in 2001, they designed the ADS by having geriatric clinicians independently rate each of 340 medications from 0 (no anticholinergic activity) to 3 (marked anticholinergic activity) based on their clinical experience.[45] Individual medication scores are summed for a total ADS. . A later pilot study in 2002[46] and validation study published in 2006[47] expanded the ADS and confirmed that it correlated well with serum anticholinergic activity.

While multiple studies have used the ADS to define PIMs in populations with cognitive impairment,[48,49] few validation studies have been conducted to determine its ability to predict cognitive decline. One retrospective cohort study did find a positive association between the ADS and cognitive decline when defined

using a multiple of measures,[50] but another prospective cohort study failed to find an association between cognitive decline in already-demented patients with an ADS score of >3.[51] Other, non-validation studies have found conflicting results regarding the relationship between ADS and cognitive decline. The ADS has been correlated with cognitive decline in subsets of populations with depression and schizophrenia. One case-control study found that use of medications with ADS score ≥ 2 was associated with risk for dementia (OR [95% CI] 1.26 [1.22-1.29]) in an elderly population with depression,[52] while another considered patients with schizophrenia and found that those with ADS scores ≥4 performed more poorly on a cognitive test than those with ADS < 4.[53] However, a retrospective cohort study found no association between the ADS of bladder antimuscarinics and cognitive performance in a large sample of older adults in long-term care.[54]

1.3.3 Sedative Load

The Sedative Load tool was first published in 2003 and divides sedative medications into four classes: primary sedatives, drugs with sedation as a prominent side effect, drugs with sedation as a potential adverse effect, and drugs with no known sedation.[55] Investigators searched the compendium of prescription drugs available in Finland from 1998-2001 using the key words of sedating, sedative, drowsiness, sleepiness, lassitude, exhaustion, tiresome, and fatigability.

Sedative load – like the ADS – is a scoring tool that includes only regularly scheduled prescription medications (not those used as-needed). Primary sedatives receive a Sedative Rating of 2, while drugs with sedation as a prominent side effect receive a rating of 1. The individual ratings of each medication are summed for the total Sedative Load.

No studies have successfully linked PIM use as measured using the Sedative Load with cognitive decline. In a cross-sectional study of community-dwelling older men in Australia, there was no relationship between participants with any level of Sedative Load and cognitive impairment.[56] Interestingly, one prospective cohort study comprising 1,444 long-term care residents in Finland

actually found a statistically significant relationship between having a higher sedative load and not being diagnosed with dementia (p=0.009).[57]

1.3.4 Drug Burden Index

The Drug Burden Index (DBI) was first reported in 2007, and is one of the few prescribing appropriateness tools that explicitly considers over-the-counter (OTC) medications in addition to prescription medications.[58] One of the things that makes the DBI unique is that it is primarily based on dosing. The DBI has been studied in Australia, Canada, Finland, New Zealand, the Netherlands, the United Kingdom, and the US.[59]

To develop the DBI, investigators first designed a formula to quantify "total drug burden," (TDB) based on physical and mental health outcomes using data from the *Physicians' Desk Reference*[60] and *Mosby's Drug Consult*[61]. TDB considers 1) drugs with anticholinergic effects (AC), and 2) drugs with sedative effects (S). Investigators hypothesized that the burden of AC and S medications would be linearly associated with physical and cognitive function, both via the presence of these medications and the extent of their exposure. Accordingly, the DBI is based predominantly on dosing of AC and S medications. Each medication receives an individual DBI score between 0 and 1, and the total DBI is calculated as in Equation 1.1, where the pharmacological effect (E) of AC and S drugs is calculated based on the daily dose (D) and the minimum daily dose according to the Food and Drug Administration (δ) where α represents a constant. A total DBI of ≥1 is considered "high."

Equation 1.1. Pharmacological Effect

$$Total\ DBI = \frac{E}{\alpha} = \sum \frac{D}{\delta + D}$$

The DBI has been extensively externally validated and positively associated with five patient-specific health outcomes (hospitalization, mortality, falls, cognitive decline, and functional decline). The initial published report found a significant positive association between DBI and cognitive function as measured using the

Digital Symbol Substitution Test in a cross-sectional study.[58] However, this is only one of four validation studies specifically exploring the relationship between cognitive outcomes and DBI. While one medical chart review found that a high DBI (≥1) was associated with nearly three times the odds of a hospital admission for delirium (OR [95% CI] 2.95 [1.34-6.51]),[62] another found no association between DBI and cognitive function as measured by the Abbreviated Mental Test.[63] A subsequent retrospective cohort study consisting of community-dwelling older men found no relationship between DBI exposure and cognitive impairment measured with two different performance tests.[64] Still another retrospective cohort study found consistent positive associations between the anticholinergic component of the DBI and cognitive decline defined with a multitude of measures.[50]

1.3.5 Anticholinergic Cognitive Burden Scale

Like the DBI and ADS, the Anticholinergic Cognitive Burden Scale (ACBS) is also a scoring tool with a focus on anticholinergic medications.[65] For this tool, anticholinergic activity of medications was determined based on a literature review of serum anticholinergic activity.[66] A medication was scored as 0 if there were no laboratory tests or clinically relevant cognitive effects, 1 if there were only laboratory tests, and 2 or 3 if there were both. ACBS scores of 1 indicate “possible” anticholinergic effects, whereas scores from 2-3 indicate “definite” anticholinergic effects.

The ACBS is the prescribing appropriateness tool that has been most extensively studied for its relationship with cognitive outcomes. Many of the studies have included long follow-up and large sample sizes. Additionally, the studies have considered nuanced definitions of exposure, including continuous vs intermittent use and measurement of the ACBS as a continuous vs categorical exposure variable. A retrospective cohort study with a follow-up time of one year found an increased risk of cognitive decline whether AC exposure was measured by duration, number dispensed at the same time, or using the ACBS.[67] Another longitudinal observational study of 1,652 community-dwelling African Americans over the age of 70, investigators found that while the risk for mild cognitive

impairment or dementia after 6 years increased with the number of definite anticholinergic medications (OR [95% CI] 1.46 [1.07-1.99]), there was no association between the number of possible anticholinergic medications and risk for cognitive decline (OR [95% CI] 0.96 [0.85-1.09]).[68] Another longitudinal study found similar results after 2 years when measuring cognitive decline using mini mental state examination.[69]

1.3.6 Anticholinergic Risk Scale

The Anticholinergic Risk Scale (ARS) was developed in response to the lack of specificity of Beers criteria in its association with cognitive outcomes. Medications with known potential to cause anticholinergic adverse effects were identified by three experts (one physician and two pharmacists) who ranked each based on their potential to cause anticholinergic adverse effects on a scale from 0 (no risk) to 3 (high anticholinergic potential). The total ARS score is the summation of individual ARS scores for each medication.

In the initial published report detailing ARS, investigators focused on the adverse effects of anticholinergic medications, dividing them into central effects (i.e., falls, dizziness, or confusion) and peripheral effects (i.e. dry eyes, dry mouth, and constipation). This investigation found that in both a retrospective and prospective cohort study of older adult inpatients, higher ARS scores were associated with a higher risk for central ADRs.[70] Another prospective cohort study found that higher ARS scores were also associated with poorer performance on a number of neuropsychological cognitive performance tests,[50] and a cross-sectional study also found an association between cognitive performance and ARS.[71] However, one chart review did find no relationship.[63]

Among these six tools (Beers criteria, ADS, Sedative Load, DBI, ACBS, and ARS), the strongest support from the literature for a relationship between the measurement tool and cognitive outcomes is for the ACBS. In addition to it being the most extensively studied with regards to cognitive outcomes, there were also no published studies with negative results. However, it should be noted that while

the other tools have been used in papers written by investigators other than those who developed it, the ACBS has only been utilized in papers authored by the original investigators.

The ADS, DBI, ACBS, and ARS tools all have scoring systems and focus heavily (or exclusively) on anticholinergic medications. Conversely, the Beers criteria is a much more extensive list of medications that is compiled into a list of explicit criteria, while the Sedative Load tools focuses only on medications with sedative effects. Some have argued that explicit criteria are more easily applied in practice,[72] and others have suggested that the sheer volume of medications included in explicit criteria make them too cumbersome for practice. Tools with a scoring system may be more easily implemented by healthcare providers as they could be integrated with computer systems and output a single score for clinical assessment.

1.4 Other Medication Appropriateness Assessment Tools

As noted previously, while only six medication appropriateness tools have been investigated for their relationship with cognitive outcomes, there are more than 40 tools available to both researchers and clinicians. In a recent systematic review,[38] investigators identified nine tools that used scoring systems to quantify PIMs; five of these have been noted above to have been investigated in relationship to cognitive outcomes (ACBS, ADS, ARS, DBI, and Sedative Load). The other 33 tools identified did not have scoring systems, and included the Beers criteria discussed above.

All but one of the tools with a scoring system has been externally validated for any health outcome, while only five of the tools without scoring systems have been externally validated. Of these, most have only been investigated in one or two external validation studies.[73–75] Conversely, the Beers criteria has been positively associated not only with cognitive outcomes, but also with hospitalizations, falls, mortality, functional decline, and ADRs in 4 out of 8 other studies.[76–79] The only other medication appropriateness assessment tool that has

been as extensively studied as the Beers criteria is the Screening Tool of Older Person's Prescriptions (STOPP). Created in 2008 by expert consensus in the European Union[80] and updated in 2015[81], STOPP is similar to Beers in that it consists of an extensive list of medications that may be potentially inappropriate for older adults. When used to measure PIM use, it too has been positively associated with hospitalizations, mortality, falls, functional decline, ADRs, and quality of life in six different investigations.[82–87]

There is significant cross-over between the medications present in the Beers and STOPP tools, with the major difference being that Beers criteria is predominantly used in North America, while STOPP is mainly utilized in Western Europe. Furthermore, STOPP has been directly compared to Beers criteria in its ability to identify PIM use in older adults. In fact, STOPP has been found to identify more PIMs than Beers criteria in older adults in numerous investigations.[88–95]

Thus, while only the ADS, ACBS, ARS, Beers criteria, DBI, and Sedative Load have been formally associated with any cognitive outcome in the published literature, it is reasonable to consider STOPP as another medication appropriateness assessment tool that may be useful in defining PIM use as it relates to cognitive outcomes given its similarity and potential superiority to the Beers criteria.

1.5 Specific Aims

While targeting cognition when managing medications in older adults may be a relatively new product of a rapidly shifting healthcare landscape, the need for improving measurement of medication appropriateness is extensive nonetheless. Without widespread consensus as to what measure of PIM use is the best to use when studying the propensity of medications to cause cognitive decline, clinicians will not have the information they need to improve outcomes for their patients. As the world awaits further developments that may one day produce an effective treatment (or even cure) for the terrible brain-destroying disease of dementia, we

can take steps today to improve medication therapy and potentially dampen the horrific impact of dementia on the lives of older adults and their loved ones.

In this work, we set out to examine the issue of measuring medication appropriateness to target cognitive outcomes with the intent of informing future research and clinical practice. While the gold-standard in evidence generation remains synthesis of data from randomized placebo-controlled clinical trials, we have seen that systematic reviews are unable to coalesce data from even the most rigorously performed trials if there is no consistency in the definition of "inappropriate medication." Groundwork must be laid to provide crucial validation and consensus to the measurement of medication appropriateness in light of cognition, and then it must be applied to numerous prospective research endeavors in order to provide a synthesized evidence-base for how medications should be managed to ensure appropriate use in older adults wishing to preserve cognition or prevent cognitive decline.

In this first section, we have provided a historical context for the importance of medication management, described worldwide approaches to medication management in older adults, and provided an overview of the available tools that have been used to measure medication appropriateness with a perspective toward cognition.

Section two will utilize a number of these tools to estimate prevalence of potentially inappropriate medication use in various populations of American older adults.

The next section will use different methodological techniques and data sources to explore how some of these tools may or may not be associated with cognitive decline in older adults. We will define both PIM use and cognitive decline in a variety of ways to determine the effect varying definitions may have on associations and effect sizes.

Finally, we will explore how the findings provided in this work may be applied to clinical practice, future research endeavors, and governmental policies.

1.6 Tables and Figures

Table 1.6.1. Prescribing Appropriateness Tools for Cognitive Outcomes

Tool	Year Created	Scoring System	Drug class focus	Dosing	Explicit Criteria
Beers	1991		None	Mentions	✓
ADS	2002	✓	Anticholinergics	Based predominantly	
Sedative Load	2003	✓	Sedatives	Does not consider	
DBI	2007	✓	Anticholinergics & sedatives	Based predominantly	
ACBS	2008	✓	Anticholinergics	Does not consider	
ARS	2008	✓	Anticholinergics	Does not consider	

ACBS: Anticholinergic Cognitive Burden Scale; ARS: Anticholinergic Risk Scale; DBI: Drug Burden Index

Table 1.6.2. List of Studies Investigating Cognitive Outcomes and PIMs

Exposure	Author	Year	Outcome	Design	N	Setting	Finding
ACBS, ADS, ARS, DBI	Kashyap[50]	2014	Cognitive battery	P. cohort	102	Community	+
ACBS	Campbell[68]	2010	MCI/Dementia	P. cohort	1,652	Community	+/-
ACBS	Fox[69]	2011	MMSE	P. cohort	12,423	Community	+
ACBS	Cai[67]	2013	Dementia	R. cohort	3,690	Community	+
ACBS, ARS	Pasina[71]	2013	SBT	Cross-sectional	1,380	Inpatient	+
ADS	Kersten[51]	2013	CERAD, MMSE	P. cohort	87	LTCF	-
ADS	Chatterjee[52]	2016	Dementia	Case-control	28,388	LTCF	+
ADS	Eum[53]	2017	BACS	P. cohort	483	Community	+
ARS	Rudolph[70]	2008	Confusion	P. cohort	132	Inpatient	+
ARS, DBI	Bostock[63]	2013	AMT	Chart review	271	Inpatient	-
Beers 2003	Fick[44]	2008	Cognitive impairment	R. cohort	17,971	Community	+
Beers 2012	Stockl[78]	2010	Delirium	R. cohort	74,716	Community	+/-
DBI	Hilmer[58]	2007	DSST	Cross-sectional	3,075	Community	+
DBI	Gnjidic[64]	2012	ACE, TMT	R. cohort	887	Community	-
DBI	Best[62]	2013	Delirium admit	Chart review	329	Inpatient	+
Sedative load	Taipale[57]	2009	Dementia	P. cohort	1,444	LTCF	-
Sedative load	Gnjidic[56]	2012	MMSE	Cross-sectional	1,696	Community	-

ACBS: anticholinergic cognitive burden scale; ACE: Addenbrooke's cognitive examination; AMT: abbreviated mental test; ARS: anticholinergic risk scale; BACS: brief assessment of cognition in schizophrenia; CERAD: Consortium to Establish a Registry for Alzheimer Disease neuropsychological test battery; DBI: drug burden index; DSST: digital symbol substitution test; LTCF: long-term care facility; MDS CPS: minimum data set cognitive performance scale; MMSE: mini mental state examination; P. cohort: prospective cohort; R. cohort: retrospective cohort; SBT: short blessed test; TMT: trail making task

+: Significantly associated with outcome measure; -: Not significantly associated with outcome measure

Figure 1.6.1. Prescribing Cascade

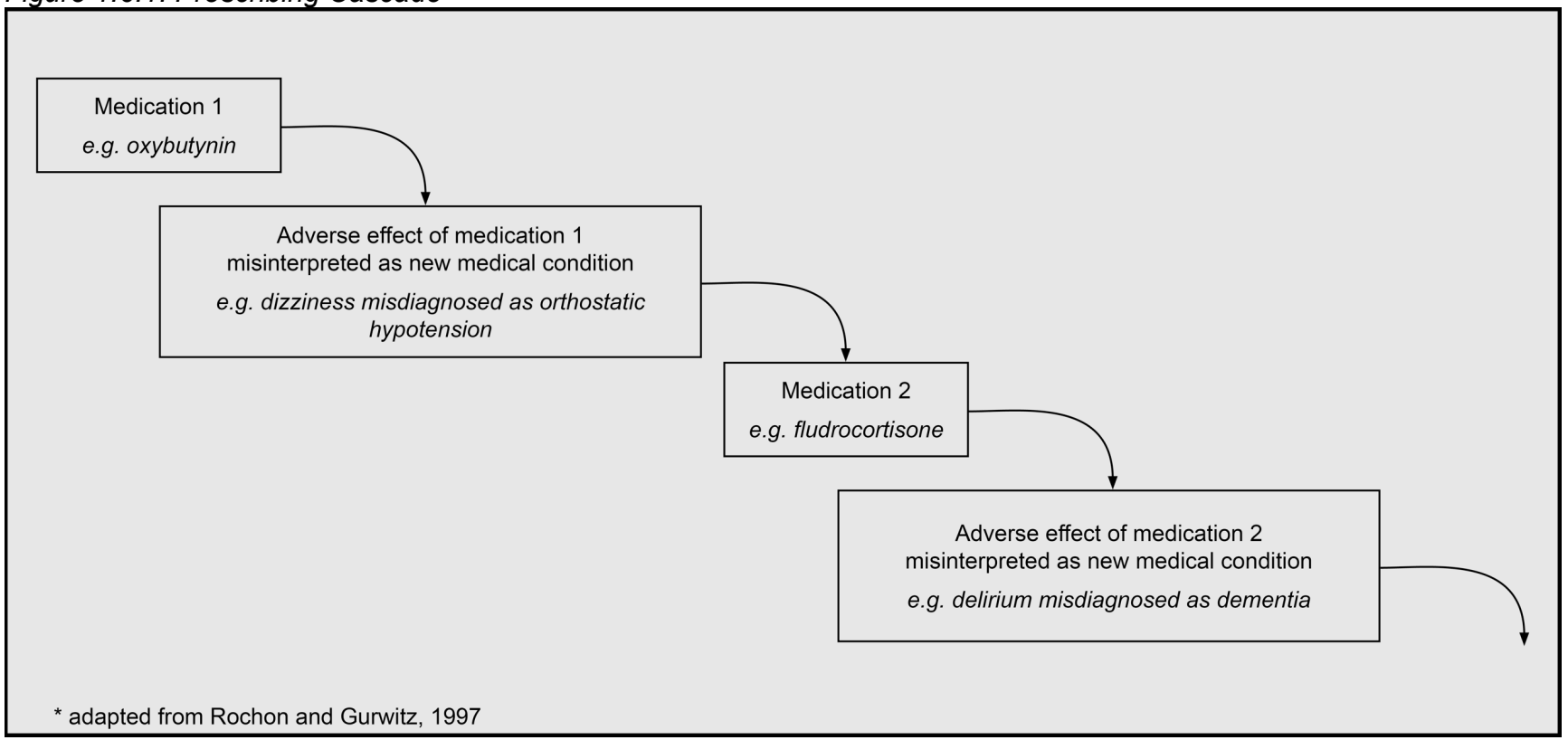
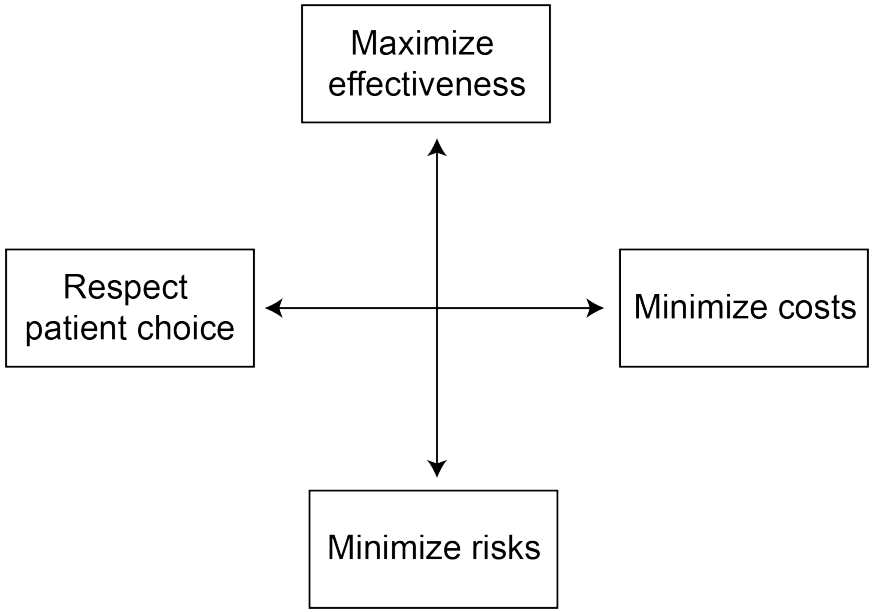


Figure 1.6.2. Good Prescribing Recommendations

Good Prescribing Recommendations

1. Evaluate and clearly define the patient's problem;
2. Specify the therapeutic objective;
3. Select the appropriate drug therapy;
4. Initiate therapy with appropriate details and consider nonpharmacologic therapies;
5. Give information, instructions, and warnings;
6. Evaluate therapy regularly (e.g., monitor treatment results, consider discontinuation of the drug);
7. Consider drug cost when prescribing;
8. Use computers and other tools to reduce prescribing errors

Figure 1.6.3. Balancing Prescribing Decisions



2 EXTENT OF POTENTIALLY INAPPROPRIATE MEDICATION USE

2.1 Introduction

In 2016, 15.2% of the US population was aged 65 years and over, representing 49.2 million Americans: a 33% increase from only ten years prior.[96] 85% of these older adults reported using at least one prescription medication, which has remained relatively constant since 2007.[97] However, there has been a marked increase in the number of older adults using five or more prescription medications from 27.1% at the start of the 21st century, to 39.1% between 2009-2012, and finally to 40.9% between 2013-2016.[98] While the increased number of medications used by older adults may be clinically appropriate due to increased multimorbidity, it is important to note that many of the most commonly used medications in this population may be potentially inappropriate. For example, 24.1% of adults aged 65 years and over used prescription proton pump inhibitors or histamine-2 receptor antagonists from 2011-2014, 16.4% used prescription analgesics, and 18.9% used antidepressants.[99] Medications in each of these classes are included in numerous medication appropriateness assessment tools as potentially inappropriate for all older adults, regardless of indication.

Thus we can see that potentially inappropriate medication (PIM) use is a widespread phenomenon in the US. However, the aforementioned trends are not unique to the Americas, nor to a specific definition of PIM use. Numerous studies throughout the world have provided estimates of PIM use in community-dwelling older adults in the last decade ranging from 15.3%[100] – 72.9%[93] when PIM use is defined as concurrent use of ≥5 medications, and 22.7-77.3%[95] when medications in the 2003 Beers Criteria or STOPP version 1 are considered PIM use. Even when more specific definitions of PIM use are used to estimate prevalence (such as anticholinergic-specific medication appropriateness assessment tools), prevalence remains high (9.56%[101] -43%[48]), especially for those with dementia.

PIM use in older adults is not a monolithic term, nor can it be used to reliably describe any one characteristic of medication use. In this section, we use two

different data sources and various medication appropriateness assessment tools to define PIM use in order to add to the literature of PIM use prevalence estimates. In the first study, we utilize medication self-reported data from initial visits to an Alzheimer's Disease Center between 2005-2018 to estimate the prevalence of PIM use in general. To do so, we defined PIM use as ≥1, ≥4, and ≥5 medications in the Beers criteria and STOPP, as well as use of ≥4 and ≥5 medications total (polypharmacy). The next study narrows the definition of PIM use to include only medications suspected to be associated with negative cognitive outcomes, using the sublist of medications considered potentially inappropriate for individuals with dementia from the Beers criteria, as well as use of medications considered to be anticholinergic according to the Anticholinergic Drug Scale. This study utilizes administrative prescription claim data from a population of older adults with fee-for-service Medicare and Medicare Part D and provides prevalence estimates from 2012-2016. Both studies stratify estimates by the presence of baseline cognitive impairment or clinical dementia in order to demonstrate whether PIM use prevalence is different in these two populations.

2.2 Prevalence of Potentially Inappropriate Medication Use in Older Adults: A Comparison of Measurement Tools

2.2.1 Background

Over the past century, the US population has been steadily aging. By 2050, it is estimated that almost one-quarter of the US will be 65 years of age or older, second only to Europe in age.[102] Aged individuals bear a high burden of comorbidity, and those aged 65 or older are especially afflicted, with 15% of community-dwelling individuals having four or more chronic health conditions, compared to only 6.7% of a similar population of individuals 55-64 years old.[6] Because of this, more than nine out of ten individuals aged 65 years and older use at least one prescription medication, while over 40% use five or more (i.e. polypharmacy).[98] With higher rates of comorbidities and polypharmacy in addition to changes in pharmacokinetic and pharmacodynamics profiles, the geriatric population is at risk for a higher rate of ADRs, including both drug-disease and drug-drug interactions.[103]

One subset of individuals within this population that is at an especially high risk for ADRs are those with cognitive impairment (CI). Individuals with CI may take medications that are potentially inappropriate for their age and condition. In fact, some studies have estimated that as many as half of adults with dementia take potentially inappropriate medications PIMs with a high potential for ADRs.[104,105]

PIM use in older adults has been associated with hospitalization and mortality, as well as cognitive decline, falls, and functional impairment.[38] Thus, it is important for healthcare providers serving older adults to appropriately prescribe and manage medication therapy to optimize health outcomes. Unfortunately, there is no universally-accepted method for identifying PIM use in older adults generally, nor in the CI population. In addition, no method has consistently been shown to be associated with CI. Over the last 20 years, more than 40 different tools have been developed to assess PIM in older adults and their use among healthcare providers varies widely. In this report, we focus on three very commonly-used methods for

assessing PIM use: presence of polypharmacy and use of medications present in the Beers or STOPP criteria.

Unfortunately, each of these tools often result in drastically different estimations of the prevalence of PIM use. It is clear from the literature that the prevalence of PIM use varies widely amongst populations, both within a single set of criteria and between different criteria. For instance, in the long-term care population PIM prevalence ranged from 21-63% with Beers 2003 criteria, 63-83% with Beers 2012 criteria, and 24-80% with STOPP criteria.[105] In a cross-sectional study of community-dwelling elderly adults, PIM prevalence was assessed as 18.7%, 37.3%, and 40.4% using STOPP version 1, Beers 2012, and STOPP version 2 criteria respectively.[93]

In this study, we aim to estimate the prevalence of PIM use for those with and without cognitive or functional impairment.

2.2.2 Methods

2.2.2.1 Study Design and Population

In this study, we utilize data obtained from participants at Alzheimer's Disease Centers (ADCs) throughout the United States. The US National Institute on Aging (NIA) began the ADC program in 1984 in a comprehensive effort to boost research on both Alzheimer disease and related disorders.[106] Today, there are 39 Centers at major medical institutions throughout the United States receiving funding from the NIA. As part of their participation in the ADC program, Centers prospectively collect demographic, clinical, neuropsychological, and diagnostic patient data and provide it to the National Alzheimer's Coordinating Center (NACC) in a standardized manner. NACC then deidentifies the data and makes it available to researchers in the form of a Uniform Data Set (UDS).[107]

This analysis used data from all reporting ADCs for UDS visits conducted between June 2005 and August 2018. We utilize a cross-sectional study design to assess the prevalence of PIM use for those with and without cognitive impairment.

Subjects were included if they were at least 65 years of age, reported living in the community (in a private residence, independent living facility, or senior community), and reporting at least one medication at the initial ADC visit.

2.2.2.2 Measurement

We considered eight different PIM definitions based on polypharmacy (≥4 and ≥5 total medications) and the number of medications present in existing explicit criteria (≥1, ≥4, and ≥5 PIMs as mentioned in the 2015 update of the Beers criteria[42] and version 2 of STOPP[81]). Each of these medication appropriateness assessment tools is widely used both in research and clinical practice. While use of medications in the Beers criteria has been investigated in relationship to cognition,[44,78] the STOPP criteria have been shown to be more sensitive at detecting PIM use than the Beers criteria.[91,93] Polypharmacy was included as a measure of PIM use in addition to the explicit criteria as it is commonly considered inappropriate to use ≥5 medications.[15]

In addition to evaluating PIM use with different definitions of the three tools noted above, we this investigation also included information on cognitive impairment baseline. CI was measured as the presence of at least mild cognitive impairment using the CDR global score (CDR-GLOB) ≥ 0.5. CDR-GLOB is a reliable and well-validated method of measuring cognitive and functional status in many studies in the field.[108]

Information on demographic characteristics at baseline including sex, age, years of education, marital status, and race was also collected. In addition, subjects' clinical profiles were documented by recording the presence (recent/active or remote/history) of the following conditions: atrial fibrillation, congestive heart failure, depression (within the last two years), diabetes, heart attack, hypercholesterolemia, hypertension, Parkinson's disease, seizures, stroke, transient ischemic attack, and urinary incontinence.

2.2.2.3 Statistical Analysis

Normality for all variables was assessed visually with Q-Q plots, and normally distributed continuous variables were described using the mean and standard

deviation (SD), while the median and interquartile range (IQR) were used to describe non-normally distributed variables. Chi-squared, Student's t, and Wilcoxon Mann-Whitney U tests were used to compare subject characteristics as appropriate.

All statistical analyses were conducted in SAS 9.4.[109]

2.2.3 Results

2.2.3.1 Study Population

The participant selection process is detailed in Figure 2.2.1. After applying all inclusion and exclusion criteria, the sample size was 26,311 participants.

As can be seen in Table 2.2.1, the mean (SD) age of participants included was 75.7 (6.9) years, and over half (56.3%) were female. The majority of participants were well-educated (median 16 years of education), white (81.2%), and were married or living as married (63.9%). Additionally, 73% of participants went to the ADC primarily to participate in a research study. While nearly half (45.7%) of participants had ever smoked cigarettes, only 3.7% had done so in the last 30 days. The most prevalent comorbidities in this sample were hypertension and hypercholesterolemia, followed by depression and urinary incontinence (53.8, 51.7, 28.6, and 16.7% respectively).

2.2.3.2 Baseline CI and PIM Use Prevalence

Of included participants, 23.7% had CI at baseline. Regardless of baseline CI, the highest prevalence of PIM use was identified when defined as ≥4 total medications, followed by ≥5 total medications, ≥1 medication in STOPP criteria, then ≥1 medication in Beers criteria (74.6, 63.2, 43.9, and 30.5% respectively). There were statistically significant differences ($p<0.0001$) in the proportion of participants with CI based on all PIM use measurements except ≥1 medication in STOPP criteria ($p=0.15$).

2.2.4 Discussion

In this study, we show that in a population of adults aged 65 years or over seeking care at ADCs, baseline PIM use varied between those with and without CI. Identification of PIM use with polypharmacy found the greatest number of PIM users, followed by report of any medication in STOPP and Beers criteria.

Other studies have explored the performance of these measures to identify PIM use, and findings in this study are consistent with what is available in the literature.[110] It is important to note that most medications included in both the Beers and STOPP criteria are not known to have adverse effects on cognition. In Beers criteria, less than half of the 38 rationales given for classifying medications as potentially inappropriate for all adults aged 65 years and older indicate that the medication (or class) may be associated with adverse cognitive or functional outcomes. However, inappropriate prescribing may be an indicator of other poorly-managed health conditions which may be associated with CI.

Furthermore, there may be more appropriate PIM measurement methods to consider when analyzing PIM use and CI. While using cut-off values is common in the literature and in clinical practice, there is debate as to the extent to which dichotomizing appropriate prescribing is an effective way to optimize health outcomes. The eight definitions using three PIM measurement tools investigated herein may not be the most optimal choice. In one randomized controlled study, investigators assessed appropriate medication therapy using the START/STOPP criteria as a gold standard, and determined the ability of different polypharmacy cut-offs to differentiate between appropriate and inappropriate medication regimens.[111] Their findings suggested that no polypharmacy cut-off was differentiated acceptably well, as the sensitivity-specificity trade-off was too steep. These investigators recommended that appropriate prescribing is context-specific and thus that general cut-offs would always be sub-optimal. Future studies should approach PIM use measurement in a more nuanced and clinically relevant manner.

Overall, this study supports the current literature that PIM use is highly prevalent in community-dwelling older adults both with and without CI. There are

many opportunities to enhance this area of research in the hopes of providing patients and their healthcare providers with more effective tools to manage medication therapy in order to optimize cognitive and functional outcomes.

2.2.5 Tables and Figures

Table 2.2.1. Baseline Characteristics

	Total n = 26311	**Impaired n = 6240**	**Unimpaired n = 20071**
Demographics			
Female, n (%)	14799 (56.25)	3315 (53.13)	11484 (57.22)
Age, mean (SD)	75.70 (6.94)	77.32 (7.01)	75.19 (6.84)
Years of education, median (IQR)	16 (12-18)	14 (12-16)	16 (13-18)
Race			
White	21353 (81.16)	4986 (79.9)	16367 (81.55)
Black or African American	3595 (13.66)	826 (13.24)	2769 (13.8)
Asian	580 (2.20)	108 (1.73)	472 (2.35)
Other	664 (2.52)	285 (4.57)	379 (1.89)
Unknown	119 (0.45)	35 (0.56)	84 (0.42)
Marital Status			
Married or living as married	16815 (63.91)	4204 (67.37)	12611 (62.83)
Widowed	5350 (20.33)	1428 (22.88)	3922 (19.54)
Divorced or separated	2952 (11.22)	436 (6.99)	2516 (12.54)
Never married	1025 (3.90)	136 (2.18)	889 (4.43)
Other or unknown	169 (0.64)	36 (0.58)	133 (0.66)
Primary Reason for Coming to ADC			
To participate in research study	19248 (73.16)	3537 (56.68)	15711 (78.28)
To have a clinical evaluation	6208 (23.59)	2486 (39.84)	3722 (18.54)
Both of above	833 (3.17)	213 (3.41)	620 (3.09)
Unknown	22 (0.08)	4 (0.06)	18 (0.09)
Visits to an ADC, median (IQR)	3 (1-5)	2 (1-3)	3 (1-5)
Health Behaviors, n (%)			
Ever smoker	12028 (45.71)	2630 (42.15)	9398 (46.82)
Smoked in last 30 days	963 (3.66)	244 (3.91)	719 (3.58)
Drank alcohol in last 3 months	2782 (10.57)	308 (4.94)	2474 (12.33)
Health Conditions, n (%)			
Atrial fibrillation	2103 (7.99)	471 (7.55)	1632 (8.13)
Cognitive impairment			
None	9952 (37.82)	0 (0)	9952 (49.58)
Questionable	10119 (38.46)	0 (0)	10119 (50.42)
Mild	4251 (16.16)	4251 (68.13)	0 (0)
Moderate	1455 (5.53)	1455 (23.32)	0 (0)
Severe	534 (2.03)	534 (8.56)	0 (0)
Cognitive impairment family history	13476 (51.22)	3155 (50.56)	10321 (51.42)
Congestive heart failure	705 (2.68)	210 (3.37)	495 (2.47)
Depression in last 2 years	7529 (28.62)	2574 (41.25)	4955 (24.69)
Diabetes	3789 (14.40)	975 (15.63)	2814 (14.02)
Heart attack	1716 (6.52)	477 (7.64)	1239 (6.17)
Hypercholesterolemia	14440 (54.88)	3270 (52.4)	11170 (55.65)
Hypertension	14942 (56.79)	3593 (57.58)	11349 (56.54)
Parkinson’s disease	624 (2.37)	191 (3.06)	433 (2.16)
Seizures	584 (2.22)	184 (2.95)	400 (1.99)
Stroke	1388 (5.28)	498 (7.98)	890 (4.43)
Transient ischemic attack	1483 (5.64)	420 (6.73)	1063 (5.3)
Traumatic brain injury	2881 (10.95)	600 (9.62)	2281 (11.36)
Urinary incontinence	4640 (17.64)	1732 (27.76)	2908 (14.49)

Figure 2.2.1. Participant Selection

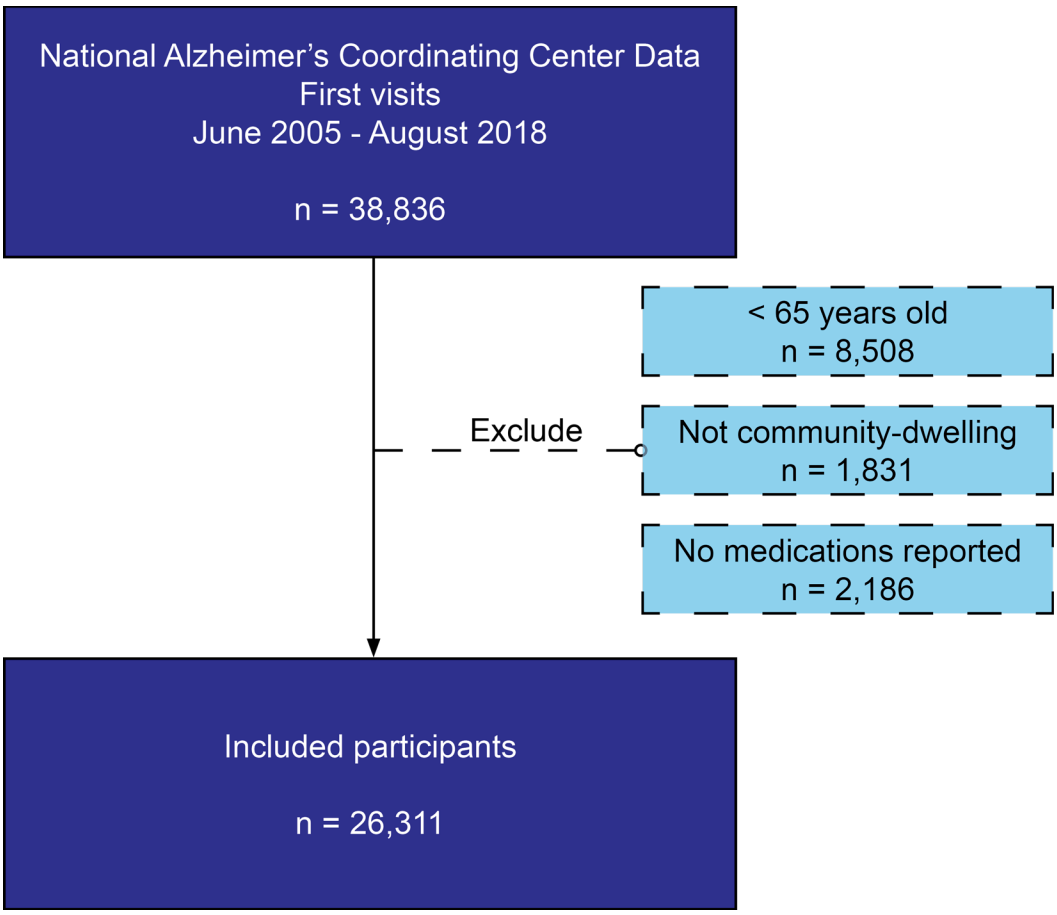
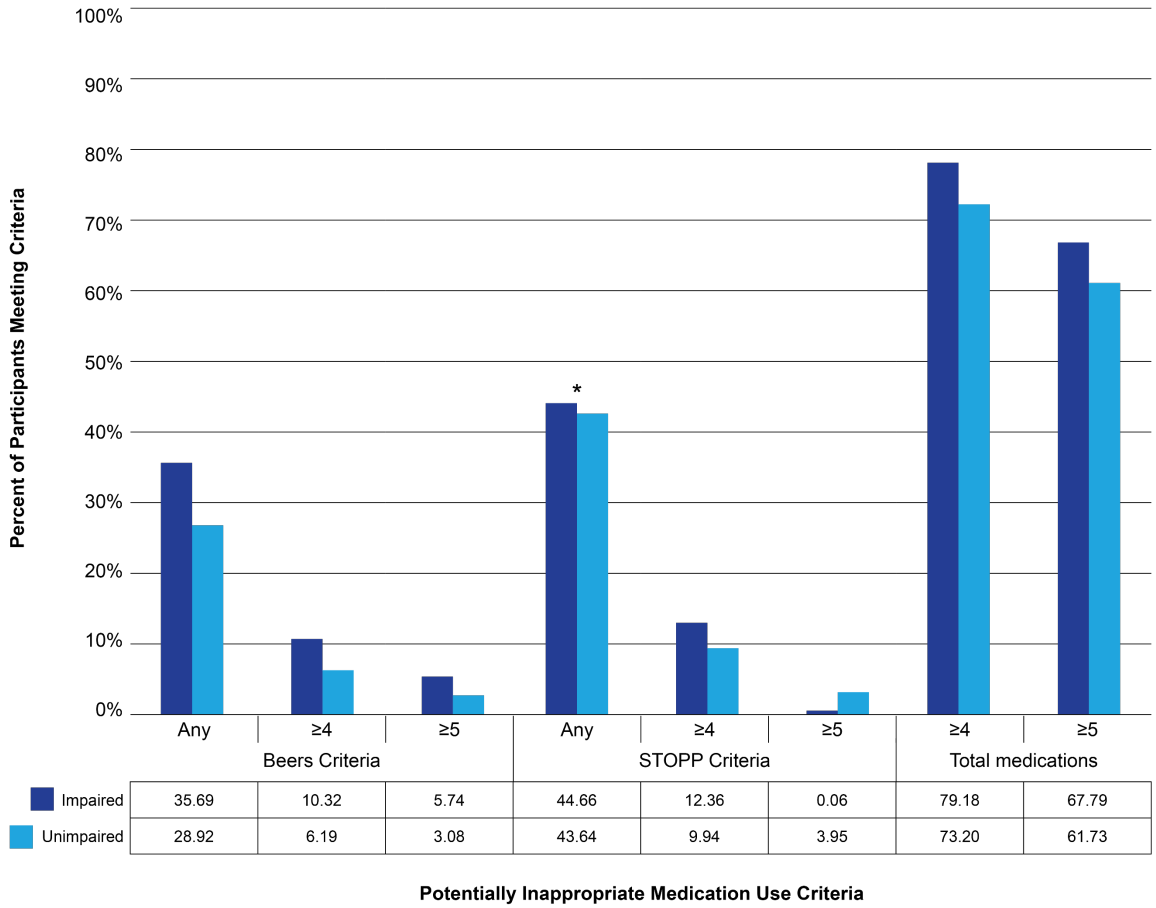


Figure 2.2.2. Potentially Inappropriate Medication Use Prevalence



	Beers Criteria			STOPP Criteria			Total medications	
	Any	≥4	≥5	Any	≥4	≥5	≥4	≥5
Impaired	35.69	10.32	5.74	44.66	12.36	0.06	79.18	67.79
Unimpaired	28.92	6.19	3.08	43.64	9.94	3.95	73.20	61.73

All impaired:unimpaired differences statistically significant a $p < 0.001$ except (*), where $p = 0.155$

2.3 Trends in Potentially Inappropriate Medication Use Among Medicare Part D Beneficiaries 2012-2016

2.3.1 Introduction

Medication use in older adults can be measured in many different ways. Information can be gathered from health records at physicians' offices and hospitals, from pharmacy dispensing records, and directly from patient self-report. Prescription medication use can also be ascertained from administrative claims made available through insurance providers and payers, provided that the medications are processed through an insurance benefit. In the US however, many older adults did not have access to prescription medication coverage until 2006 when the Medicare Prescription Drug, Improvement, and Modernization Act created Medicare Part D and in so doing, provided access to a voluntary medication benefit for Medicare beneficiaries.[112] This new program not only provided critical access to life-saving therapies for a population in dire need, but also paved the way for researchers to begin to analyze prescription medication use trends in a large portion of the American population.

Specifically, increased medication use among older adults has given rise to renewed concerns about potentially inappropriate medication (PIM) use. While a broad definition of what is considered to be "appropriate" might include patient wants, scientific rationalism, and the general good,[37] clinicians must exercise a fair amount of clinical judgment when determining whether a medication therapy is appropriate in the context of certain health outcomes.

For example, the American Geriatrics Society has maintained an explicit list of medications since 1991 that they consider to be potentially inappropriate in all older adults, regardless of concomitant medication use or comorbidity. By 2003, they had added a list of medications that would be potentially inappropriate when used in the context of 20 diseases/conditions, including dementia.[113] The sub-list of medications considered to be inappropriate for older individuals with dementia in what is now known as the Beers criteria (Cog-Beers) was compiled based on medications that the American Geriatrics society considered to have strong

evidence for adverse central nervous system effects and includes benzodiazepines, histamine-2 receptor antagonists, sedative hypnotics, antipsychotics, and anticholinergics. Because anticholinergics specifically have been shown to negatively impact cognition in many different studies,[67] numerous tools have been developed to measure their use in this vulnerable population, including the Anticholinergic Drug Scale (ADS).

In this study, we use Medicare Part D administrative prescription claims data to estimate the prevalence of PIM use as defined according to the 2012 Beers Criteria, Cog-Beers, and the ADS in a population of adults 65 years old and above with and without Alzheimer's disease or related dementias (ADRD) from 2012-2016.

2.3.2 Methods

2.3.2.1 Population and Study Design

The population for this study was drawn from Medicare Part D (MPD) administrative claims data provided by the Centers for Medicare and Medicaid Services (CMS). While MPD is a voluntary outpatient prescription drug benefit for Americans enrolled in Medicare, approximately 62% of all Medicare enrollees chose to utilize MPD in 2012, increasing to 72% in 2016.[114] Beneficiaries can choose either a stand-alone plan (which provides administrative claims data directly to CMS), or can choose to receive all Medicare benefits including medications through a Medicare Advantage plan (for which CMS does not receive administrative prescription claims data).

After permission was granted by CMS and the University of Kentucky Institutional Review Board, we received data for the years 2012-2016 on a random 5% sample of Medicare beneficiaries who had MPD and were ≥65 years old at some point during 2012-2016, and who had at least some period of being non-dually eligible for Medicaid and/or Medicare Advantage was received from CMS.

For the purposes of this study, we included beneficiaries each year from 2012-2016 who were 1) enrolled in a stand-alone PTD plan for the entire year, 2)

not dually-eligible for Medicaid at any point during the year, 3) not enrolled in a Medicare Advantage plan at any point during the year, and 4) at least 65 years old at the beginning of the year. We were not able to analyze prescription medication use for beneficiaries enrolled in Medicare Advantage or Medicaid because not all prescription claims are sent to CMS.

2.3.2.2 Measurements

For each year from 2012-2016, we compared the prevalence of PIM use among continuously enrolled MPD beneficiaries by applying three PIM criteria. First, we used the Beers 2012 Criteria[115] to identify all beneficiaries who filled any prescription considered potentially inappropriate for all adults ≥ 65 years old. To provide prevalence of PIMs that have more evidence of a relationship to cognitive outcomes, we also defined PIM users each year as those who had any prescription claims for medications included in the sub-list of Beers 2012 Criteria specifically for individuals with dementia (Cog-Beers PIMs). Finally, because there have been numerous studies attempting to validate the ADS[47] for its association to cognitive outcomes, we also identified beneficiaries each who had any claims for medications classified as anticholinergic according to this scale.

All estimates were stratified by diagnosis of ADRD. Presence of ADRD each year was determined based on a validated algorithm from the CMS Chronic Conditions Data Warehouse (CCW).[116] If the first date a beneficiary met the criteria for an ADRD diagnosis was in or before the reference year, the beneficiary was considered to have ADRD during that entire year. In addition to ADRD, we also had access to information on the following common chronic conditions: acute myocardial infarction, anxiety, atrial fibrillation, bipolar disorder, depression, diabetes, hyperlipidemia, hypertension, and stroke.

2.3.2.3 Statistical Analysis

We used descriptive statistics to summarize baseline characteristics of beneficiaries continuously enrolled in 2012, including basic demographics and the common chronic conditions listed above. All information on comorbidities was identified according to algorithms from the CCW. We present annual period

prevalence of PIM use according to three criteria for MPD beneficiaries with and without ADRD from 2012-2016. Additionally, to determine what beneficiary characteristics are associated with PIM use for each definition, we performed logistic regressions to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusting for repeated measures for subjects present in multiple years assuming an unstructured covariance matrix (see Code Block 2.3.1). In addition to calendar year, demographic characteristics (age, sex, and race), beneficiary region (Northeast, South, Midwest, and West), original entitlement reason, and ADRD in addition to three common psychiatric comorbidities (anxiety, depression, and bipolar disorder) were also included in this regression. All statistical analyses were conducted in SAS 9.3.[109]

2.3.3 Results

After excluding all beneficiaries in each year who were dually eligible for Medicaid or enrolled in a Medicare Advantage plan, and those who were not at least 65 years old at the beginning of the year, the sample size ranged from 1,337,741 to 1,467,344 between 2012-2016 (34.4% to 46.7% of available beneficiaries) this analysis (see Table 2.3.1). In 2012, beneficiaries were on average 75 years old, approximately 60% were female, and over half had hyperlipidemia and/or hypertension (see Table 2.3.2). 8.1% of beneficiaries were diagnosed with ADRD in or before 2012, and these beneficiaries were on average 8 years older than those without ADRD. Those with ADRD had a greater burden of comorbidity compared to those withut ADRD. Beneficiary characteristics were consistent across each year of the study, and thus characteristics for 2013-2016 are not presented, but are available upon request.

A greater proportion of beneficiaries with ADRD were PIM users according to each definition compared to those without ADRD (see Figure 2.3.1). PIM use prevalence was highest when defined as a claim for any medication identified in the Beers 2012 criteria, followed by medications in Cog-Beers, and finally those in the ADS. In 2012, 51.9% of beneficiaries with ADRD were identified as PIM users

with the Beers criteria, compared to 43.5 and 38.1% when Cog-Beers and ADRD were used. For beneficiaries without ADRD, 40.7, 25.8, and 22.3% were identified as PIM users using the respective definitions. PIM use prevalence was highest in 2013, after which it consistently decreased until 2016. However, PIM use prevalence remained higher in 2016 than it began in 2012.

Beneficiaries originally entitled to Medicare services due to both disability and end-stage renal disease had the highest odds of PIM use, regardless of PIM definition (see Table 2.3.3). The presence of anxiety, bipolar disorder and depression comorbidities were also highly associated with PIM use of all definitions. ADRD was associated with between 1.26 – 1.47 times the odds of PIM use, being most highly associated with ADS PIM use.

2.3.4 Discussion

In this analysis of fee-for-service Medicare beneficiaries enrolled in Medicare Part D, we have shown that prevalence of PIM use varies over a five-year period depending on what criteria are used to define it, ranging from about 22% in beneficiaries without ADRD when measured using the ADS to almost 58% in beneficiaries with ADRD when measured using the Beers Criteria.

These findings are consistent with other prevalence estimates throughout the world. A recent systematic review found that when defined as use of medications in Beers criteria, PIM prevalence ranged from 20.6-80.5% in studies where cognitive status was reported.[117] Although this review only considered studies of in-hospital patients, the range is similar to what was found in this study.

This study was able to analyze PIM use trends among more than 500,000 older adults living in the United States, making these results widely generalizable to the approximately 45 million Americans with Medicare Part D benefits.[118] However, there are a number of limitations to using this data source to measure PIM use. While the data used in this study is a rich source of information on prescription drug use in the older adult population, it has limitations due to its administrative nature. Specifically, the data only include information on

prescription medications that are processed and ultimately billed to the MPD plan. This means that in addition to providing no information on over-the-counter medication use, this data source also does not provide information on prescription medications received by beneficiaries but not billed to MPD plans. Particularly important for this study of PIMs, benzodiazepines, barbiturates, and many gabapentinoids were excluded from coverage by MPD until to the implementation of the Patient Protection and Affordable Care Act in 2013.[119] The sharp increase in PIM use observed from 2012-2013 may reflect this phenomenon. Indeed, the literature has shown that many beneficiaries paid out-of-pocket and continued to receive these medications despite their non-coverage or were switched to other PIMs by their providers. [120,121] Thus, the low prevalence estimates in this study from 2012 may be due to misclassification due to these medications not appearing in the administrative claims data.

Additionally, we were not able to include any beneficiaries who are enrolled in Medicare Part D plans, but receive services through a managed care plan, due to CMS not receiving administrative claims data on these plans. While these beneficiaries only represented about 11% of all Part D beneficiaries in 2012, the proportion of Part D enrollees utilizing Medicare Advantage managed care plans has increased annually to almost 20% as of 2019.[114]

The cross-sectional nature of this study precludes it from providing information on causality because while we are able to assess whether participants had an ADRD diagnosis before the start of the study, we cannot ascertain PIM use prior to 2012. Nevertheless, it is intriguing that PIM use was so much more prevalent among beneficiaries with ADRD. As noted, those with ADRD were older and had more health conditions than those without ADRD, so these beneficiaries may have been using more medications in general and thus been more likely to use a PIM. On the other hand, it may be that use of certain medications by beneficiaries before they developed ADRD may have contributed to its development. The high prevalence of Cog-Beers and ADS PIM use is a striking finding, given that the medications in these criteria have significant evidence suggesting that their use can worsen cognitive function.[122,123]

Overall, the wide range of prevalence estimates shown in this study supports the need for a more targeted definition of PIM use, both for research purposes and clinical use.

2.3.5 Tables and Figures

Table 2.3.1. Included Beneficiaries

Year	Entire sample, n	Included beneficiaries, n	%
2012	1,337,741	459,773	34.37
2013	1,385,329	568,326	41.02
2014	1,423,479	603,925	42.43
2015	1,452,823	642,936	44.25
2016	1,467,344	685,531	46.72

Table 2.3.2. Beneficiary Characteristics in 2012

	Total n = 459773	**ADRD n = 37272**	**No ADRD n = 422501**
Demographics			
Age, mean (SD)	74.79 (7.38)	82.02 (7.55)	74.16 (7.02)
Female, n (%)	273296 (59.44)	24354 (65.34)	248942 (58.92)
Nonwhite race, n (%)	42510 (9.25)	3387 (9.09)	39123 (9.26)
Comorbidities, n (%)			
AMI	3318 (0.72)	597 (1.6)	2721 (0.64)
Anxiety	39355 (8.56)	7046 (18.9)	32309 (7.65)
Atrial fibrillation	45071 (9.8)	6255 (16.78)	38816 (9.19)
Bipolar disorder	4064 (0.88)	1305 (3.5)	2759 (0.65)
Depression	53079 (11.54)	11700 (31.39)	41379 (9.79)
Diabetes	122496 (26.64)	11252 (30.19)	111244 (26.33)
Hyperlipidemia	252316 (54.88)	19838 (53.22)	232478 (55.02)
Hypertension	290300 (63.14)	27956 (75.01)	262344 (62.09)
Stroke	16195 (3.52)	4146 (11.12)	12049 (2.85)

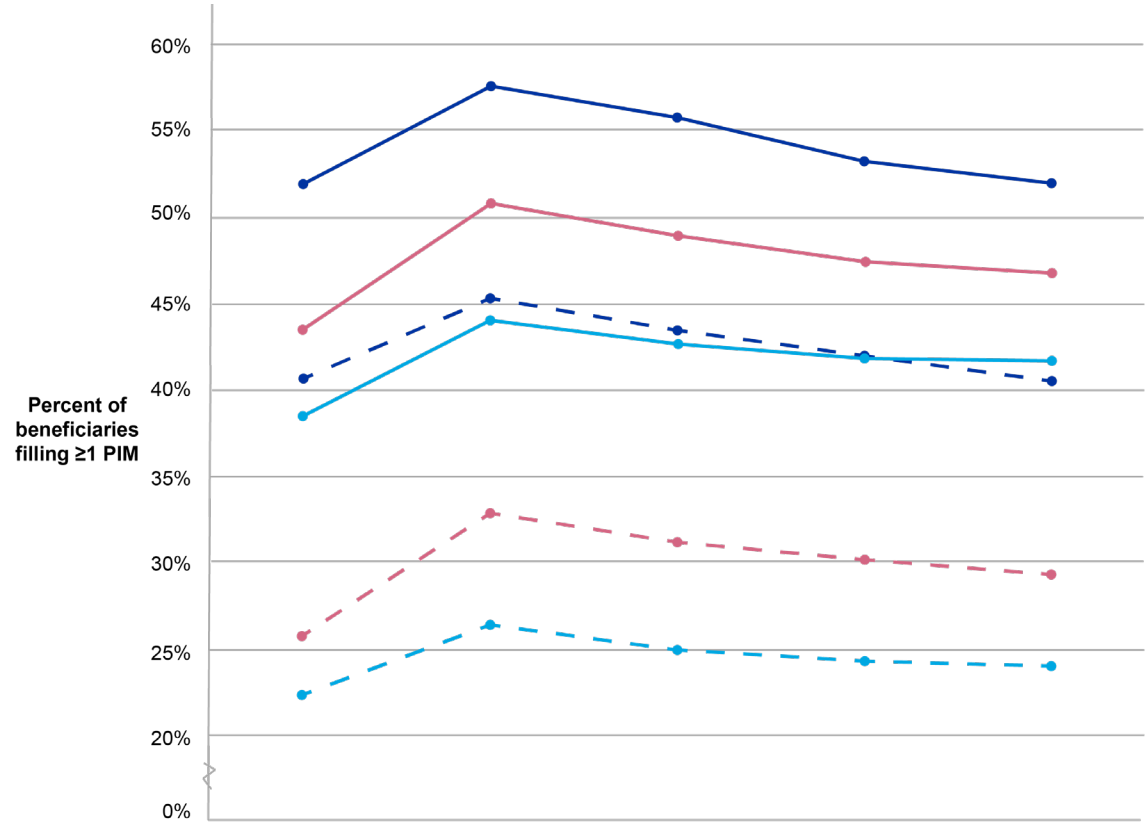
ADRD: Alzheimer's disease and related dementias; AMI: acute myocardial infarction
All group differences significant at p < 0.0001

Table 2.3.3. Odds of PIM Use

	Beers 2012	Cog-Beers	ADS
Age	0.999 (0.999-1)	1.002 (1.001-1.002)	1.009 (1.008-1.009)
Female	1.153 (1.144-1.161)	1.518 (1.506-1.53)	1.5 (1.488-1.513)
White	0.886 (0.877-0.896)	0.773 (0.763-0.782)	0.863 (0.852-0.874)
Year			
2013	1.224 (1.217-1.231)	1.423 (1.414-1.432)	1.255 (1.246-1.264)
2014	1.132 (1.125-1.138)	1.306 (1.298-1.315)	1.159 (1.15-1.167)
2015	1.052 (1.046-1.059)	1.233 (1.224-1.241)	1.114 (1.106-1.122)
2016	0.984 (0.978-0.991)	1.176 (1.168-1.185)	1.096 (1.088-1.105)
Region			
Midwest	1.038 (1.027-1.049)	0.952 (0.941-0.963)	1.026 (1.014-1.039)
South	1.41 (1.397-1.424)	1.23 (1.217-1.243)	1.245 (1.232-1.259)
West	1.095 (1.082-1.107)	1.049 (1.036-1.062)	0.997 (0.984-1.01)
Entitlement reason			
DIB	0.647 (0.306-1.367)	1.572 (0.538-4.596)	1.742 (0.622-4.88)
ESRD	1.348 (0.857-2.119)	1.533 (0.861-2.729)	1.264 (0.69-2.314)
DIB & ESRD	2.505 (1.005-6.244)	2.436 (1.012-5.864)	4.073 (1.739-9.544)
Comorbidities			
ADRD	1.26 (1.247-1.273)	1.458 (1.442-1.474)	1.467 (1.45-1.483)
Anxiety	2.011 (1.994-2.028)	2.275 (2.256-2.295)	1.894 (1.877-1.911)
Bipolar disorder	1.809 (1.76-1.86)	2.024 (1.969-2.08)	1.872 (1.821-1.924)
Depression	1.513 (1.502-1.524)	1.676 (1.663-1.689)	1.639 (1.626-1.652)

Cog-Beers: medications considered potentially inappropriate for individuals with dementia according to Beers 2012 criteria; ADS: anticholinergic drug scale; DIB: disability insurance benefit; ESRD: end-stage renal disease; ADRD: Alzheimer's disease and related dementias

Figure 2.3.1. Period Prevalence of PIM Use, 2012-2016



		2012	2013	2014	2015	2016
ADRD, n		37,272	45,490	47,735	51,710	58,386
% with Beers PIMs		51.89	57.61	55.78	53.28	52.01
% with Cog-Beers PIMs		43.54	50.81	48.92	47.47	46.78
% with ADS PIMs		38.51	44.07	42.64	41.86	41.68
No ADRD, n		422,501	522,836	556,190	591,226	627,145
% with Beers PIMs		40.69	45.34	43.51	41.99	40.55
% with Cog-Beers PIMs		25.86	32.88	31.22	30.21	29.36
% with ADS PIMs		22.37	26.45	25.01	24.35	24.07

PIM: potentially inappropriate medication; Beers: Beers 2012 Criteria; Cog-Beers: potentially inappropriate medications for olders adults with dementia according to Beers 2012; ADS: anticholinergic drug scale

2.3.6 Code Blocks

Code Block 2.3.1. Logistic Regression on PIM Use

```
ods exclude ObStats(persist);
title 'Logistic Regression on Beers 2012';
proc genmod data=usramart.cms_finalpimprev_20200329 desc;
        class beers2012(ref="0") alzh_demen_yn(ref="0")
bene_enrollmt_ref_yr(ref="2012") female(ref="0") white(ref="1") region(ref="1")
entlmt_rsn_curr(ref="0")
                anxi_medicare_yn(ref="0") bipl_medicare_yn(ref="0")
depression_yn(ref="0") bene_id;
        model beers2012 = alzh_demen_yn bene_enrollmt_ref_yr female white region
entlmt_rsn_curr age anxi_medicare_yn bipl_medicare_yn depression_yn / d=bin link=logit
cl;
        repeated subject=bene_id / type=un;
        estimate 'ADRD Effect' alzh_demen_yn 1 -1 /exp;
        estimate '2013 Year Effect' bene_enrollmt_ref_yr 1 0 0 0 -1 /exp;
        estimate '2014 Year Effect' bene_enrollmt_ref_yr 0 1 0 0 -1 /exp;
        estimate '2015 Year Effect' bene_enrollmt_ref_yr 0 0 1 0 -1 /exp;
        estimate '2016 Year Effect' bene_enrollmt_ref_yr 0 0 0 1 -1 /exp;
        estimate 'Female Effect' female 1 -1 /exp;
        estimate 'White Effect' white 1 -1 /exp;
        estimate 'Midwest Region Effect' region 1 0 0 -1 /exp;
        estimate 'South Region Effect' region 0 1 0 -1 /exp;
        estimate 'West Region Effect' region 0 0 1 -1 /exp;
        estimate 'DIB Effect' entlmt_rsn_curr 1 0 0 -1 /exp;
        estimate 'ESRD Effect' entlmt_rsn_curr 0 1 0 -1 /exp;
        estimate 'DIB w/ESRD Effect' entlmt_rsn_curr 0 0 1 -1 /exp;
        estimate 'Anxiety Effect' anxi_medicare_yn 1 -1 /exp;
        estimate 'Bipolar Effect' bipl_medicare_yn 1 -1 /exp;
        estimate 'Depression Effect' depression_yn 1 -1 /exp;
run; quit; title;
```

2.4 Discussion

The studies in this section have demonstrated that the prevalence of PIM use among older adults in the United States can range from 3.1% to 79.2% depending on the definition of PIM use, whether the individual is cognitively impaired, and the data source used to ascertain estimates. PIM prevalence was highest when defined using criteria unspecific to disease state with low cut-offs, and lowest when more stringent definitions were applied. While this range is large, it highlights the the necessity of a clear definition for PIM use if it is to be used as a tool to prevent cognitive decline.

When the most general tools (such as the Beers criteria) are used to define PIM use, prevalence estimates are highest. According to self-report by participants at ADCs, prevalence of PIM use when defined as use of any medication in the 2015 Beers Criteria was 28.9% and 35.7% among individuals without and with cognitive impairment respectively. However, when this same definition of PIM use was applied to a population of older adults with Medicare Part D and ascertained from administrative claims data, prevalence was significantly higher: 40.6-45.7% among individuals without ADRD and 52.0-57.65 among individuals diagnosed with ADRD.

This difference may be explained by numerous factors. First, data in NACC is provided by self-report only annually, and participants are asked to recall medications used in the last two weeks. While this data can provide important information on over-the-counter medication use that would not be included in administrative prescription claims, it also excludes medications that participants do not recall using, use sparingly, or used outside the requested time range.

Additionally, the extent and type of exposure misclassification varies between the two data sources. In the survey data, the false positive rate is likely to be low because participants have no incentive to falsely report using a medication. However, the false negative rate may be higher due to lack of recollection, misunderstanding of what medications should be reported, and the previously discussed time constraints. In the administrative claims data, however, the misclassification issues are the opposite. The false positive rate has the

potentially to be quite high if medications are billed to the insurance plan, but beneficiaries are not using them. Some studies suggest that this phenomenon is quite common, especially due to financial concerns or memory problems.[124,125] Prescription administrative claims data also have the potential for false negatives, as the only medications that are captured are those that are billed to the insurance plan and ultimately covered, and claims exclude almost all non-prescription medications.[126,127]

In both studies, regardless of the PIM definition used, PIM prevalence was higher among individuals who were not cognitively normal. This finding is in line with other estimates globally,[40,128] and is concerning given the available evidence linking many medications in these appropriateness tools to negative cognitive outcomes. However, due to the cross-sectional nature of the studies in this section, it is not possible to determine whether use of these PIMs causes cognitive abnormalities. While the presence of ADRD was associated with between 1.26 – 1.47 times the odds of PIM use in the second study presented in this section, other factors including psychiatric comorbidities and frailty (as measured by original Medicare entitlement reasons) were more highly associated with potentially inappropriate medication use. Thus, it is possible that the relationship between ADRD and PIM use is confounded by both measured and unmeasured factors.

The wide range of prevalence estimates presented in this section supports the need for a more targeted definition of PIM use, both for research purposes and clinical use. For researchers, depending on whether PIM use is used as an exposure or an outcome, the variability in its prevalence can have dire consequences on research findings. In clinical practice, both patients and their providers should have access to a validated tool that can identify potentially inappropriate medications when concerns about negative impacts on cognition reign supreme.

3 TARGETING MEDICATION APPROPRIATENESS MEASURES TO COGNITION

3.1 Introduction

The previous section highlighted the near ubiquity of potentially inappropriate medication (PIM) use in older adults, yet at the same time underlined the variance in how different definitions of PIM use can lead to a lack of clinical and academic utility. We showed that the more stringent definitions of PIM use result in lower prevalence estimates, but regardless of how one defines PIM use, individuals with cognitive impairment are more highly afflicted by its use. Unfortunately, the cross-sectional nature of the previous studies prevents them from providing inference into the potential causal relationship between PIM use and cognition.

At the outset of this work, we summarized results from nearly twenty different studies that investigated the link between cognitive decline and eight different medication appropriateness assessment tools. We showed that while some studies professed to find evidence for a link between the studied tool and proposed measure of cognitive decline, other studies of those same tools failed to find such evidence. This lack of consistency occurred whether the studied tool was more general or specific to certain medication classes such as anticholinergics or sedatives. Notably, every one of these studies utilized an observational study design in which the strongest control for confounding was statistical adjustment by adding measured covariates to regressions. Thus, despite the questions asked by these researchers being largely causal in nature, they have not made use of the many extensions to the standard statistical language that make causal analysis of observational data possible.

Since the nine "aspects of association" were proposed by Bradford Hill in 1965,[129] causal analysis has been revolutionized.[130] Statisticians, epidemiologists, economists, and researchers from many other disciplines now rely upon recent advances in counterfactual analysis, nonparametric structural equations, graphical

models, and combinations of these techniques[131] to solve such causal problems as we find ourselves concerned with in this work.

Due to the lack of consensus regarding the relationship between PIM use and cognition and the lack of research using advanced techniques to resolve many shortcomings to study design, we will undertake to provide evidence that answers the following question: "Does potentially inappropriate medication use, as defined by certain clinically meaningful explicit criteria, increase the risk and/or rate of cognitive decline?" In this section, we will explore different PIM assessment tools including both general criteria and those purporting to pertain specifically to cognitive outcomes. In addition to exploring the effect of different definitions of PIM use, we will also utilize varying measurements of cognitive decline in various data sources. This section will build upon the previous by moving forward from simply estimating how many people would be considered PIM users, to investigating characteristics of PIM users and comparing them to PIM nonusers to determine if there are differences in either the incidence or rate of cognitive decline. Each study will incorporate modern statistical and study design techniques in an attempt to limit the interference of confounding and arrive upon a more accurate and precise conclusion.

The first study in this section will examine one of the most general PIM use tools, the 2015 Beers criteria. However, instead of including only the first list of medications deemed potentially inappropriate in all older adults (as most studies utilizing do[40]), this study will examine the effect of potentially inappropriate drug-disease and drug-drug interactions therein in an attempt to determine whether more patient-specific factors are more predictive of cognitive decline. This study is conducted in a national population of older adults with employer-sponsored health insurance, using administrative prescription claims. It utilizes standardized survival curves and a new-user study design to improve causal inference.

The next study will make use of the same longitudinal cohort of patients as the first prevalence study from Section Two (namely, data from NACC), but will implement a new-user design into the retrospective cohort study and apply inverse probability for treatment and censoring weights will remove much of the selection

bias traditionally associated with studies in this unique population. In addition to investigating general criteria such as Beers and STOPP, it will also consider the sub-lists within each of these criteria that specify certain medications as inappropriate for those with dementia or cognitive impairment. We will apply this definition to individuals with and without cognitive impairment at baseline and determine whether there are any clinically significant declines in a specific measure of cognitive performance over approximately one year.

The last study in this section will again employ the Medicare Part D administrative prescription claims data from CMS to estimate whether there the association seen between cognitive decline PIM use defined as medications deemed inappropriate in the context of dementia by the Beers Criteria is dose-related. This study will use different modeling techniques in an attempt to remove confounding by indication, a common culprit of confounding in studies of PIM use and cognition.

3.2 Drug-drug interactions modify dementia risk associated with potentially inappropriate medication use: a retrospective cohort study

3.2.1 Introduction

Although dementia is a major cause of death, disability, and dependency among older adults worldwide[132], it remains the only one of the top ten causes of death without an effective treatment or cure[133]. As the scientific community continues to make advances in identifying potential therapeutic targets, preventing or delaying dementia has become increasingly important[134]. A novel modifiable risk factor for dementia is the use of inappropriate medications by older adults. While evidence linking the use of various medications to increased risk for dementia is mounting, it can be conflicting. Studies have been published both implicating and exonerating medications including anticholinergics, antidepressants, antipsychotics, benzodiazepines, and proton-pump inhibitors for their links to dementia[123,135–139].

Deprescribing is the process of removing or reducing the doses of inappropriate medications (PIMs)[140]. However, it can be difficult for prescribers to synthesize the vast literature in order to practice evidence-based deprescribing because of constraints on time, resources, and patient engagement[141,142]. Thus, many healthcare providers look to tools developed by professional organizations to guide deprescribing decisions. The American Geriatrics Society manages one such resource: the Beers criteria. Originally developed in 1991, the current Beers criteria comprise a list of PIMs that should be avoided in all adults aged 65 years and older, and also lists of medications that may be inappropriate as a result of their interactions with other medications (known henceforth as potentially inappropriate drug-drug interactions, or PI-DDIs)[43]. A PI-DDI may or may not include a medication otherwise considered to be potentially inappropriate when used alone. Thus, PI-DDIs are more patient-specific than PIMs because they take into consideration the entire medication regime. While the Beers criteria can serve as a helpful guide when deprescribing, it remains unclear whether deprescribing PIMs reduces the risk for incident dementia.

A number of studies have used the Beers criteria to identify PIMs and directly assess their link with cognition in non-demented individuals and those with cognitive impairment, but none have used the more patient-specific PI-DDI criteria as a potential cause of reduced cognition.[40] The American Geriatrics Society stressed that these PI-DDIs were "highly associated with harmful outcomes in older adults,"[42] and even highlighted the use of multiple anticholinergic medications as a PI-DDI due the increased risk of cognitive decline.[69] However, many of the other PI-DDIs can increase the risk of falls, which have also been shown to increase the rate of cognitive decline.[143] Targeting PI-DDIs in deprescribing efforts is a more patient-centered approach as it takes into account individual medication regimens, and thus PI-DDIs are an important component of PIM use that requires studying.

The purpose of this study was to investigate whether use of PIMs in the Beers criteria was associated with an increased risk of dementia in older adults. In addition to use of any medication in the Beers criteria, use of specific classes of medications (including those acting on the central nervous, endocrine, cardiovascular, and gastrointestinal systems, as well as analgesics and strong anticholinergic medications), and PI-DDIs were also investigated.

3.2.2 Methods

3.2.2.1 Study Population and Design

This study was a retrospective cohort analysis of patients enrolled in employer-sponsored private health plans from 2009-2017. Data were obtained from the Truven Health MarketScan Commercial and Medicare Supplemental Databases.[144] Both databases are collected by Truven Health from employers and health plans and consist of service-level claims throughout the continuum of care, including physician office visits, hospital stays, and pharmacy services for a combined total of nearly 240 million covered lives serviced by over 350 unique carriers. Individuals in the Medicare Supplemental Database are generally retirees with Medicare supplemental insurance paid by employers.[145]

The data that support the findings of this study are available from Truven Health Analytics,[144] which were used under license for the current study. Restrictions apply to the availability of these data, and so they are not publicly available. Data are however available from the authors upon reasonable request and with permission of Truven Health Analytics.

This retrospective cohort study investigated the association between PIM use and incident dementia diagnosis (see Figure 3.2.1). Patients ≥ 65 years old were included if they had at least three medical claims and no dementia diagnoses during the three-year run-in period, and at least one prescription claim in the last six months of the run-in period. A three-year run-in period was chosen based on validated algorithms for identifying dementia in administrative claims databases.[146]

3.2.2.2 Measurements

The exposure in this study was PIM use, defined as any claim for a PIM in the last six months of the run-in period. Exposure to PIMs was considered as the presence/absence of 1) any PIM, 2) specific classes of PIMs, and 3) PI-DDIs, as specified in Tables 2 and 5 of the 2015 updated Beers criteria,[42] with some exceptions described in Table 3.2.1. Specific PIM classes included strong anticholinergics, cardiovascular agents, central nervous system (CNS-active) agents, endocrine agents, gastrointestinal agents, and analgesic agents. Ten PI-DDIs are described in the Beers Criteria, of which four contain at least one agent included as a PIM when used alone (see Table 3.2.2). PI-DDIs include the use of: angiotensin-converting enzyme inhibitors (ACEi) with potassium-sparing diuretics, more than one anticholinergic medication, more than two CNS-active medications, corticosteroids with nonsteroidal anti-inflammatory drugs (NSAIDs), lithium with either an ACEi or loop diuretic, peripheral alpha-1 blockers ($P\alpha_1B$) with a loop diuretic, theophylline with cimetidine, and warfarin with either amiodarone or NSAIDs.

The outcome was incident dementia diagnosis, which was defined using International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis codes and/or presence of a prescription claim for a cognition-enhancing medication. Previously validated ICD-9 codes for dementia subtypes

were used and cross-referenced to ICD-10 codes using General Equivalence Mappings (GEMs) as shown in Supplementary Table 3.2.1.[147] Cognition-enhancing medications were identified using the Generic Product Identifier (GPI)[148] secondary classification of "antidementia agents" and included the following single and combination agents: acetylcarnitine, donepezil, galantamine, memantine, rivastigmine, and tacrine. Follow-up began on the index date, defined as the first day following the satisfied run-in period. Time-to-event was defined as the interval between the index date and the first claim with a dementia diagnosis or prescription; patients without a dementia diagnosis were censored on the earlier date of disenrollment from the health plan or December 31, 2017 (see Figure 3.2.1).

Covariates were selected using a directed acyclic graph (see Figure 3.2.2) and included age and sex, along with the number of prescription claims for distinct medications (identified using the first eight digits of the GPI) in the six months prior to the index date as a measure of polypharmacy. Additionally, the following set of comorbidities were measured using the Clinical Classification System or ICD diagnosis codes in the year prior to the index date: atherosclerotic cardiovascular disease (ASCVD), delirium, depression, diabetes, fractures, hypertension, insomnia, Parkinson disease, seizures, and substance use disorder.

3.2.2.3 Statistical Analysis

Descriptive statistics were used to compare exposed and unexposed groups, including chi-squared tests, Wilcoxon-Mann-Whitney tests, and Student's t-tests.

For each exposure, a Cox proportional hazard regression model was used to calculate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the association between the different exposures and dementia. Models were adjusted for sex and age (centered at the mean of 74.2 years), in addition to comorbidities and the baseline medication count (truncated at the top 1%). To determine whether the association of PIM use with hazard of dementia diagnosis was modified by PI-DDIs, dummy indicators were specified to denote whether the patient used any PIM without PI-DDI (P_1D_0), any PIM with PI-DDI (P_1D_1), or no PIMs with PI-DDI (P_0D_1). Corresponding stratum-specific HRs were estimated with

the reference group as no PIM use without PI-DDIs (P_0D_0). Corresponding SAS code is available in Code Block 3.2.1.

To aid in the interpretation of HRs[149] and to visualize the difference in risk, standardized survival curves were plotted by averaging over all observed patient-specific survival curves. These curves were generated with the SAS macro program `%ADJSURV`, which calculates the direct adjusted survival probabilities based on regular and stratified Cox models.[150] Figures were created using the SAS code found in Code Block 3.2.2.

Analyses of specific PIM classes followed the same procedures, except that any specific PIM class with less than 1% prevalence was excluded to avoid bias introduced due to sparse data.[151,152]

In addition, two sensitivity analyses were performed. The first modified the definition of PIM use to exclude use in the six months prior to the index date, since some PIMs may be used to treat prodromal symptoms of dementia[153–155] which could introduce protopathic bias. The second modified the outcome definition to exclude receipt of cognition-enhancing medications to avoid misclassifying patients who may have received these medications for diagnoses other than dementia (for example, off-label use for psychiatric disorders or traumatic brain injury[156,157]).

All statistical analyses were conducted in SAS Enterprise Guide.[158]

3.2.3 Results

3.2.3.1 Study Population

A total of 2,380,986 patients were included in this study, 42.8% of whom used at least one PIM in the six months prior to the index date (Table 3.2.3). Patients were an average of about 74 years old at the index date, and the majority were female. The most prevalent comorbidities identified during the last year of the 3-year run-in period were hypertension, ASCVD, and diabetes, with each being more prevalent among PIM users than non-users. PIM users had almost twice as many prescription claims for distinct medications in the six months prior to the index date

than non-users (median [IQR] 6 [4-9] and 3 [2-5] for users and non-users respectively), and also had more PI-DDIs than non-users (13.3% versus 0.4%).

3.2.3.2 PIM Use and Dementia

Patients contributed a median of 26.3 person-months (range 0.03 to 73 months) of time at risk. PIM users contributed more time at risk (29.4 vs 24.3 person-months; $p<0.001$) compared to non-users. During follow-up, 182,929 patients were newly diagnosed with dementia. A diagnosis of dementia "not otherwise specified" was the most common first diagnosis of dementia (66.5%), followed by receipt of a cognition-enhancing prescription (18.1%) and a diagnosis of Alzheimer's dementia (11.8%). Supplementary Table 3.2.1 describes the distribution of dementia subtypes identified.

Dementia was diagnosed at a higher rate among PIM users than nonusers in unadjusted analyses (HR [95% CI] 1.17 [1.16-1.18]), but this association moved to the null after adjusting for known and measurable confounders (0.99 [0.98, 1.00]; see Figure 3.2.3). While use of any PIM was not significantly associated with dementia diagnosis, a significant association between use of two specific PIM medication classes and dementia was observed: CNS-active medications (1.28 [1.27-1.30]) and strongly anticholinergic medications (1.17 [1.15-1.19]). Use of gastrointestinal PIMs (defined as use of metoclopramide or proton pump inhibitors) was associated with a lower rate of dementia diagnosis compared to those who do not use these PIMs (0.79 [0.78-0.81]). Only one PI-DDI was associated with an increased hazard for dementia: >2 CNS-active medications (1.36 [1.32-1.40]). It is notable that only 8% of CNS-active PIM users used >2 CNS-active PIMs, and only 9% of anticholinergic PIM users used >1 anticholinergic (see Figure 3.2.3). The associations between dementia and use of >1 anticholinergic (0.95 [0.93-0.98), corticosteroids with NSAIDs (0.93 [0.88-0.99), and warfarin with amiodarone (0.92 [0.86-0.99]) were near the null.

There was a statistically significant interaction between PIM use and PI-DDIs. Neither those in the P_1D_0 group nor the P_0D_1 group had increased hazards of dementia (0.99 [0.98-1.00] and 0.84 [0.75-0.94] respectively). However, those

in the P_1D_1 group had an increased hazard of dementia (1.30 [1.17-1.46]). These HRs reference patients in the P_0D_0 group; see Figure 3.2.4.

3.2.3.3 Sensitivity Analyses

The primary exposure was also defined as any use of a PIM during the run-in period, excluding the most recent 6 months to remove users who may have been treating prodromal dementia symptoms[159]. This exposure definition identified 65.8% of patients as PIM users, and increased the effect sizes for most hazard ratios compared to the original analysis.

Additionally, when receipt of cognition-enhancing prescription medications was excluded from the dementia outcome, the number of dementia cases decreased by about 20% to 146,487. There were no significant changes in effect sizes for any of the exposures, except the use of ACEi with potassium-sparing diuretics, which decreased to a HR of 0.73 (95% CI 0.67-0.80; see Supplementary Tables).

3.2.4 Discussion

The results from this retrospective cohort study corroborate existing evidence implicating potentially inappropriate CNS-active and anticholinergic medications in an increased hazard for dementia. In addition, this study demonstrates that the use of PI-DDIs as identified in the Beers Criteria modify the relationship between PIM use and dementia, indicating that PIM users with PI-DDIs have the highest rate of dementia diagnosis. To our knowledge, this is the first study to consider cognitive outcomes related to both PIMs and PI-DDIs in the Beers Criteria. The use of patient-specific measures such as PI-DDIs is relatively new in the 28-year history of the Beers Criteria. The AGS acknowledged the need to add more patient-centered criteria to the tool in 2015, and went so far as to publish a companion article alongside the 2015 update wherein clinicians and payers were encouraged to take patient desires and attributes into consideration when applying the Beers Criteria in practice[160].

The finding that use of any PIM as identified in the Beers Criteria is not associated with an increased risk for dementia diagnosis, while use of any PIM with a PI-DDI is associated with an increased risk is a novel finding, and in line with AGS's recommendation that deprescribing based on the Beers Criteria should be more patient-centered. Such results may be useful for healthcare providers who are in need of evidence in order to prioritize optimization of medication regimens. In fact, physicians report that one of the greatest barriers to deprescribing is agreeability of patients and caregivers[10]. The ability to not only use the Beers Criteria as a tool to identify PIMs, but also to rank necessary deprescribing decisions in order of their importance to preventing future cognitive decline may make medication appropriateness tools such as the Beers Criteria even more valuable for clinicians when working with their patients.

However, the Beers Criteria are not the only medication appropriateness tool available to clinicians. While clinicians in North America rely primarily on the Beers Criteria, several other evidence-based tools are used in practices in Europe and around the world. These tools vary based on whether they include many different classes of medication as in the Beers Criteria (such as the START-STOPP Criteria[80] or the Drug Burden Index[58]) or focus on specific classes of medications (including the Anticholinergic Drug Scale[47], and Sedative Load[55]). While these other PIM measurement tools are not generally used in practice in the United States, they have been more well-studied than the Beers Criteria for their link to cognition[50,53,58,69,71]. Still, the Beers Criteria remains the only one of these tools to consider PI-DDIs, which appear to modify the association between PIM use and dementia.

The results of this study also demonstrate that PI-DDIs may have heterogenous effects with regard to dementia hazard. Notably, while PIM users with PI-DDIs had an increased hazard of dementia, PIM non-users with PI-DDIs appeared to have a decreased hazard of dementia. Although we have less confidence in this finding due to the small sample size (only 0.4% of PIM non-users also had a PI-DDI), it is notable that the most common PI-DDI among PIM non-users was the use of an ACEi with a potassium-sparing diuretic (89.9%, results not

shown). The lack of variability in PI-DDIs among PIM-nonusers may indicate that the estimate is not measuring PI-DDIs in PIM non-users, but rather the effect of a particular type of antihypertensive therapy among PIM non-users. Given that such therapy has been associated with a decreased dementia risk[161,162], further studies able to adjust for blood pressure should be conducted.

It is possible that the definition of exposure to PIMs as use within 6 months of the index date may have meant that the PIMs were being used to treat prodromal symptoms of dementia[159], potentially indicating reverse causation. Despite the fact that the median follow-up time was 26.3 months (indicating that most patients did not obtain a dementia diagnosis or prescription for at least two years after this exposure) a sensitivity analysis was performed that excluded the most recent 6 months of PIM use from the exposure definition and found it did not appreciably change the results. These findings are consistent with other available literature[123], indicating that defining a PIM use exposure as use within six months of the index date does not introduce reverse causation. We also stress that the purpose of this analysis was to study dementia diagnosis, not whether the medications used in this study are associated with changes in the underlying neuropathology.

Of all cases of dementia identified, 18.1% were identified at least in part through receipt of cognition-enhancing prescription medications. For 95.9% of those patients, use of such a medication was the sole method of dementia diagnosis. Thus, these patients received a prescription for a cognition-enhancing medication before they received a diagnosis for dementia. This finding could occur because these patients did not meet the qualifications for a dementia diagnosis but nevertheless were experiencing cognitive impairment that warranted medication treatment, or because of anomalies in the administrative data source. Nevertheless, to determine whether these patients were differentially affected by PIM use, a sensitivity analysis was performed that excluded these patients from the analysis. Again, the results did not change appreciably, lending confidence to the use of this novel outcome definition.

Despite our efforts to reduce confounding by verifying the sensitivity of both our exposure and outcome measurements, some findings in this study warrant

consideration. While use of strong anticholinergic prescriptions was associated with an increased rate of dementia diagnosis, use of more than one strong anticholinergic was not. It may be that the 10% of anticholinergic users who used multiple strong anticholinergic prescriptions were substantially different than those who only used one in ways that our data could not detect. For instance, if providers are aware of the strong evidence base linking anticholinergics to dementia, they may reserve the use of multiple anticholinergics to patients who they feel are at a much lower risk for reasons such as no family history of cognitive impairment, no obesity or tobacco use, or higher level of education. These factors cannot be assessed in the data, indicating there may be some residual confounding.

Additionally, use of gastrointestinal PIMs (defined as use of metoclopramide or proton pump inhibitors [PPIs]) was associated with a lower rate of dementia diagnosis compared to those who do not use these PIMs. The overwhelming majority of these PIM users were identified based on receipt of PPI prescription rather than of metoclopramide. The relationship between PPIs and dementia is unclear, and studies have been published suggesting that PPIs both increase and decrease the risk[136,137,163,164], though major organizations still recommend their deprescription in older adults[33]. In this study, only PPIs obtained through private prescription healthcare insurance can be measured, but because many PPIs are currently available without a prescription it is likely that not all true PPI users are identified. Given that PPI use is on the rise in the older adult population[165], this finding warrants further consideration. This limitation is true of any medications that are not routinely paid for by prescription health insurance (including over-the-counter and supplemental medications that may be used to improve cognition).

The nature of the data source in this study also affects generalizability of these findings. Patients in this study receive healthcare benefits supplemental to Medicare, which has declined substantially in the US, with only approximately 28% of retirees receiving supplemental healthcare insurance coverage through their employers in 2013 [118]. Individuals who receive retiree health benefits are more likely to be government employees, those with higher wages, and those in large unionized firms. In addition, most of the employers who provide data to Truven

Health are medium or large firms, so retirees of smaller firms, or those with lower wages are likely underrepresented in this data. However, the large size of this data offers a significant advantage when studying dementia due to its ability to capture many cases.

Overall, this study supports the current body of literature that implicates anticholinergic and CNS-active medications in cognitive decline and adds the nuance that users of any PIM who also have a PI-DDIs are at a higher risk for dementia than those who use PIMs without PI-DDIs. Thus, the Beers Criteria can be a valuable tool to optimize medication regimens with the goal of reducing dementia risk by incorporating patient-specific factors such as drug-drug interactions instead of only considering use of PIMs. Further research should utilize different data sources to reduce residual confounding, especially due to factors unmeasured in this study, and explore other medication appropriateness tools.

3.2.5 Tables and Figures

Table 3.2.1. Exceptions to Potentially Inappropriate Medication Definition

Exception	Medications	Reasoning
Excluded	Nitrofurantoin	No data on creatinine clearance
Excluded	Diltiazem, verapamil	No data on ejection fraction
Excluded	Ergoloid mesylates, isoxuprine, mineral oil	Rarely used in United States, removed from 2019 Beers' Criteria
Included unconditionally	Any PIM qualified as only potentially inappropriate for first-line therapy	Cannot differentiate between treatment patterns or trajectories
Included unconditionally	Androgens, desmopressin, metoclopramide, non-steroidal anti-inflammatory drugs, proton-pump inhibitors	Cannot identify clinical characteristics providing exceptions

Table 3.2.2. Potentially Inappropriate Drug-Drug Interactions

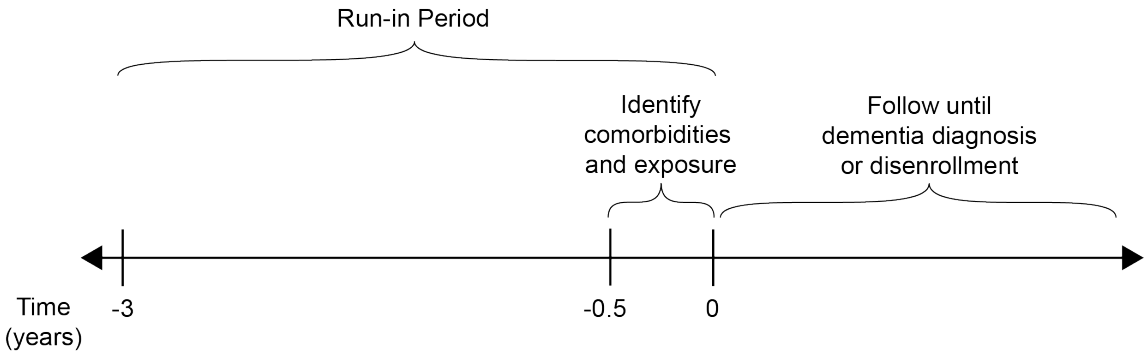
Potentially inappropriate medications	Appropriate Medications
Anticholinergic	Angiotensin converting enzyme inhibitor
Antidepressant	Amiloride
Central nervous system-active	Triamterene
Antipsychotics	Corticosteroid
Benzodiazepine	Lithium
Nonsteroidal anti-inflammatory drug	Loop diuretic
Peripheral alpha blocker	Opioid
Amiodarone	Theophylline
	Warfarin
	Cimetidine

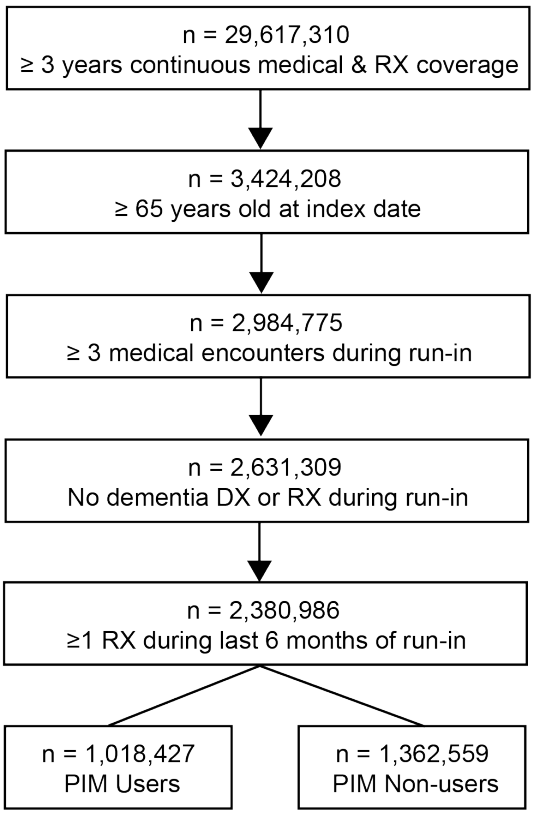
Table 3.2.3. Baseline Characteristics

	Total n=2,380,986	PIM[a] Users n=1,018,427	PIM Non-users n=1,362,559
Demographics			
Age, mean (SD)	74.16 (7.68)	74.30 (7.67)	74.05 (7.69)
Female, n (%)	1,299,996 (54.60)	585,229 (57.46)	714,767 (52.46)
Comorbidities, n (%)			
ASCVD[b]	725,183 (30.46)	349,065 (34.27)	376,118 (27.60)
Delirium	2,189 (0.09)	1,403 (0.14)	786 (0.06)
Depression	150,779 (6.33)	94,829 (9.31)	55,950 (4.11)
Diabetes	701,719 (29.47)	322,276 (31.64)	379,443 (27.85)
Fractures	328,312 (13.79)	155,892 (15.31)	172,420 (12.65)
Hypertension	1,457,950 (61.23)	652,059 (64.03)	805,891 (59.15)
Insomnia	11,812 (0.50)	7,285 (0.72)	4,527 (0.33)
Parkinson's Disease	18,534 (0.78)	9,212 (0.90)	9,322 (0.68)
Seizures	26,233 (1.10)	13,265 (1.30)	12,968 (0.95)
Substance Use Disorder	24,277 (1.02)	13,649 (1.34)	10,628 (0.78)
Medication Use			
Distinct RX, median (IQR)	4 (2-7)	6 (4-9)	3 (2-5)
Any PI-DDI, n (%)	139,924 (5.88)	135,066 (13.26)	4,858 (0.36)

[a] potentially inappropriate medication; [b] atherosclerotic cardiovascular disease
All group differences statistically significantly different at p < 0.001.

Figure 3.2.1. Study Design





DX: diagnosis; PIM: potentially inappropriate medication; RX: prescription

Figure 3.2.2. Directed Acyclic Graph for PIM Use on Dementia

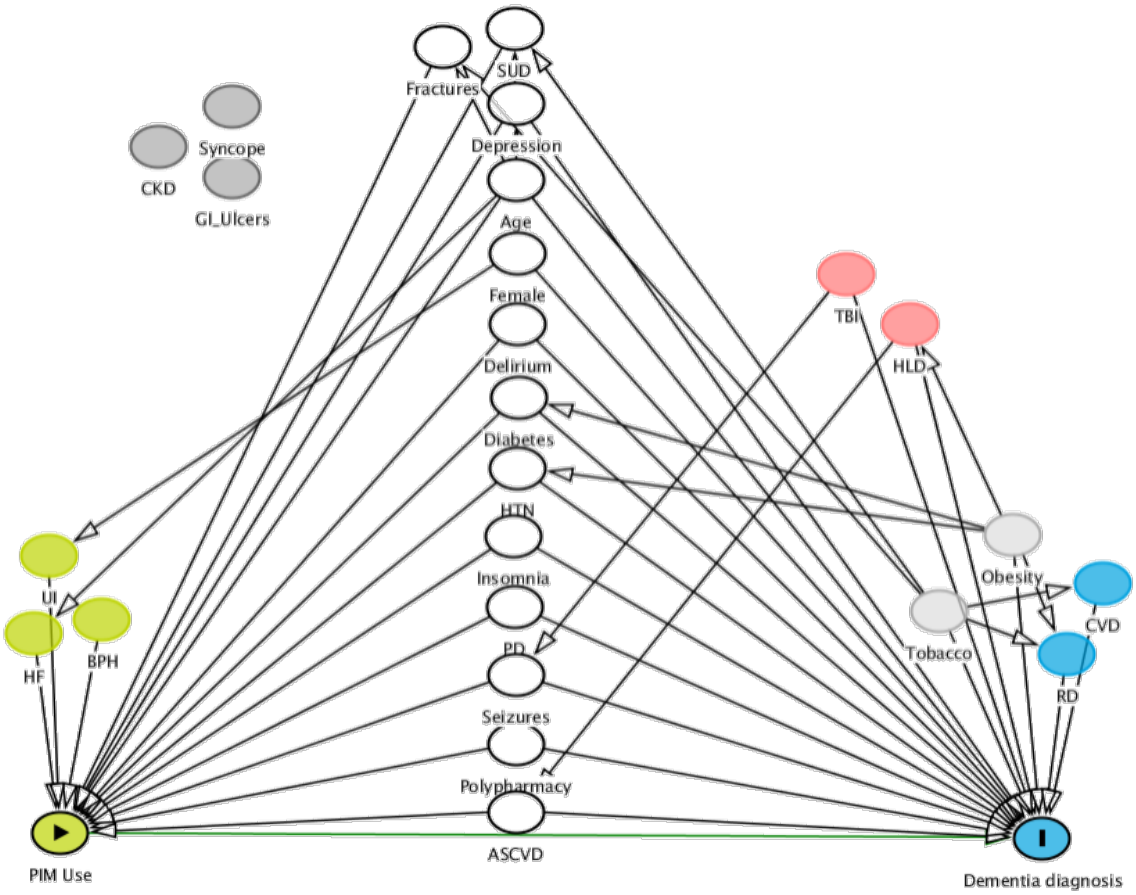
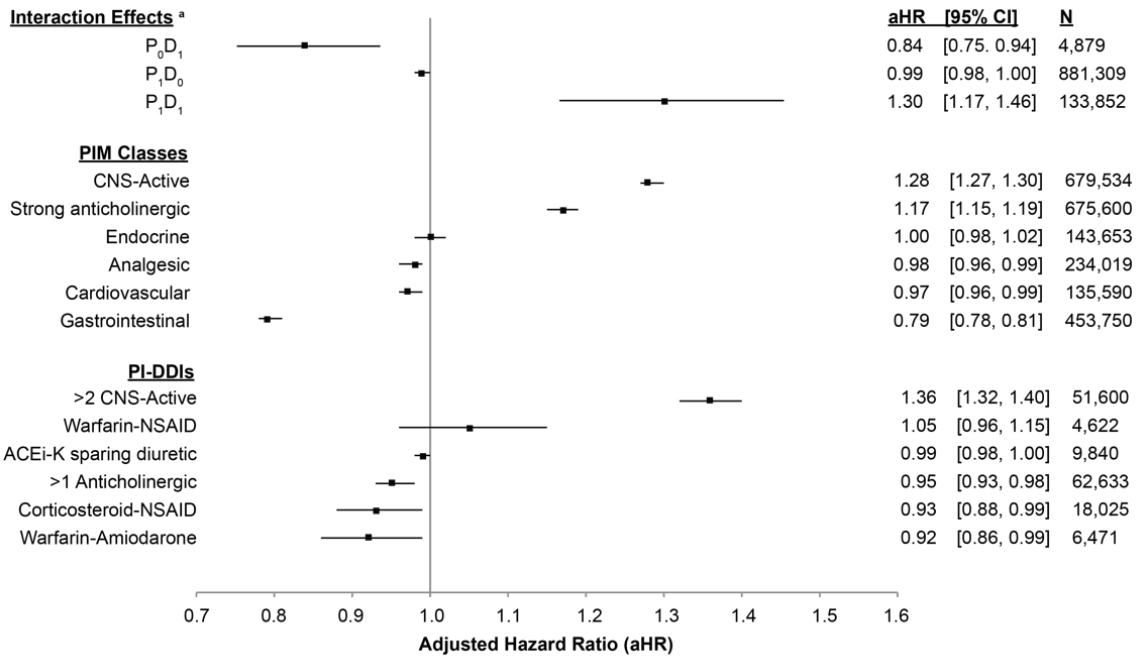


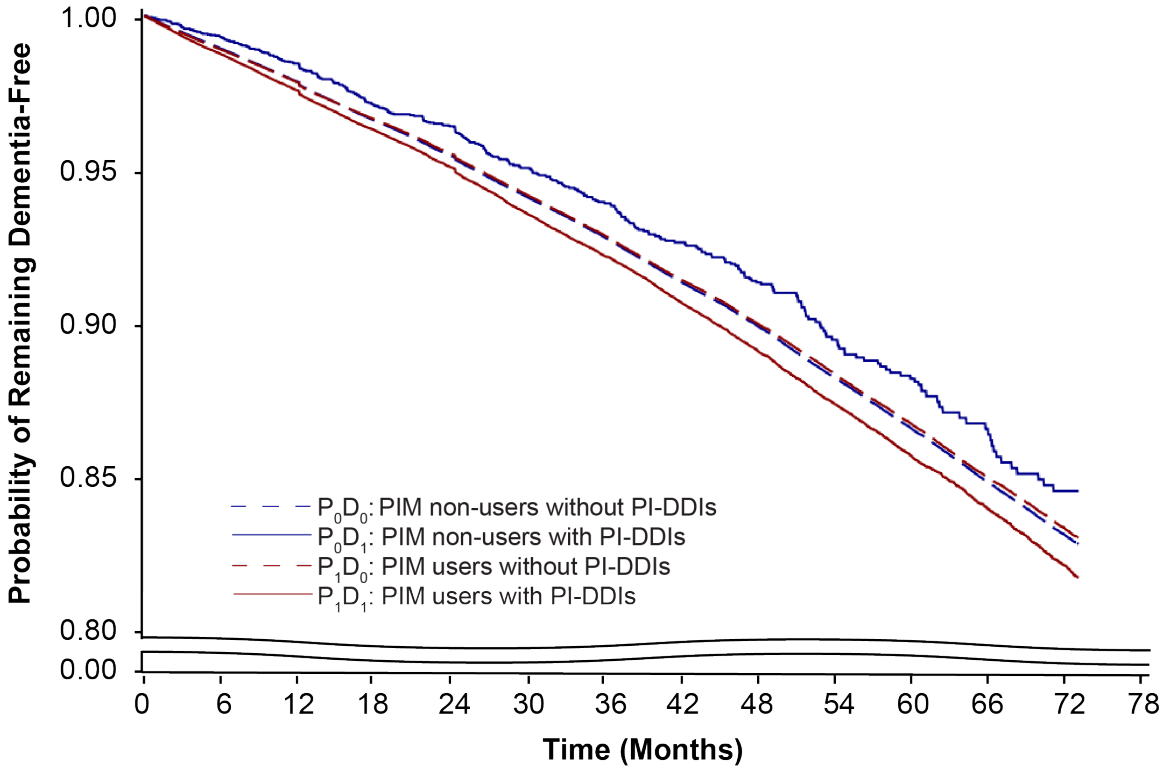
Figure 3.2.3. Associations between PIMs and Dementia



[a] Reference group is PIM non-users without PI-DDIs (P_0D_0)

Abbreviations
ACEi-K sparing diuretic: angiotensin-converting enzyme-potassium sparing diuretic; CNS: central nervous system; NSAID: non-steroidal anti-inflammatory drug; PI-DDI: potentially inappropriate drug-drug interaction; PIM: potentially inappropriate medication; P_0D_1: PIM non-users with PI-DDIs; P_1D_0: PIM users without PI-DDIs; P_1D_1: PIM users with PI-DDIs

Figure 3.2.4. Standardized Time-to-Event Curves



3.2.6 Supplementary Data

Supplementary Table 3.2.1. Dementia Diagnosis Codes and Distribution

Subtype	ICD-9 Codes	ICD-10 Codes	First, n	Sole, n
AD	331.0	G300, G301, G308, G309	21,593	15,859
Vascular	290.40-290.43	F015.0, F015.1	10,001	8,657
Lewy body	331.82 or (332.0 and 331.0)	G318.3 or (G020/G214 and G300/G301/G308/G309)	2,156	1,656
Frontotemporal	331.1, 331.11, 331.19	G310.9, G310.1	721	520
Alcohol-induced	291.2	F102.7	421	365
Other	046.11, 046.19, 292.82, 333.4	A8100, A8101, A8109, F1327, F1397, F1817, F1827, F1897, F1917, F1927, F1997, G10	255	236
Not otherwise specified	290.0-290.3, 290.9, 294.1-294.21, 294.8, 331.2, 797	F0280, F0281, F0390, F0391, F061, F068, G311, R4181, R54	121,694	113,127
Prescription	--	--	33,159	31,788

Supplementary Table 3.2.2. Sensitivity Analyses

	Analysis, Hazard Ratio [95% CI]		
	Original	**Exclude recent PIM use**	**Exclude prescriptions in diagnosis**
Overall			
Any PI-DDI	0.84 [0.75, 0.94]	1.19 [1.17, 1.20]	0.79 [0.70, 0.90]
Any PIM	0.99 [0.98, 1.00]	1.09 [1.08, 1.10]	0.97 [0.96, 0.98]
Any PIM + Any PI-DDI	1.30 [1.16, 1.45]	1.34 [1.31, 1.37]	1.37 [1.21, 1.56]
PIM classes			
CNS-active	1.28 [1.27, 1.30]	1.24 [1.22, 1.25]	1.30 [1.28, 1.32]
Strong anticholinergic	1.17 [1.15, 1.19]	1.13 [1.12, 1.14]	1.16 [1.14, 1.18]
Endocrine	1.00 [0.98, 1.02]	1.08 [1.06, 1.09]	0.97 [0.95, 1.00]
Analgesic	0.98 [0.96, 0.99]	0.97 [0.96, 0.98]	0.95 [0.94, 0.97]
Cardiovascular	0.97 [0.96, 0.99]	1.06 [1.05, 1.08]	0.99 [0.97, 1.01]
GI	0.79 [0.78, 0.81]	0.93 [0.92, 0.94]	0.77 [0.75, 0.78]
PI-DDIs			
>2 CNS	1.36 [1.32, 1.40]	1.37 [1.36, 1.39]	1.37 [1.33, 1.42]
Warfarin-NSAID	1.05 [0.96, 1.15]	1.07 [1.03, 1.11]	1.05 [0.95, 1.17]
ACEi-K sparing diuretic	0.99 [0.98, 1.00]	0.94 [0.90, 0.98]	0.73 [0.67, 0.80]
>1 anticholinergic	0.95 [0.93, 0.98]	1.00 [0.99, 1.01]	0.92 [0.89, 0.95]
Corticosteroid-NSAID	0.93 [0.88, 0.99]	0.92 [0.89, 0.94]	0.90 [0.84, 0.97]
Warfarin-amiodarone	0.92 [0.86, 0.99]	1.02 [0.98, 1.06]	0.96 [0.89, 1.04]

CI: confidence interval; PI-DDI: potentially inappropriate drug-drug interaction; PIM: potentially inappropriate medication; CNS: central nervous system; GI: gastrointestinal; NSAID: non-steroidal anti-inflammatory drug

3.2.7 Code Blocks

Code Block 3.2.1. Survival Analysis with Standardized Survival Times

```
/* survival analysis */
proc sort data=usramart.truven; by descending anypim; run;

proc phreg data = usramart.truven;
        class anypim(ref="0") anypimdi(ref="0") sex ascvd delirium dep diabetes frac htn insom park sx sud;
        model totfu*event(0) = anypim|anypimdi
                                                age_mean_cent sex rxcount_trunc1 ascvd delirium dep diabetes frac htn insom park sx
sud;
        hazardratio "Effect of PIM" anypim / diff=ref at(anypimdi=all);
        hazardratio "Effect of PIM-DI" anypimdi / diff=ref at(anypim=all);
run;


/* run macro to generate dataset with standardized survival times */
%ADJSURV(truven_nomiss2, totfu, event, pim_pimdi_inx, age_mean_cent sex rxcount_trunc1 ascvd delirium dep diabetes frac htn insom
park sx sud, 1, outdata);
```

Code Block 3.2.2. Creation of Standardized Survival Curves by PIM and PI-DDI Use

```
data usramart.outdata2;
        set outdata;
        label surv1="No PIMs or PI-DDIs";
        label surv2="PI-DDIs without PIMs";
        label surv3="PIMs without PI-DDIs";
        label surv4="PIMs with PI-DDIs";
        months = time/30;
run;

ods listing gpath='\\file2\amartinez\Dementia\SAS';
ods graphics / imagename="survival" imagefmt=epsi;
proc sgplot data=usramart.outdata2;
        series x=months y=surv1 / lineattrs=(pattern=4 color=darkblue);
        series x=months y=surv2 / lineattrs=(pattern=1 color=darkblue);
        series x=months y=surv3 / lineattrs=(pattern=4 color=darkred);
        series x=months y=surv4 / lineattrs=(pattern=1 color=darkred);
        yaxis ranges=(0-0.005 0.8-1) values=(0 0.8 0.85 0.9 0.95 1) label="Probability
of Remaining Dementia-Free";
        xaxis label="Time (Months)" values=(0 6 12 18 24 30 36 42 48 54 60 66 72 78);
run; quit;
ods graphics off
```

3.3 Meaningful measurement matters: potentially inappropriate medication use and its effect on cognition in older adults

3.3.1 Introduction

The importance of properly managing medication use in older adults is growing, highlighted by an increased focus on deprescribing, or the process of removing or reducing the dose of inappropriate medications.[166] In fact, over the last five years, several countries have established national networks aimed at improving the deprescribing process specifically for the older adult population.[167–170] Though there are many reasons why older adults may need to withdrawal or reduce the dose of a medication, one growing concern is that certain medications may be associated with negative cognitive outcomes, including such common medications as benzodiazepines, antidepressants, and anticholinergic medications.[122,171,172] While the research literature is rife with studies of individual medications or medication classes and their links to cognitive outcomes, it can be difficult for healthcare providers to maintain accurate and timely knowledge on the ever-changing research landscape.

Recognizing that providers need tools to aid in medication therapy decisions, professional organizations have created and maintained lists of explicit criteria that identify potentially inappropriate medications (PIMs) for older adults. In North America, the Beers Criteria[43] is widely used, and lists 30 medication classes that are potentially inappropriate for any adult aged 65 years or older. Similarly in Europe, the Screening Tool for Older Persons Prescriptions (STOPP) cites 80 criteria for deprescribing.[81] Outside of these explicit lists of criteria, the concurrent use of five or more medications concurrently (polypharmacy) is often considered potentially inappropriate regardless of the specific medications used[15]. While these tools were developed to improve medication use in older adults, their use in healthcare practice varies as practitioners attempt to put patients at the center of care and adapt the tools to each clinical scenario.

Unfortunately, clinical nuance is often difficult to capture in research settings, where the lack of a consistent definition of PIM use has led to conflicting evidence regarding its effect on clinical outcomes[40]. Currently, all studies using existing PIM measurement tools to investigate PIM use do so by defining PIM use as an "ever-never" dichotomous exposure, based on whether study participants ever use any medication in a given tool. However, new evidence in studies of specific PIMs (not necessarily defined using PIM measurement tools) suggests that PIM use may be better-measured when the extent of use by participants is considered[123,135]. While this newer evidence is valuable, it can be difficult for clinical practitioners to stay abreast of every possible medication that may be linked to negative cognitive outcomes.

Thus, it is important to determine whether existing PIM measurement tools can be used to define PIM use as more than an "ever-never" exposure when investigating cognitive outcomes of such use. To address this gap in the literature, this study uses existing PIM measurement tools to identify varying extents of exposure to PIM use and to investigate whether such use is significantly associated with one-year cognitive decline.

3.3.2 Methods

3.3.2.1 Population and Study Design

Data used in this study was obtained from participants at Alzheimer's Disease Centers (ADCs) throughout the United States from June 2005 to December 2019. The US National Institute on Aging began the ADC program in 1984 in a comprehensive effort to boost research on Alzheimer's disease and related disorders.[106] As part of their participation in the ADC program, Centers prospectively collect demographic, clinical, neuropsychological, and diagnostic patient data and provide it to the National Alzheimer's Coordinating Center (NACC) in a standardized manner. NACC then deidentifies the data and makes it available to researchers in the form of a Uniform Data Set (UDS).[107] Due to its deidentified

nature, use of data obtained from NACC was exempted from review by the Institutional Review Board.

In this retrospective cohort study with a new-user design, we used data from participants' second visit to establish baseline characteristics, and data from participants' initial visit to determine user status at the second visit (new, prevalent, or never user). Participants living in the community that had a second visit to an ADC in or before October 2018 while aged at least 65 years were included to ensure all participants had equal opportunity for follow-up. Participants were excluded if they reported no medication use or if their cognitive status could not worsen at their second visit (i.e. a maximum score on the cognitive scale described below). Participants were considered lost to follow-up if there was no subsequent visit to an ADC, or if a subsequent visit occurred but was outside a 6-25 month period after the second visit, and were administratively censored at the end of the data in December 2019.

3.3.2.2 Potentially Inappropriate Medication Identification

ADCs are required to ask participants to report all prescription medications taken in the two weeks before each visit. While non-prescription medications need not be reported, centers are permitted to include them in a participants' medication list if desired. Centers are permitted to list up to forty medications for each participant, which are classified according to the Cerner Multum^{TM} Lexicon Plus nomenclature.[173]

For the purposes of this study, PIM users were identified based on participants self-report of current medication use at their second visit to the ADC. Included ADC participants were identified as PIM users at different levels based on whether their medication use met the cutoff definition from any of the three PIM assessment tools. These definitions included polypharmacy (defined as both ≥4 and ≥5 total medications) and medications present in existing explicit criteria (≥1, ≥2, and ≥3 PIMs as identified in Beers 2015 and STOPP v2). In addition, both Beers and STOPP criteria include a sub-list of medications that are potentially inappropriate for older adults with cognitive impairment or dementia based on existing evidence suggesting that these medications may negatively impact

cognition. Thus, we also defined PIM users as those who use ≥1 or ≥2 medications included in such lists as "Cog-Beers" and "Cog-STOPP" medications. Cog-Beers medications included all anticholinergic and antimuscarinic medications, benzodiazepines, histamine-2 receptor antagonists, hypnotics, and antipsychotics. Cog-STOPP medications included tricyclic antidepressants, all anticholinergic and antimuscarinic medications, antipsychotics, and hypnotics.

Users were considered "new" if they reported any medication that met the above definitions at the second visit, but not at the first visit. PIM users were considered "prevalent" if they reported said medications at both the initial and second visits. Participants who reported no such medications at either initial or second visit were considered "never" users. Prevalent and past users were not included in this analysis to avoid selection bias that might occur if long-term PIM users are more likely to experience cognitive decline.[174]

At the time this study was conducted, Beers 2015 was the most recent version of this tool available. Due to information on presence of insomnia and arthritis type only being reported in the UDS since 2015, no medications considered inappropriate only in the presence of these comorbidities were included as PIMs for the purposes of this study.

3.3.2.3 Degree of Cognitive Decline

Using PIM use at the enrollment visit as the exposure, this study investigated the effect each level of baseline PIM exposure had on the degree of participants' cognitive decline after approximately one year (6-25 months). Cognition at the second and next ADC visit was measured using the CDR® Staging Instrument summated score (CDR-SOB).[175] The primary outcome in this study, cognitive decline, was defined as the difference in CDR-SOB between the second and next ADC visit. If a participant's cognition improved after the second visit (a negative difference), the outcome was coded as a 0 (in other words, "no degree of cognitive decline") because such a finding is likely due to misclassification, differences in diagnostic criteria, or within-patient variability.[176]

3.3.2.4 Covariates

Participants' demographic characteristics (including sex, age, years of education, marital status, and race) at baseline were included as covariates in this study. Additionally, clinical profiles were documented by recording the presence (recent/active or remote/history) of the following conditions: atherosclerotic cardiovascular disease, depression (within the last two years), diabetes, hypertension, Parkinson's disease, and seizures. The directed acyclic graph used to select these covariates can be found in Figure 3.3.2. Additionally, any covariates unable to be balanced using the inverse probability of treatment and censoring weights were included in the final model.

Genetic predisposition to cognitive impairment is an important confounding factor in any analysis investigating cognitive decline risk factors[177], but only about 70% of ADC participants provide this information. Thus, while heredity was not included as a covariate in primary analyses a supplemental analysis, stratified by the presence of a first-degree family member with cognitive impairment was conducted.

3.3.2.5 Statistical Analysis

Normality for all variables was assessed visually with Q-Q plots, and normally distributed continuous variables were described using the mean and standard deviation (SD), while the median and interquartile range (IQR) were used to describe non-normally distributed variables. Chi-squared, Student's t, and Wilcoxon Mann-Whitney U tests[178] were used to compare characteristics as appropriate.

Each exposure was modeled in a negative binomial regression with inverse probability of treatment and censoring weights (IPW) adjusted for covariates described above in the primary and supplemental analyses. IPWs were constructed to account for both PIM exposure definition and differential loss to follow-up. Each model provided an estimate of the rate ratio (RR) for one-year cognitive decline, with robust standard errors and 95% confidence intervals (CI),[179] using the Dunnett-Hsu's adjustment for multiple comparisons (see Code Block 3.3.1). An offset was included as the natural log of follow-up time.

In order to ensure that the IPWs were constructed correctly, we first checked the average weight and pseudo-population size for each exposure definition. Then, to check that conditional exchangeability held, we checked that the differences that existed between PIM user groups in the unweighted data were eliminated in the weighted data. Positivity was checked by verifying that at there was at least one participant in each exposure group. Though consistency could not be checked directly with the data, by carefully constructing exposure definitions to match clinical usage patterns, we did our best to ensure that each exposure definition corresponded to only one version of treatment.

All statistical analyses were conducted in SAS 9.4.[109] This work was supported by the National Institutes of Health (NIH)/National Institute on Aging (NIA) Grant R01 AG054130. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P30 AG062428-01 (PI James Leverenz, MD) P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P30 AG062421-01 (PI Bradley Hyman, MD, PhD), P30 AG062422-01 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P30 AG062429-01(PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P30 AG062715-01 (PI Sanjay

Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

3.3.3 Results

3.3.3.1 Baseline Participant Characteristics

Of 27,657 ADC participants, 14,109 were ultimately included in the study (see Figure 3.3.1). The most common reason for study exclusion was age < 65 years at the baseline visit, and the most common reason for loss to follow-up was lack of a subsequent visit.

Among all included participants, the median time to next visit was approximately 12.5 months. As can be seen in Table 3.3.1, included participants were an average of 77 years old at their baseline visit, slightly more than half of the participants were female, and a large majority were of white race. While the median CDR-SOB was only 0.5, approximately 50% of participants had impaired cognition at baseline based on clinical diagnoses.

After applying inverse probability weights for treatment and censoring, participants who were new users of any Cog-Beers medication were not different from those who never used Cog-Beers medications, except that Cog-Beers users reported more medications than nonusers (see Table 3.3.1). These findings persisted for all exposure definitions, and both weighted and unweighted baseline characteristics can be found in Supplementary Table 3.3.2 through Supplementary Table 3.3.5.

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3.3.3.2 Exposure Definitions

There was significant participant overlap amongst the various PIM exposure definitions (see Figure 3.3.3). Nearly all (99.5%) Cog-STOPP users were also Cog-Beers users, but only 46.5% of Cog-Beers users were also Cog-STOPP users. Only 27.5% of Beers users were also Cog-Beers users. Similarly, only 19.4% of STOPP users were also Cog-STOPP users. Over half of participants with four or

more medications were Beers and/or STOPP users, while 23.8 and 10.6% of those participants were also Cog-Beers and Cog-STOPP users respectively. Approximately three-quarters of Cog-Beers, Cog-STOPP, Beers, and STOPP users also used at least four medications concurrently.

Regardless of PIM exposure definition the most common medication class used was nutritional products, ranging from 19.3% of medications reported in new Beers criteria medication users to 12.3% of medications reported for participants with polypharmacy (see Table 3.3.2). Analgesics were the second most common medication class followed by antihyperlipidemics. Complete data on medication class prevalence for exposed and unexposed participants will be available upon request.

The most commonly reported Cog-Beers medication class was antidepressants, compared to benzodiazepines for Cog-STOPP. Antidepressants, bladder antimuscarinics, benzodiazepines and antihistamines were the most prevalent Cog-Beers and Cog-STOPP medications reported. Whereas antidepressants were 33.0% of reported Cog-Beers medications, they only represented 10.0% of Cog-STOPP medications. Similarly, 32.0% of Cog-STOPP medications were benzodiazepines, compared to only 10.7% of Cog-Beers medications.

3.3.3.3 Checking Model Assumptions

The average weight for each exposure definition was approximately 0.95, making each pseudo-population approximately the same size as the original population without missing values (see Supplementary Table 3.3.1).

The values of each covariate between PIM use groups were compared from the unweighted conditions to weighted conditions, confirming that standardized mean differences between groups were lower after weighting (see Table 3.3.1 and Supplementary Table 3.3.2 through Supplementary Table 3.3.5). The exception to this finding is the covariate for number of medications participants reported using at baseline. Because this covariate is closely related to the exposure, it was unable to be balanced using the IPW. Thus, for all models except the Polypharmacy PIM

use definition, an indicator for polypharmacy was also included as a covariate in the model, as described in Section 3.3.2.4.

After running the negative binomial regression model, we determined that the mean of the outcome was significantly lower than the standard deviation, suggesting that the model is the appropriate choice.

3.3.3.4 Rate of Cognitive Decline

After adjusting for known confounders and applying inverse probability weights for treatment and censoring, the mean rate of cognitive decline was significantly lower for PIM nonusers who were cognitively unimpaired at baseline compared to nonusers who were cognitively impaired at baseline (see Table 3.3.3). The highest rate of nonuser cognitive decline was for impaired Cog-STOPP nonusers (mean [95% CI] increase of 2.1 [1.7-2.6] CDR-SOB per person-year). Unimpaired nonusers of STOPP PIMs had the lowest rate of cognitive decline amongst the unimpaired and unexposed (0.16 [0.07-0.36] per person-year).

Amongst participants who were cognitively impaired at baseline, new use of one Cog-Beers or Cog-STOPP medication was associated with a significant increase in the rate of cognitive decline per person-year compared to never having used a medication in either PIM criteria (RR [95% CI] 1.20 [1.04-1.39] and 1.26 [1.07-1.47], respectively; see Figure 3.3.4). In most exposure definitions, use of more medications in the criteria was associated with a larger point estimate for rate of person-year cognitive decline with the exception of use of ≥2 medications in Cog-STOPP and ≥3 medications in Beers criteria.

Amongst participants who cognitively normal at baseline, no definition of PIM use was associated with a significantly different rate of cognitive decline per person-year.

A sensitivity analysis excluding participants whose CDR-SOB score decreased at the second visit (i.e., back-transitioners) did not reveal significantly different results (see Supplementary Figure 3.3.1). A sensitivity analysis excluding participants for whom no family history was known revealed the same trends as the main analysis, with significant effects on rate of cognitive decline only for new

users of Cog-Beers and/or Cog-STOPP PIMs with baseline cognitive impairment and family history of cognitive impairment (see Supplementary Table 3.3.6).

3.3.4 Discussion

It is currently unknown whether any of the widely used explicit criteria for identifying potentially inappropriate medication use in older adults can be used to direct clinical decisions regarding the effect of these potentially inappropriate medications on cognitive outcomes. In this study, we used varying cutoffs for PIM use definitions based on widely used medication assessment tools, including Beers and STOPP criteria, and polypharmacy. We investigated whether participants in a large, national cohort identified as new PIM users had a higher rate of cognitive decline per person-year compared to participants who were not PIM users according to any of the cutoffs.

We found that new users of one PIM in the Cog-Beers or Cog-STOPP criteria declined at 1.20 or 1.26 times the rate per person-year compared to nonusers. These criteria are more specific to cognitive outcomes than the complete Beers and STOPP criteria, and the findings in this study provide further evidence that use of medications in these sub-lists by patients with cognitive impairment may be detrimental to preserving cognition. However, there were no significant effects of Cog-Beers or Cog-STOPP PIM use on cognitive decline amongst participants who were cognitively normal at baseline. This finding could be attributed to the fact that rates of cognitive decline in participants never exposed to PIMs were so low that small effects could not be identified in such small sample sizes. Repeating a similar study in a larger population over longer periods of time may provide a more meaningful result.

Interestingly, while over 90% of participants identified as Cog-STOPP PIM users were also Cog-Beers PIM users, only approximately 45% of Cog-Beers PIM users were also Cog-STOPP PIM users. This is likely because Cog-Beers includes such commonly used medications as benzodiazepines and histamine-2 receptor antagonists, while Cog-STOPP does not. Despite this difference in the definition

of PIM use, however, the effect sizes for PIM use on cognitive decline were similar. This suggests that the effect may be driven by the medications in common between the two criteria: anticholinergics, antipsychotics, and hypnotics.

However, despite the fact use of one medication in the Cog-Beers and Cog-STOPP criteria was associated with an increased rate of per-person year cognitive decline after approximately one year, the confidence intervals of each estimate indicate that there is no statistically significant difference in the rate of cognitive decline between new PIM users and nonusers amongst the various PIM use definitions. These results suggest that none of the widely used explicit criteria perform exceptionally different when attempting to identify PIM use to protect cognitive function. While most point estimates indicated an increased rate of cognitive decline with increased use of PIMs, sample sizes were too small and variability too high to confidently infer an association.

Previous studies have concluded that the odds of being diagnosed with dementia over a six-year period increased by a factor of 2.3 for every point increase in the CDR-SOB.[180] We did not see such a drastic increase in the CDR-SOB, which may be because of the significantly shorter follow-up time in this study (median time to next visit ~13 months). Furthermore, while a clinical diagnosis of dementia was not used as the outcome in this study due to the short follow-up, the CDR-SOB outcome correlated well with a clinician's assessment of meaningful decline in memory, non-memory cognitive abilities, behavior, ability to manage his/her affairs, or there are motor/movement changes (see Supplementary Table 3.3.7).

This study undertook rigorous statistical adjustment methods to account for bias introduced in many observational investigations of cognitive decline. Namely, because cognitive decline is a strong risk factor for loss to follow-up, this study weighted participants according to their probability of being lost to follow-up and their probability of being classified as PIM users in the various definition schema. In so doing, selection and indication bias have been largely eliminated.

While the NACC UDS provides longitudinal information on many important health outcomes and behaviors for older adults, there are shortcomings to using

survey data when investigating questions of causality. While we attempted to minimize the effect of extended unobserved time periods between participants' visits to ADCs by restricting only to participants who had follow-up visits within 6-25 months, the data remains interval-censored. The assumption that participants' medication reports at the second visit represent their actual use until the follow-up visit is a strong assumption that may introduce confounding. However, misclassifying nonusers as new users or vice-versa would bias effect estimates toward the null. This misclassification may be one reason why only PIM use defined by Cog-Beers and Cog-STOPP criteria showed statistically significant effect sizes.

Overall, these results add evidence to using the sub-lists within Beers or STOPP criteria to identify targeted PIMs in patients with cognitive impairment, particularly those with a family history of cognitive decline. However, there were no statistically significant differences in rate of cognitive decline amongst the various cutoffs of various definitions of PIM use. Accordingly, this study does not support the use of one PIM measurement tool over another for clinicians interested in managing medication regimens. Future studies should continue this work, taking into account the potential cumulative dosage effect and considering a longer follow-up time.

3.3.5 Tables and Figures

Table 3.3.1. Baseline Characteristics of Cog-Beers Use in NACC Population

	Unweighted	Unweighted			Weighted		
	Total n = 9108	**New Cog-Beers n = 891**	**Never Cog-Beers n = 8217**	**|SMD|**	**New Cog-Beers n = 875**	**Never Cog-Beers n = 7785**	**|SMD|**
Demographics							
Age, years, mean (SD)	76.43 (7.03)	76.9 (7.25)	76.38 (7)	0.077	77.19 (7.27)	76.59 (6.82)	0.084
Female	5010 (55.01)	509 (57.13)	4501 (54.78)	0.079	478 (54.63)	4329 (55.61)	0.024
White race	7585 (83.28)	710 (79.69)	6875 (83.67)	0.083	685 (78.29)	6408 (82.31)	0.104
Years education, mean (SD)	15.28 (3.39)	14.93 (3.66)	15.31 (3.36)	0.123	14.92 (3.72)	15.09 (3.4)	0.046
Days to next visit, median (IQR)	379 (357-430)	384 (358-437)	378 (357-429)	0.043	384 (357-433)	378 (357-429)	0.028
Clinical characteristics							
ASCVD	1227 (13.47)	151 (16.95)	1076 (13.09)	0.117	108 (12.34)	1180 (15.16)	0.068
Depression	2232 (24.51)	300 (33.67)	1932 (23.51)	0.224	214 (24.46)	2257 (28.99)	0.073
Diabetes	1252 (13.75)	166 (18.63)	1086 (13.22)	0.147	147 (16.8)	1120 (14.39)	0.080
Hypertension	5365 (58.9)	575 (64.53)	4790 (58.29)	0.127	539 (61.6)	4691 (60.26)	0.028
Impaired cognition*	4866 (53.43)	544 (61.05)	4322 (52.6)	0.161	527 (60.23)	4446 (57.11)	0.070
Parkinson's disease	130 (1.43)	20 (2.24)	110 (1.34)	0.067	15 (1.71)	153 (1.97)	0.017
Seizures	190 (2.09)	27 (3.03)	163 (1.98)	0.073	19 (2.17)	184 (2.36)	0.008
Medications, median (IQR)	6 (3-8)	8 (5-10)	5 (3-8)	0.592	7 (10-5)	6 (3-8)	0.517
CDR-SOB, median (IQR)	0.5 (0-3.5)	1 (0-5)	0.5 (0-3)	0.245	1 (0-5)	0.5 (0-4)	0.132

Cog-Beers: medications affecting cognition in Beers Criteria; SMD: standardized mean difference; ASCVD: atherosclerotic cardiovascular disease; CDR-SOB: CDR Staging Instrument sum of boxes

** Based on clinical assessment*

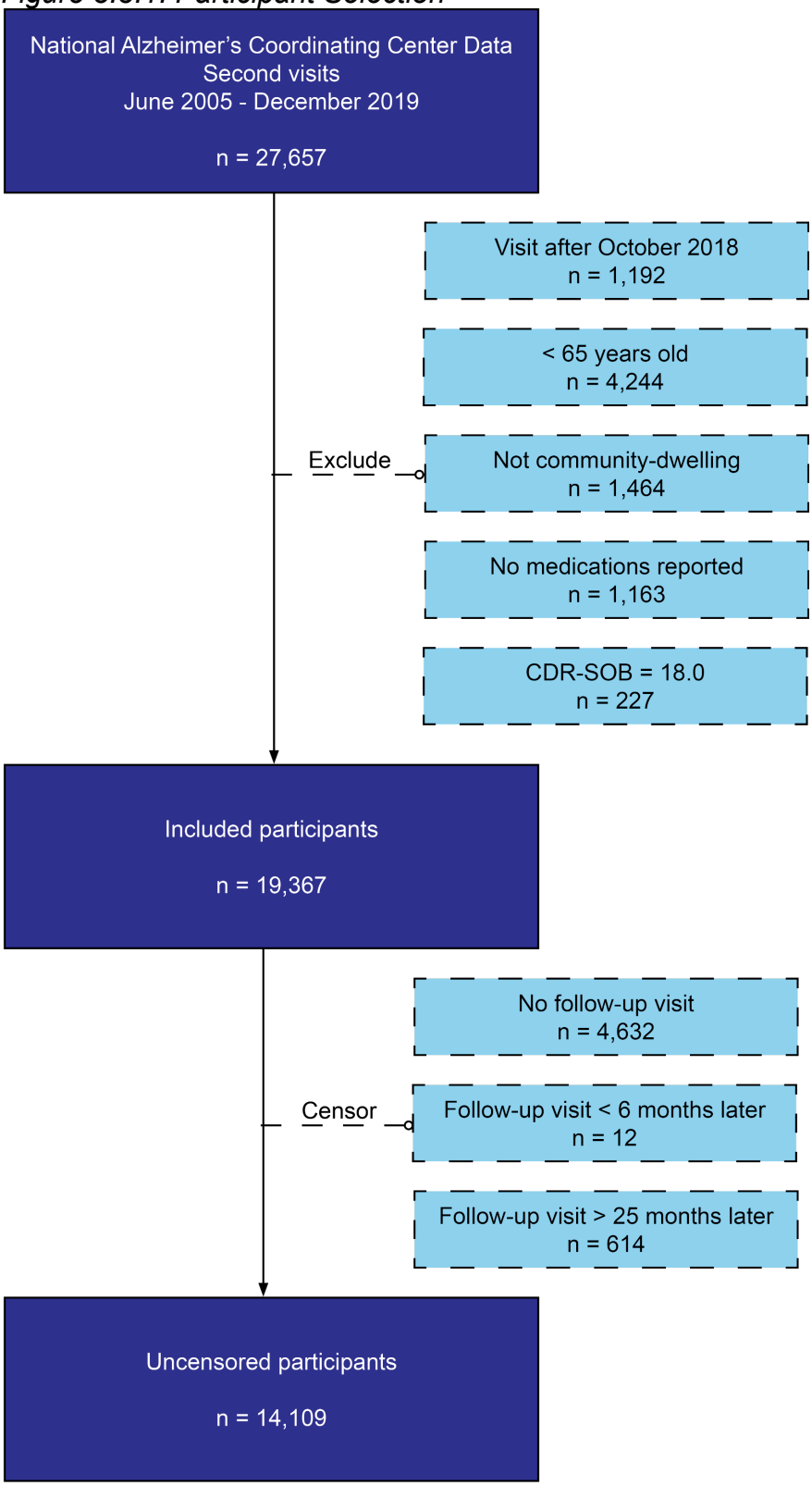
Table 3.3.2. Distribution of PIM Use by Medication Class

	Cog-Beers	Cog-STOPP	Beers	STOPP	Polypharmacy
nutritional products	15.25%	14.29%	19.34%	18.90%	12.25%
analgesics	9.14%	8.58%	11.72%	11.32%	8.23%
antihyperlipidemic agents	6.53%	6.37%	7.50%	6.97%	10.50%
antidepressants	5.80%	4.40%	3.22%	3.16%	4.90%
alternative medicines	4.62%	4.34%	5.77%	5.75%	2.79%
cholinesterase inhibitors	4.46%	4.26%	4.55%	3.77%	7.66%
hormones/hormone modifiers	4.40%	4.55%	4.34%	4.28%	5.82%
respiratory agents	3.16%	3.32%	2.58%	3.74%	1.93%
diuretics	3.05%	3.06%	3.13%	3.31%	3.90%
beta-adrenergic blocking agents	2.98%	2.69%	3.49%	3.09%	4.59%
topical agents	2.96%	2.62%	2.36%	2.43%	2.29%
ACE inhibitors	2.89%	2.65%	3.31%	2.77%	4.85%

Table 3.3.3. Adjusted Mean Cognitive Decline Per Unexposed Person-Year

	Impaired		Unimpaired	
	Mean	**95% CI**	**Mean**	**95% CI**
Cog-Beers	2.12	1.72-2.61	0.26	0.11-0.59
Cog-STOPP	2.11	1.73-2.58	0.27	0.12-0.59
Beers	1.94	1.40-2.69	0.20	0.09-0.44
STOPP	1.84	1.26-2.70	0.16	0.07-0.36
Polypharmacy	1.33	0.77-2.32	0.42	0.15-1.22

Figure 3.3.1. Participant Selection



CDR-SOB: Clinical Dementia Rating Sum of Boxes

Figure 3.3.2. Directed Acyclic Graph for PIM Use on Cognitive Decline

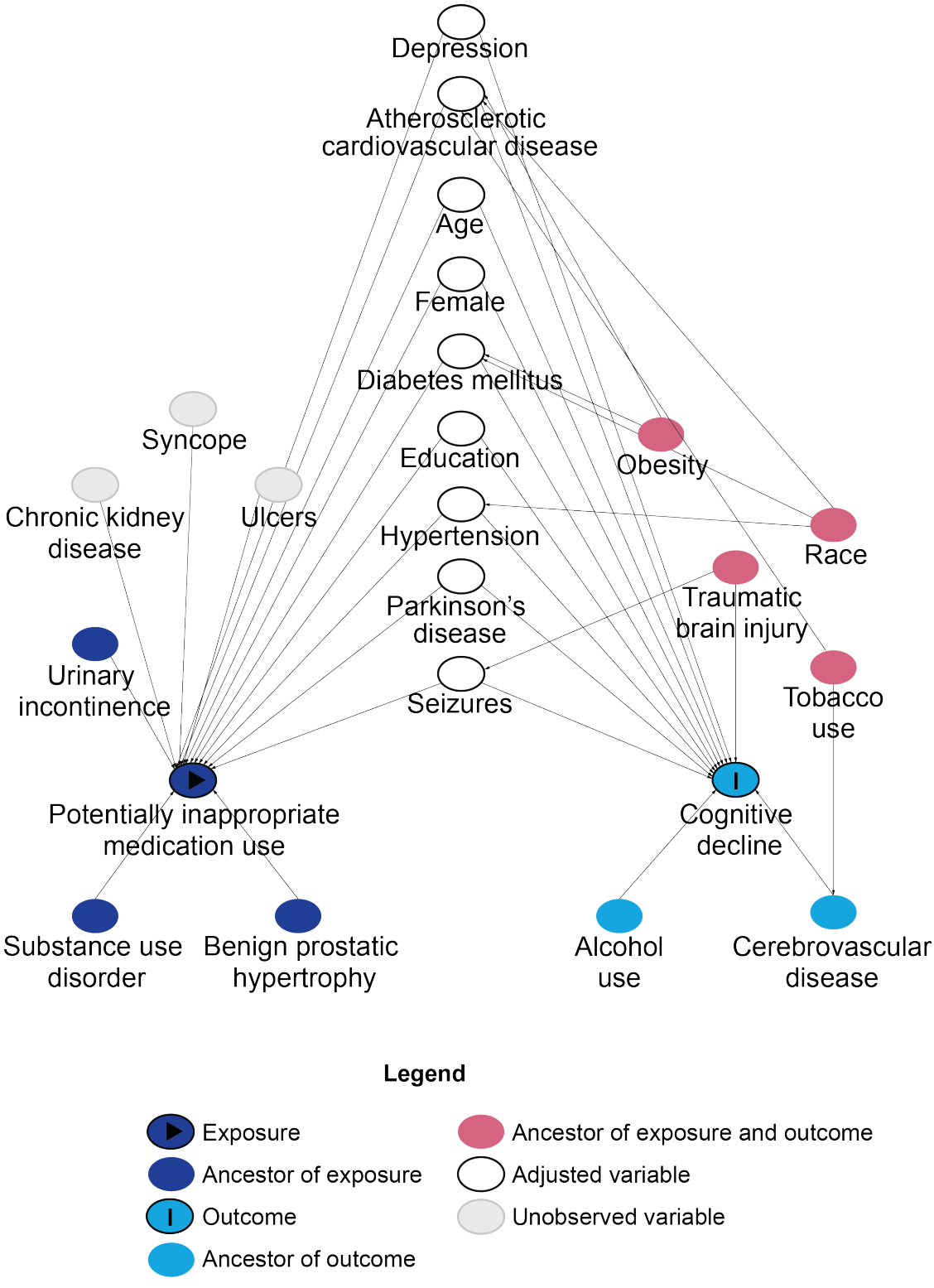


Figure 3.3.3. Overlap in PIM Exposure Definitions

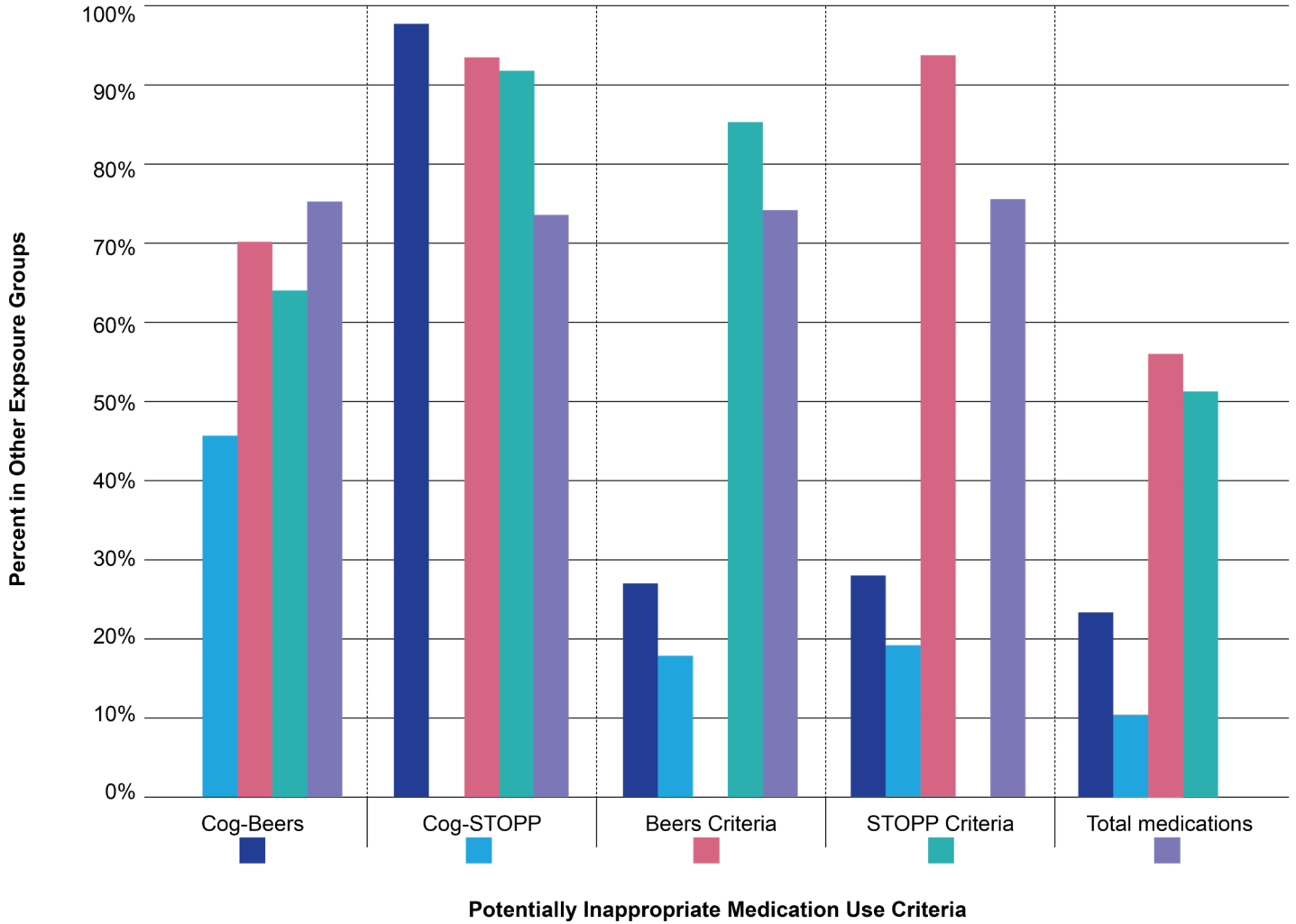
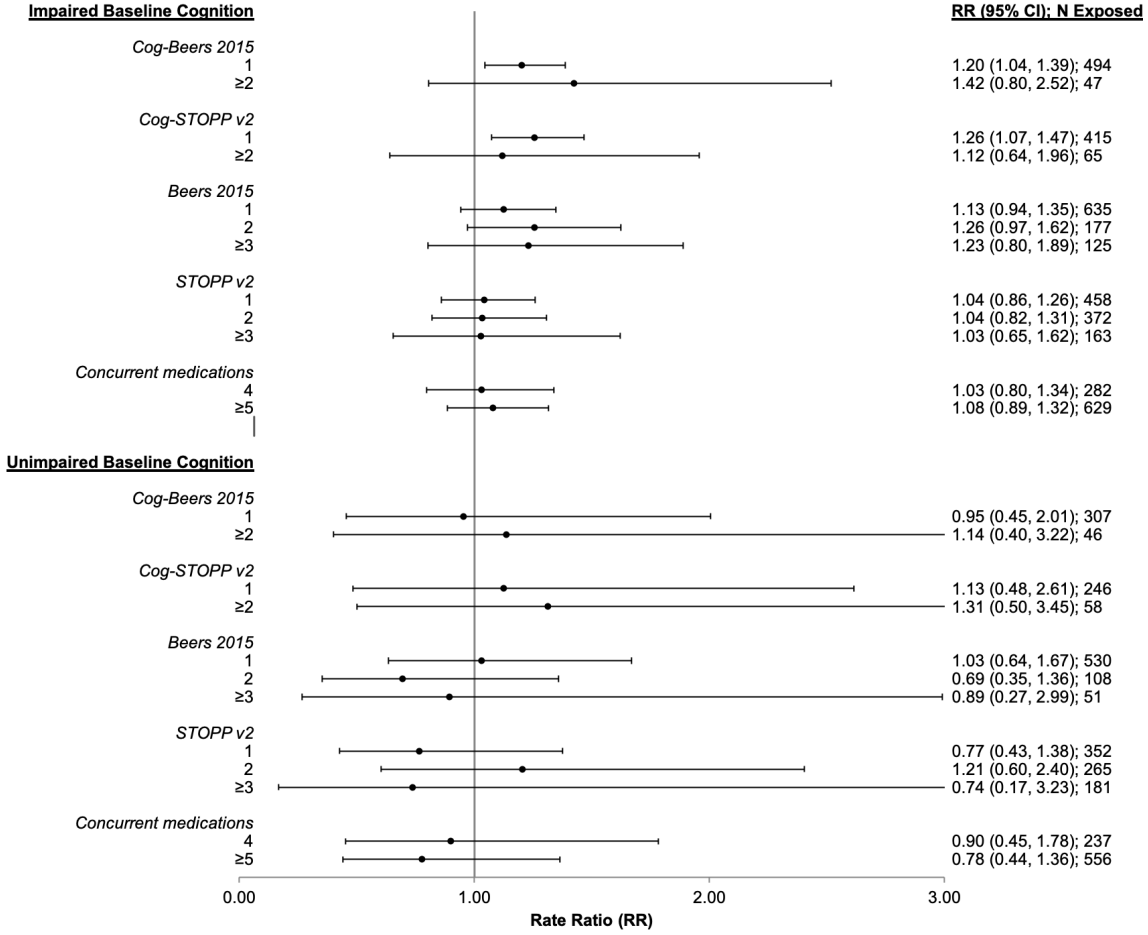


Figure 3.3.4. Cognitive Decline by PIM Exposure Definition



3.3.6 Supplementary Data

Supplementary Table 3.3.1. Distribution of Inverse Probability Weights

Exposure	Weight, mean	n, weighted	n, unweighted
Cog-Beers	0.955	8659	9108
Cog-STOPP	0.955	9171	9649
Beers	0.948	4538	4857
STOPP	0.950	5243	5549
Polypharmacy	0.919	3435	3754

Supplementary Table 3.3.2. Baseline Characteristics by Cog-STOPP Use

	Unweighted	Unweighted			Weighted		
	Total n = 9649	New Cog-STOPP n = 767	Never Cog-STOPP n = 8882	|SMD|	New Cog-STOPP n = 752	Never Cog-STOPP n = 8418	|SMD|
Demographics							
Age, years, mean (SD)	76.55 (7.06)	76.94 (7.21)	76.52 (7.04)	0.054	77.42 (7.17)	76.66 (6.88)	0.109
Female	5290 (54.82)	442 (57.63)	4848 (54.58)	0.087	405 (53.86)	4707 (55.92)	0.042
White race	8059 (83.52)	620 (80.83)	7439 (83.75)	0.068	600 (79.79)	6931 (82.34)	0.065
Years education, mean (SD)	15.27 (3.4)	14.99 (3.6)	15.29 (3.38)	0.106	15.02 (3.59)	15.06 (3.45)	0.014
Days to next visit, median (IQR)	379 (357-430)	385 (358-441)	378 (357-429)	0.041	384 (358-434)	378 (357-429)	0.03
Clinical characteristics							
ASCVD	1435 (14.87)	118 (15.38)	1317 (14.83)	0.029	108 (14.36)	1291 (15.34)	0.028
Depression	2383 (24.7)	277 (36.11)	2106 (23.71)	0.272	182 (24.2)	2456 (29.18)	0.113
Diabetes	1345 (13.94)	140 (18.25)	1205 (13.57)	0.129	127 (16.89)	1210 (14.37)	0.07
Hypertension	5725 (59.33)	503 (65.58)	5222 (58.79)	0.139	472 (62.77)	5081 (60.36)	0.049
Impaired cognition*	5143 (53.3)	483 (62.97)	4660 (52.47)	0.213	463 (61.57)	4800 (57.02)	0.091
Parkinson's disease	138 (1.43)	18 (2.35)	120 (1.35)	0.073	13 (1.73)	173 (2.06)	0.029
Seizures	203 (2.1)	25 (3.26)	178 (2)	0.085	18 (2.39)	194 (2.3)	0.001
Medications, median (IQR)	6 (4-8)	8 (5-11)	6 (3-8)	0.592	8 (5-10)	6 (4-8)	0.527
CDR-SOB, median (IQR)	0.5 (0-3.5)	1 (0-5)	0.5 (0-3)	0.304	1 (0-5)	0.5 (0-4.5)	0.12

Cog-STOPP: medications affecting cognition in STOPP Criteria; SMD: standardized mean difference; ASCVD: atherosclerotic cardiovascular disease; CDR-SOB: CDR Staging Instrument sum of boxes

** Based on clinical assessment*

Supplementary Table 3.3.3. Baseline Characteristics by Beers Use

	Unweighted	Unweighted			Weighted		
	Total n = 4857	New Beers n = 1666	Never Beers n = 3191	|SMD|	New Beers n = 1610	Never Beers n = 2973	|SMD|
Demographics							
Age, years, mean (SD)	76.58 (7.21)	76.61 (7.12)	76.56 (7.26)	0.026	76.84 (7.06)	76.72 (7)	0.017
Female	2796 (57.57)	909 (54.56)	1887 (59.14)	0.083	913 (56.71)	1641 (55.2)	0.031
White race	4012 (82.6)	1352 (81.15)	2660 (83.36)	0.066	1285 (79.81)	2421 (81.43)	0.04
Years education, mean (SD)	15.24 (3.38)	15.06 (3.5)	15.34 (3.31)	0.088	14.92 (3.54)	15.14 (3.35)	0.062
Days to next visit, median (IQR)	378 (357-430)	378 (357-430)	378 (357-430)	0.003	378 (357-430)	378 (357-430)	0.006
Clinical characteristics							
ASCVD	617 (12.7)	246 (14.77)	371 (11.63)	0.105	218 (13.54)	444 (14.93)	0.04
Depression	1140 (23.47)	427 (25.63)	713 (22.34)	0.082	402 (24.97)	851 (28.62)	0.083
Diabetes	529 (10.89)	236 (14.17)	293 (9.18)	0.164	211 (13.11)	389 (13.08)	0.001
Hypertension	2674 (55.05)	1021 (61.28)	1653 (51.8)	0.191	936 (58.14)	1766 (59.4)	0.026
Impaired cognition*	2565 (52.81)	913 (54.8)	1652 (51.77)	0.072	923 (57.33)	1663 (55.94)	0.028
Parkinson's disease	79 (1.63)	30 (1.8)	49 (1.54)	0.025	33 (2.05)	57 (1.92)	0.009
Seizures	102 (2.1)	34 (2.04)	68 (2.13)	0.006	35 (2.17)	71 (2.39)	0.016
Medications, median (IQR)	5 (3-7)	6 (4-9)	4 (2-6)	0.773	6 (4-8)	4 (2-6)	0.733
CDR-SOB, median (IQR)	0.5 (0-3.5)	0.5 (0-4)	0.5 (0-3.5)	0.042	0.5 (0-4.5)	0.5 (0-4)	0.051

Beers: medications in Beers Criteria; SMD: standardized mean difference; ASCVD: atherosclerotic cardiovascular disease; CDR-SOB: CDR Staging Instrument sum of boxes

** Based on clinical assessment*

Supplementary Table 3.3.4. Baseline Characteristics by STOPP Use

	Unweighted	Unweighted			Weighted		
	Total n = 5549	New STOPP n = 1762	Never STOPP n = 3787	|SMD|	New STOPP n = 1698	Never STOPP n = 3545	|SMD|
Demographics							
Age, years, mean (SD)	76.5 (7.2)	76.77 (7.14)	76.37 (7.22)	0.069	76.89 (7.07)	76.7 (7)	0.027
Female	3253 (58.62)	972 (55.16)	2281 (60.23)	0.111	977 (57.54)	1995 (56.28)	0.026
White race	4632 (83.47)	1445 (82.01)	3187 (84.16)	0.054	1384 (81.51)	2879 (81.21)	0.008
Years education, mean (SD)	15.23 (3.38)	15.11 (3.46)	15.29 (3.34)	0.074	15.01 (3.44)	15.04 (3.44)	0.009
Days to next visit, median (IQR)	378 (357-430)	380 (357-432)	378 (357-430)	0.014	379 (357-430)	378 (357-432)	0.017
Clinical characteristics							
ASCVD	701 (12.63)	261 (14.81)	440 (11.62)	0.117	228 (13.43)	518 (14.61)	0.034
Depression	1349 (24.31)	474 (26.9)	875 (23.11)	0.09	439 (25.85)	1030 (29.06)	0.072
Diabetes	582 (10.49)	248 (14.07)	334 (8.82)	0.172	209 (12.31)	468 (13.2)	0.027
Hypertension	2872 (51.76)	1106 (62.77)	1766 (46.63)	0.327	951 (56.01)	2079 (58.65)	0.054
Impaired cognition*	2901 (52.28)	976 (55.39)	1925 (50.83)	0.121	969 (57.07)	1980 (55.85)	0.025
Parkinson's disease	89 (1.6)	29 (1.65)	60 (1.58)	0.009	32 (1.88)	70 (1.97)	0.007
Seizures	116 (2.09)	39 (2.21)	77 (2.03)	0.016	38 (2.24)	82 (2.31)	0.006
Medications, median (IQR)	5 (3-7)	6 (5-9)	4 (2-6)	0.807	6 (5-9)	4 (3-6)	0.748
CDR-SOB, median (IQR)	0.5 (0-3)	0.5 (0-3.5)	0.5 (0-3)	0.049	0.5 (0-4)	0.5 (0-4)	0.016

STOPP: medications in STOPP v2 Criteria; SMD: standardized mean difference; ASCVD: atherosclerotic cardiovascular disease; CDR-SOB: CDR Staging Instrument sum of boxes

** Based on clinical assessment*

Supplementary Table 3.3.5. Baseline Characteristics by Polypharmacy Use

	Unweighted	Unweighted			Weighted		
	Total n = 3754	New Polypharmacy n = 1708	Never Polypharmacy n = 2046	|SMD|	New Polypharmacy n = 1706	Never Polypharmacy n = 1729	|SMD|
Demographics							
Age, years, mean (SD)	76.42 (7.27)	76.43 (7.17)	76.41 (7.36)	0.014	76.53 (7.19)	76.79 (6.95)	0.036
Female	2163 (57.62)	976 (57.14)	1187 (58.02)	0.006	985 (57.74)	1002 (57.95)	0.004
White race	3133 (83.46)	1396 (81.73)	1737 (84.9)	0.068	1386 (81.24)	1391 (80.45)	0.022
Years education, mean (SD)	15.18 (3.35)	15.09 (3.43)	15.26 (3.28)	0.062	14.96 (3.48)	15.06 (3.14)	0.030
Days to next visit, median (IQR)	379 (359-433)	379 (360-437)	379 (358-430)	0.052	379 (359-436)	380 (358-433)	0.036
Clinical characteristics							
ASCVD	384 (10.23)	230 (13.47)	154 (7.53)	0.192	202 (11.84)	226 (13.07)	0.039
Depression	736 (19.61)	401 (23.48)	335 (16.37)	0.181	383 (22.45)	430 (24.87)	0.057
Diabetes	263 (7.01)	173 (10.13)	90 (4.4)	0.222	151 (8.85)	211 (12.2)	0.110
Hypertension	1653 (44.03)	881 (51.58)	772 (37.73)	0.282	789 (46.25)	962 (55.64)	0.189
Impaired cognition*	1793 (47.76)	889 (52.05)	904 (44.18)	0.17	912 (53.46)	888 (51.36)	0.042
Parkinson's disease	40 (1.07)	22 (1.29)	18 (0.88)	0.044	23 (1.35)	30 (1.74)	0.032
Seizures	62 (1.65)	36 (2.11)	26 (1.27)	0.064	34 (1.99)	33 (1.91)	0.008
Medications, median (IQR)	3 (2-5)	5 (4-7)	2 (1-3)	2.168	5 (4-7)	2 (2-3)	2.158
CDR-SOB, median (IQR)	0 (0-2.5)	0.5 (0-3)	0 (0-1.5)	0.123	0.5 (0-3.5)	0.5 (0-3)	0.019

SMD: standardized mean difference; ASCVD: atherosclerotic cardiovascular disease; CDR-SOB: CDR Staging Instrument sum of boxes
** Based on clinical assessment*

Supplementary Table 3.3.6. PIM Use on Cognitive Decline by Family History

	Impaired Baseline Cognition						Normal Baseline Cognition					
	FH			No FH			FH			No FH		
	RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI	
Cog-Beers 2015												
1	1.3453	1.1277	1.6049	0.9842	0.7759	1.2484	1.106	0.3783	3.2335	0.7326	0.2712	1.9792
≥2	1.5131	0.7811	2.931	1.2155	0.4957	2.9805	0.8165	0.2048	3.2558	1.6148	0.4598	5.6709
Cog-STOPP v2												
1	1.4381	1.1867	1.7428	1.0148	0.776	1.3271	1.2354	0.3723	4.0989	1.0046	0.2896	3.4854
≥2	1.1482	0.5691	2.3165	0.9831	0.5007	1.9302	0.8513	0.2412	3.0044	1.55	0.4994	4.8109
Beers 2015												
1	1.0484	0.8366	1.3138	1.2106	0.8637	1.6968	0.9511	0.4506	2.0077	0.8352	0.4345	1.6056
2	1.249	0.8985	1.7362	1.2757	0.7341	2.2169	0.6869	0.2179	2.1655	0.863	0.3779	1.9706
≥3	1.4462	0.7603	2.751	0.982	0.5901	1.6343	1.2764	0.334	4.8779	0.8532	0.08375	8.6924
STOPP v2												
1	1.0241	0.805	1.3027	1.1499	0.7997	1.6534	1.1684	0.5874	2.3241	0.6002	0.2057	1.7511
2	1.126	0.8621	1.4707	0.9769	0.6371	1.4979	1.6542	0.51	5.3655	0.9844	0.4431	2.1871
≥3	1.2479	0.7701	2.0221	0.7839	0.3398	1.8085	0.2997	0.05905	1.5215	0.8395	0.2337	3.016
Total medications												
4	1.0541	0.7599	1.462	1.1614	0.7182	1.8782	0.7147	0.2767	1.8458	0.8832	0.3249	2.4009
≥5	1.2487	0.9892	1.5762	0.9682	0.6819	1.3747	0.6251	0.2677	1.4598	0.8771	0.4378	1.7569

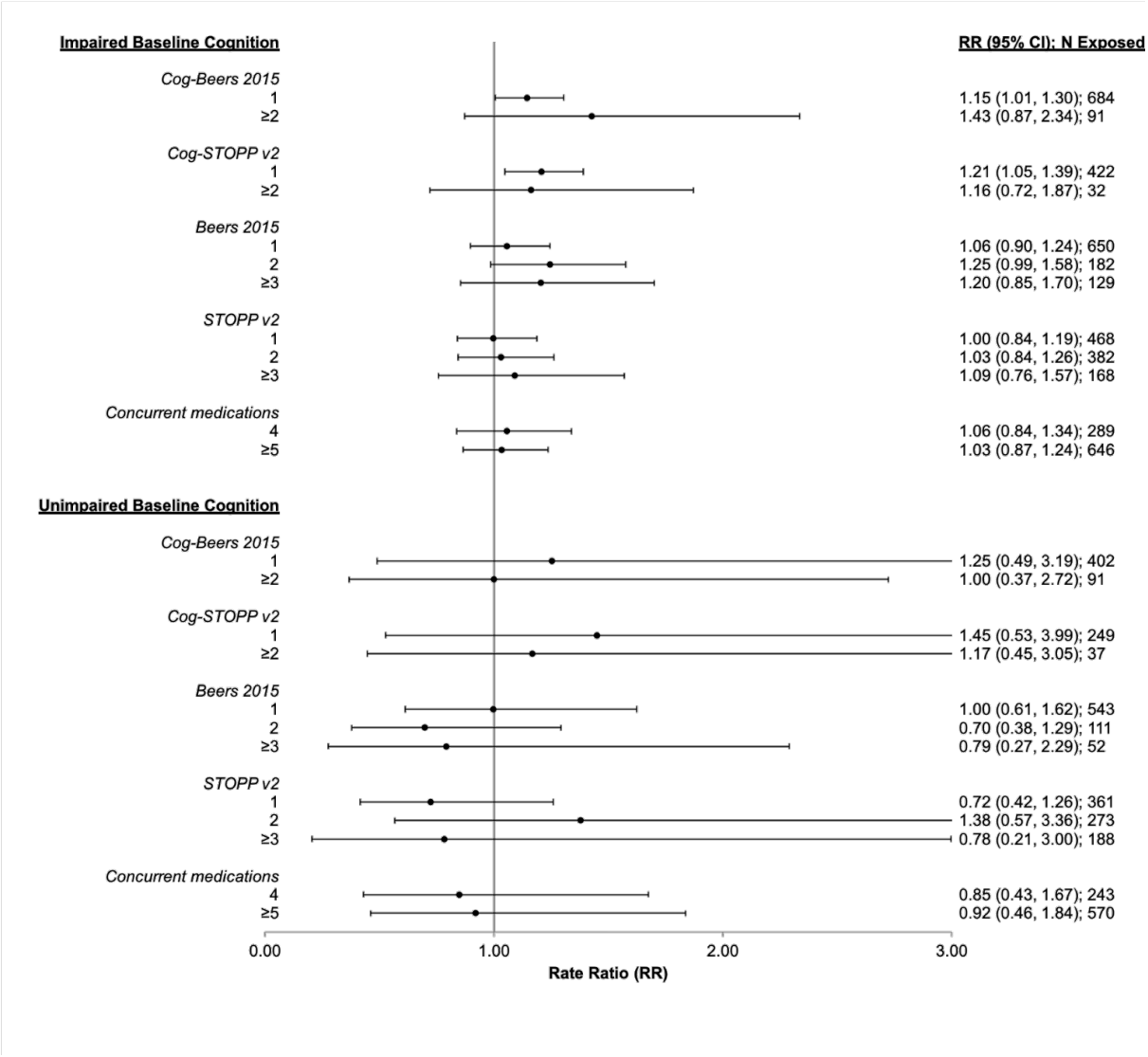
FH: family history of cognitive impairment; CI: confidence interval; RR: rate ratio

Supplementary Table 3.3.7. Validity of CDR-SOB Outcome by PIM Use

Possible Gold Standards	Cog-Beers PIM Users Ss	Sp	PPV	NPV	Cog-Beers PIM Nonusers Ss	Sp	PPV	NPV
Subject reports a decline in memory	0.55	0.75	0.77	0.54	0.55	0.78	0.72	0.62
Co-participant reports a decline in memory	0.63	0.50	0.55	0.58	0.62	0.88	0.86	0.65
Clinician believes there is a meaningful decline in memory, non-memory cognitive abilities, behavior, ability to manage his/her affairs, or there are motor/movement changes	0.63	0.91	0.93	0.55	0.62	0.91	0.91	0.65

Ss: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value

Supplementary Figure 3.3.1. Sensitivity Analysis Excluding Back-Transitions



3.3.7 Code Blocks

Code Block 3.3.1. Negative Binomial Regression for Degree of Cognitive Decline

```
proc sort data=final; by impair; format _all_; run;
title "Cog-Beers Count: New vs Never";
proc genmod data = final;
        by impair;
        class cnsb_new(ref="0") sex(ref="0") dep2yrs(ref="0") cardiodz(ref="0")
diabetes(ref="0") pd(ref="0") seizures(ref="0") hyperten(ref="0") naccid;
        model cdrchange_trunc = cnsb_new sex naccage educ dep2yrs cardiodz diabetes pd
seizures hyperten cdrsum2 poly4 / type3 link=log dist=negbin offset=ln_fuyrs; *log link
assumed and not necessary;
        weight swcnsb;
        repeated subject = naccid;
        lsmeans cnsb_new / ilink diff exp cl pdiff=control('0') adjust=dunnett; /*
estimates rate ratios */
run; quit;title;
```

3.4 Cumulative dose effects of potentially inappropriate medication use on dementia diagnosis in an older adult Medicare population

3.4.1 Introduction

Potentially inappropriate medication (PIM) use in older adults is highly prevalent throughout the world.[40] There are many ways researchers and clinicians identify and define PIMs, ranging from nuanced implicit criteria that require a great deal of clinical judgment but are generally highly accurate, to broad explicit criteria containing lists of many medication classes that may not be applicable to all patients, to targeted criteria of one or a few medication classes known to be detrimental for certain health outcomes. Because dementia is the fifth leading cause of death for Americans over 65 years of age, there is no effective treatment or cure, and many with dementia also have other comorbidities,[181] it is important that medication therapy in these individuals not contribute to negative cognitive outcomes. However, the multimorbid state of many older adults with dementia can lead to polypharmacy and increase the chances that any one medication may be potentially inappropriate.

In fact, a recent systematic review found that 14-74% of older adults with dementia used PIMs, driven by benzodiazepines, hypnotics, and anticholinergics.[40] Given that there is evidence linking each of these individual medication classes to a variety of negative cognitive effects,[65,122] it is important that their use is effectively and accurately measured so that interventions can be designed to reduce consumption of these potentially inappropriate medications. While there have been numerous tools developed to aid in PIM use measurement over the last few decades, there is inconsistency in their application clinically and in research,[38,40] as well as in their association to health outcomes, specifically cognitive decline. One of the most widely-used medication appropriateness assessment tool in the United States is the Beers Criteria. Initially developed in 1991, and currently in its sixth update, the Beers Criteria explicitly list medications

that should be avoided in all older adults. Beginning in 2003, the Beers Criteria included a sub-list of medications that should be considered potentially inappropriate in older adults with dementia or cognitive impairment (Cog-Beers). This list includes medications with strong anticholinergic properties, benzodiazepines, non-benzodiazepine hypnotics, histamine-2 receptor antagonists, and antipsychotics.[115] Previous studies have defined PIM use by use of any medication in this sub-list,[128,182] and found that nearly one-quarter of older adults with dementia used these potentially inappropriate medications, and we have previously shown that using any medication in the Cog-Beers list may be associated with and increased rate of cognitive decline over approximately one year (see previous chapter).

However, no studies have investigated whether there is a dose-response relationship in the association between Cog-Beers PIM use and cognitive decline. While estimates of "ever-never" PIM use can be helpful in research, most relationships yet to be elucidated are more nuanced in nature. The practice of simplifying a complex exposure into inflexible dichotomous or ordinal variables certainly has its flaws, but continues to be employed in medical research due to the taxing computational and statistical tools required to analyze a more nuanced exposure.[183] Outside of the statistical power lost, a primary concern when defining PIM use as a single exposure is that mounting evidence indicates the risks anticholinergics,[57,123] proton pump inhibitors[184], and sedatives[185] to cognition may be dose-related,[123] While it is not reasonable to expect that all future studies use complex statistical techniques required to model such a nuanced exposure, it is important to determine whether taking into account a dose-related effect when using explicit criteria to define PIM use even matters.

Since 2006, Americans eligible for Medicare have had access to a prescription drug benefit, which in addition to providing critical access to life-saving therapies for a population in dire need, also paved the way for researchers to begin to analyze prescription medication use trends in a large portion of the American population. The Centers for Medicare and Medicaid Services (CMS) makes deidentified administrative prescription claims processed through this program

(Medicare Part D) available to researchers. In this study, we use these data to investigate the effect of Cog-Beers PIM use on time to diagnosis of ADRD in a population of adults 65 years old and above from 2012-2016.

3.4.2 Methods

3.4.2.1 Study Population and Data Source

This study utilized a random 5% sample of Medicare Part D (MPD) administrative claims data for beneficiaries who were ≥ 65 years old at any point from 2012-2016, had fee-for-service Medicare Parts A and B and were not dually eligible for Medicaid for at least some point in that same time period. In addition to MPD claims, this study also had access to enrollment files containing basic demographic information, and a summary file detailing information on chronic and other potentially disabling conditions.

Beneficiaries entered the study the day after their first six months of continuous MPD eligibility (index date). Continuous enrollment was defined as enrollment with no more than a one-month gap. In cases where gaps exceeded one month, the end of continuous enrollment was the last day of the month prior to the gap. Adults aged < 65 years, those with a diagnosis of Alzheimer's Disease or related Dementias (ADRD), and those with any PIM use before the index date were excluded. Beneficiaries exited the study at the first of: end of continuous enrollment in MPD, diagnosis of ADRD, death, or the end of the data (12/31/2016).

3.4.2.2 Exposure

Medication use was derived from Medicare Part D (MPD) administrative claims data. The data included the NDC, service date, quantity, and days supply for each medication dispensed by a pharmacy that billed the patient's MPD plan.

Medications identified in the 2012 and 2015 Beers criteria as potentially inappropriate for adults aged ≥ 65 years with Alzheimer's dementia and related disorders (including anticholinergics, benzodiazepines, histamine-2 receptor

antagonists, nonbenzodiazepine hypnotics, and antipsychotics) were considered PIMs for the purposes of this study.

Cumulative PIM exposure was defined by first calculating the total dose dispensed for each PIM identified in a prescription claim (strength x quantity). Then, this total dose per prescription was converted to a standardized dose by dividing the total dose per prescription claim by the minimum effective daily dose for the most common indication according to the Geriatric Handbook in Lexicomp[186] (see Supplementary Table 3.4.1).

For each 28-day exposure period, the cumulative standardized doses (CSDs) of PIMs were calculated as the summation of all standardized PIM doses in prescription claims dispensed during that period. 28-day exposure periods were chosen because previous studies have shown that this period is sufficient to simulate a model with infinitely small intervals.[187] Due to dose data having an extremely right-skewed distribution, the top 1% of CSDs were truncated.

3.4.2.3 Outcome(s)

Clinical cognitive impairment was defined as a medical claim including a Alzheimer's dementia and related disorders (ADRD) diagnosis. ADRD diagnoses were defined as the presence of validated diagnosis codes at any position on an inpatient, skilled nursing facility, home health agency, hospital outpatient, or ambulatory claim. While using any position of the diagnosis code to identify ADRD does increase sensitivity at the expense of specificity, the only data available to us was this flag.

Previous studies have suggested that at least three years of continuous eligibility are required to sufficiently identify Alzheimer's dementia and related disorders in Medicare claims. The reason we do not need a 3-year run-in period is because this has already been calculated by the Chronic Conditions Warehouse and provided to us as a flag when at least 1 inpatient, SNF, HHA, HOP or carrier claim with the included diagnosis codes was present in any of the 3 years prior to inclusion in our study.

3.4.2.4 Covariates

Based on published evidence, we created a directed-acyclic graph (DAG) to model the relationship between factors involved with the exposure and outcome. Covariates were included in the model based on their ability to control for confounding identified by the DAG and their availability in the data (see Figure 3.4.1). Available and included covariates were as follows: age, sex, anxiety disorder, depression, schizophrenia, bipolar disorder. Parkinson's disease could not be included in the model because of its unavailability in the data.

3.4.2.5 Statistical Analysis

Data was converting into a counting process using the SAS macro program `%CPDATA`,[188] after the SAS procedure `PROC PHREG` was used to perform a Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) (see Code Block 3.4.1). Survival curves were constructed for never exposed beneficiaries, as well as those with (0,50], (50,100], (100,200], and (200,400] CSDs of Cog-Beers PIMs based on the distribution of CSDs seen in the data.

Data was structured to include one row per person-time interval, with columns to indicate the current exposure status (Cog-Beers PIM doses in the current interval), cumulative exposure status (sum of standardized Cog-Beers PIM doses over all earlier intervals in which a PIM prescription was current = CSDs), covariate (i.e. age and comorbidity) status at the beginning of the interval, and outcome status at the end of the interval.

To determine whether Cog-Beers PIM use was associated with the hazard for ADRD, we used Cox proportional hazards regressions as in a previous study investigating cumulative dose effects.[187] In the first model, we included only an indicator for ever-never use along with potential confounders, as specified above. In the second model, we also included a linear term for cumulative exposure to jointly control for time-invariant allocation bias (indication bias). Indication bias occurs when the risk for the outcome is related to the exposure's indication, but not the exposure itself. In this case, confounding by indication may be present because ADRD is related to common PIM indications, which will cloud any

association with PIMs themselves. Mathematically, this modeling is valid if one considers the generalized linear model with terms for ADRD diagnosis (y), cumulative exposure (x), an indicator for ever-never PIM use (z), and the link function (g) (see Equation 3.1). As such, we can interpret the ever-exposure parameter as the difference between ADRD risk at the start of PIM exposure ($\alpha+\beta_0$) and the ADRD risk in person-time intervals that are completely unexposed (α).

Equation 3.1. Generalized Linear Model

$$\mathbb{E}\langle y\rangle = g^{-1}(\alpha + \beta_0 z + \beta x)$$

We further examined the form of the relationship of ADRD risk to cumulative PIM exposure by coding total standardized doses as a categorical variable with reference values of either no exposure or ≤ 25 standardized doses of exposure, in separate regressions.

Because we expect our outcome (ADRD) to be relatively rare, we calculate the E-value[189] for new-never PIM exposure and linear cumulative PIM exposure as a sensitivity analysis to determine whether our results might be influenced by confounding. The E-value is a type of sensitivity analysis that calculates the minimum strength of association that a theoretical confounder would need to have with both the exposure and outcome in order to completely explain the observed association. If it is plausible that there is an unmeasured confounder associated with both PIM use and ADRD by the E-value, then this would be evidence that the estimated effect may be confounded.

3.4.3 Results

3.4.3.1 Baseline Characteristics

The raw data provided from CMS included information on 1,645,058 unique beneficiaries, 634,238 of whom were ultimately included in the study (see Figure 3.4.2). Beneficiaries were on average 72 years old when they entered the study,

and about 54% were female. Cog-Beers PIM nonusers had a median (IQR) of 3 (1-6) chronic conditions, compared to PIM users who had 5 (3-8). Consistent with this finding, beneficiaries who were new users of Cog-Beers PIMs had higher rates of all comorbidities that may potentially confound the relationship between PIM use and ADRD, with the most striking differences in the prevalence of anxiety and depression.

3.4.3.2 Cog-Beers PIM Use

32.7% of the study sample were identified as new users at some point during follow-up. The median (IQR) CSDs of PIMs among new users was 70.8 (25-296.7) after truncating the top 1% at 4,171 CSDs. While 51/93 (54.8%) of medications classified as Cog-Beers PIMs are strongly anticholinergic according to the 2012 Beers Criteria, only 36.9% of Cog-Beers PIMs used by beneficiaries in this study were anticholinergic (see Table 3.4.2). The most commonly used PIM medication class was benzodiazepines (34.7%) followed by non-benzodiazepine hypnotics (15.1%), and antidepressants (12.7%).

3.4.3.3 Hazard of ADRD Diagnosis

The median (IQR) follow-up time in this study was 45 (23-57) 28-day periods, and 43,983 (6.93%) of beneficiaries were diagnosed with ADRD. 7.4% were censored due to death, 1.7% were censored due to end of enrollment, and 83.9% were administratively censored at the end of the data on 12/31/16.

In the first model of Cog-Beers PIM use on ADRD hazard, at any particular time between 2012-2016, 1.228 times as many Cog-Beers PIM new users were being diagnosed with ADRD compared to PIM nonusers (95% CI 1.200-12.56; see Table 3.4.3). Adding a linear term for cumulative exposure to PIMs changes the hazard ratio associated with new use of PIMs to 1.211 [1.183-1.241], and estimates each increase of 100 CSDs among PIM new users increased the hazard rate of ADRD diagnosis by 0.5% (HR [95% CI] 1.005 [1.002-1.007]). While the association between increasing PIM CSDs and ADRD hazard rate is statistically significant, there is significant overlap amongst groups of PIM users at various CSDs (see Figure 3.4.3). The E-value for new-versus-never PIM use is 1.72 (95%

CI 1.65-1.79), and 1.08 (1.05-1.09) for the linear term measuring cumulative PIM exposure.

When we modeled cumulative Cog-Beers PIM use categorically with unexposed person-time intervals as the reference group, new PIM users with ≤25 SDDs have 1.209 times the rate of ADRD diagnoses (HR [95% CI] 1.209 [1.164-1.256]; see Table 3.4.4) compared to non-using beneficiaries, but all PIM users have at least 1.144 times the hazard of ADRD diagnosis. However, when the reference group was new PIM users with ≤ 25 CSDs, the hazard for ADRD diagnosis is only statistically significantly different at CSDs > 100. The E-value for PIM use at > 200 CSDs is 1.54 (1.36-1.72).

3.4.4 Discussion

In this study, we examined the nature of the relationship between rate of ADRD diagnosis and use of medications considered potentially inappropriate for older adults with cognitive impairment or dementia according to the 2012 Beers Criteria in a population of older adults with stand-alone Medicare Part D prescription medication coverage.

We found that new use of Cog-Beers PIMs is associated with approximately 1.2 times the rate of incident ADRD diagnoses compared to no use of Cog-Beers PIMs. This finding was fairly consistent regardless of the modeling technique used to estimate it. While there are no published studies investigating the association between PIMs when defined as medications considered potentially inappropriate for individuals with cognitive impairment or dementia according to the 2012 Beers criteria, other studies with similar definitions have shown similar effect sizes.[64,190]

In addition to using a PIM use definition that is targeted to cognitive outcomes, this study also investigated the effect of PIM dose on rate of incident ADRD diagnosis. We found that among new users of Cog-Beers PIMs, the rate of ADRD diagnosis increased by 0.5% for each 100 CSDs. For reference, 100 CSDs amounts to using the minimum effective daily dose of one PIM for 100 days. Similarly, 100 CSDs is also equivalent to using twice the minimum effective daily

dose of one PIM for 50 days, or of two PIMs for 25 days. In 2011, the national average annual incidence of Alzheimer's disease alone was 0.4% among those 65-74 years old, and 3.2% among those 75-84 years old.[191] Thus, an increased rate of ADRD diagnosis of 0.5% per 100 CSDs amounts to 15% of the increased rate seen over a decade of aging – not an insignificant risk.

For context, an individual who remained in the study for the median follow-up time (approximately 42 months), would amass approximately 1,260 CSDs if they used 1 standardized PIM dose daily for the entire follow-up. When cumulative PIM use was categorized, only beneficiaries who used more than 100 CSDs had a significantly higher rate of ADRD diagnosis when compared to beneficiaries who used PIMs, but less than 25 CSDs. Notably, the distribution of PIM CSDs among new users was highly right-skewed, such that while the median CSDs for users was merely 70, the mean was almost 350, and 10% of all PIM users filled at least 1,014 CSDs during follow-up. These findings suggest that high dose users may be driving the association between PIM use and ADRD. While it is possible that some confounding by indication still exists (high-dose PIM users have statistically, but not clinically, significantly higher rates of ADRD than low-dose PIM users), the consistent findings throughout our modeling techniques suggest that we were able to control for this potential source of confounding. Our sensitivity analysis suggested that a confounder would need to be associated with both new PIM use and ADRD with a hazard ratio of at least 1.72 (95% CI 1.65-1.79) for new-versus-never PIM use and at least 1.08 (1.05-1.09) for cumulative PIM use, above and beyond the measured confounders to explain away our estimate. The two unmeasured confounders according to our DAG (see Figure 3.4.1) are insomnia and Parkinson's disease, both of which have the potential to meet these criteria. Thus, it is important that further studies be undertaken to capture the true potential for confounding.

In addition to the consistency of our findings and the support for a dose-response relationship, the long follow-up in this study adds to its strength. While we restricted to beneficiaries' first continuous enrollment period, future studies

could utilize more advanced techniques with adjustments for interval censoring to gather additional information by allowing larger gaps between coverage.

Furthermore, while the definition of a diagnosis for ADRD in this study has been validated,[102] Medicare claims have been shown to contain both false negative and false positive outcome misclassifications. One study estimated that while Medicare claims that failed to identify dementia were correct in doing so 97% of the time, the positive predictive value of dementia diagnosis in Medicare claims was merely 0.56.[192] This type of outcome misclassification could bias our results if it is differential, which may be the case if PIMs mimic the symptoms of dementia leading to a diagnosis without actual pathology. Future studies should link these administrative claims to survey data with more sensitive outcome measures to determine the true impact of potential differential misclassification.

Overall, this study highlights the importance of both exposure and outcome definition when investigating the effect of PIM use on cognitive outcomes in older adults. We have shown through various modeling techniques that there is likely a dose-response relationship to the association between Cog-Beers PIM use and rate of ADRD diagnosis in a large population of fee-for-service Medicare beneficiaries with Medicare Part D prescription drug coverage.

3.4.5 Tables and Figures

Table 3.4.1. Baseline Characteristics of Medicare Population

	Total n = 634238	**Cog-Beers[a] Users n = 207109**	**Cog-Beers Nonusers n = 427129**
Demographics			
Age, mean (SD)	72.31 (7.23)	72.89 (7.01)	72.02 (7.311)
Female, n (%)	344746 (54.36)	126437 (61.05)	218309 (51.11)
Nonwhite race, n (%)	67345 ()	19009 (9.18)	48336 (11.32)
CCW[b] conditions, median (IQR)	4 (1-7)	5 (3-8)	3 (1-6)
Comorbidities, n (%)			
Acute myocardial infarction	17375 (2.74)	6427 (3.1)	10948 (2.56)
Anxiety	44781 (7.06)	26174 (12.64)	18607 (4.36)
Atrial fibrillation	61841 (9.75)	22743 (10.98)	39098 (9.15)
Bipolar disorder	2983 (0.47)	1693 (0.82)	1290 (0.3)
Congestive heart failure	86039 (13.57)	33555 (16.2)	52484 (12.29)
Depression	80419 (12.68)	40080 (19.35)	40339 (9.44)
Diabetes	161860 (25.52)	59034 (28.5)	102826 (24.07)
Epilepsy	5018 (0.79)	2290 (1.11)	2728 (0.64)
Hyperlipidemia	392404 (61.87)	145786 (70.39)	246618 (57.74)
Hypertension	393284 (62.01)	145722 (70.36)	247562 (57.96)
Ischemic heart disease	202774 (31.97)	79499 (38.39)	123275 (28.86)
Obesity	58877 (9.28)	24556 (11.86)	34321 (8.04)
Schizophrenia	3535 (0.56)	1473 (0.71)	2062 (0.48)
Stroke	43625 (6.88)	17517 (8.46)	26108 (6.11)
Tobacco use	19412 (3.06)	8176 (3.95)	11236 (2.63)
Traumatic brain injury	2157 (0.34)	1109 (0.54)	1048 (0.25)

[a]Medications listed as potentially inappropriate for older adults with dementia or cognitive impairment in 2012 Beers Criteria; [b]Chronic Conditions Warehouse

All group differences statistically significant at p <0.0001

Table 3.4.2. Distribution of Cog-Beers Medication Classes

	Total, n (%)	% Strongly anticholinergic
Antihistamines, H1	181674 (4.39)	100
Antidepressants	523737 (12.65)	100
Antiparkinsonian agents	9478 (0.23)	100
Antipsychotics	241572 (5.84)	49.48
Antispasmodics	83694 (2.02)	100
Benzodiazepines	1435974 (34.7)	0
Antihistamines, H2	420735 (10.17)	0
Non-benzodiazepine hypnotics	624730 (15.09)	0
Skeletal muscle relaxants	149518 (3.61)	100

Table 3.4.3. Hazard of ADRD in Models with New-Never Exposure

	Model with only new-never term				Model with new-never and linear cumulative terms			
	HR	**95% CI Bounds**		**p-value**	**HR**	**95% CI Bounds**		**p-value**
Cog-Beers new vs never exposure	1.228	1.2	1.256	<0.0001	1.211	1.183	1.241	<0.0001
Cumulative Cog-Beers exposure	---	---	---	---	1.005	1.002	1.007	0.0002

All models adjusted for age, female sex, number of chronic conditions, as well as anxiety, depression, schizophrenia, and bipolar disorder

Table 3.4.4. ADRD Hazard in Models with Categorical Cumulative Exposure

	Reference: Unexposed person-time intervals				Reference: Person-time intervals with >0 to 25 CSDs			
	HR	**95% CI Bounds**		**p-value**	**HR**	**95% CI Bounds**		**p-value**
0 < CSDs ≤ 25	1.209	1.164	1.256	<0.0001	---	---	---	---
25 < CSDs ≤ 50	1.144	1.093	1.197	<0.0001	0.961	0.909	1.016	0.1588
50 < CSDs ≤ 100	1.209	1.157	1.264	<0.0001	1.018	0.964	1.076	0.5256
100 < CSDs ≤ 200	1.272	1.212	1.335	<0.0001	1.077	1.016	1.141	0.0127
200 < CSDs ≤ 400	1.333	1.268	1.402	<0.0001	1.142	1.076	1.213	<.0001
CSDs > 400	1.258	1.208	1.309	<0.0001	1.090	1.034	1.148	0.0012

Adjusted for age, sex, number of CCW conditions, anxiety, depression, schizophrenia, and bipolar disorder

Figure 3.4.1. Directed Acyclic Graph for CMS Data

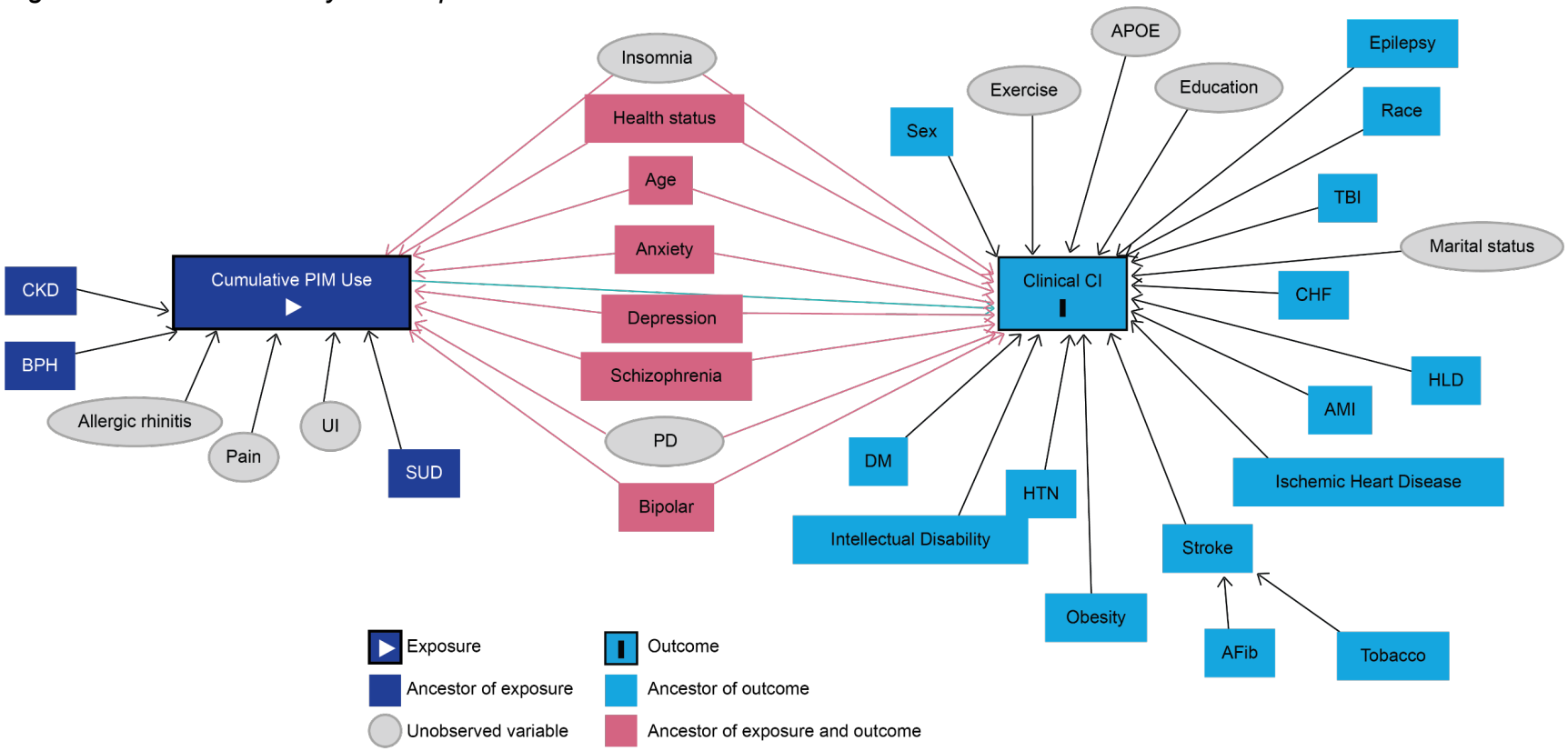


Figure 3.4.2. Beneficiary Selection

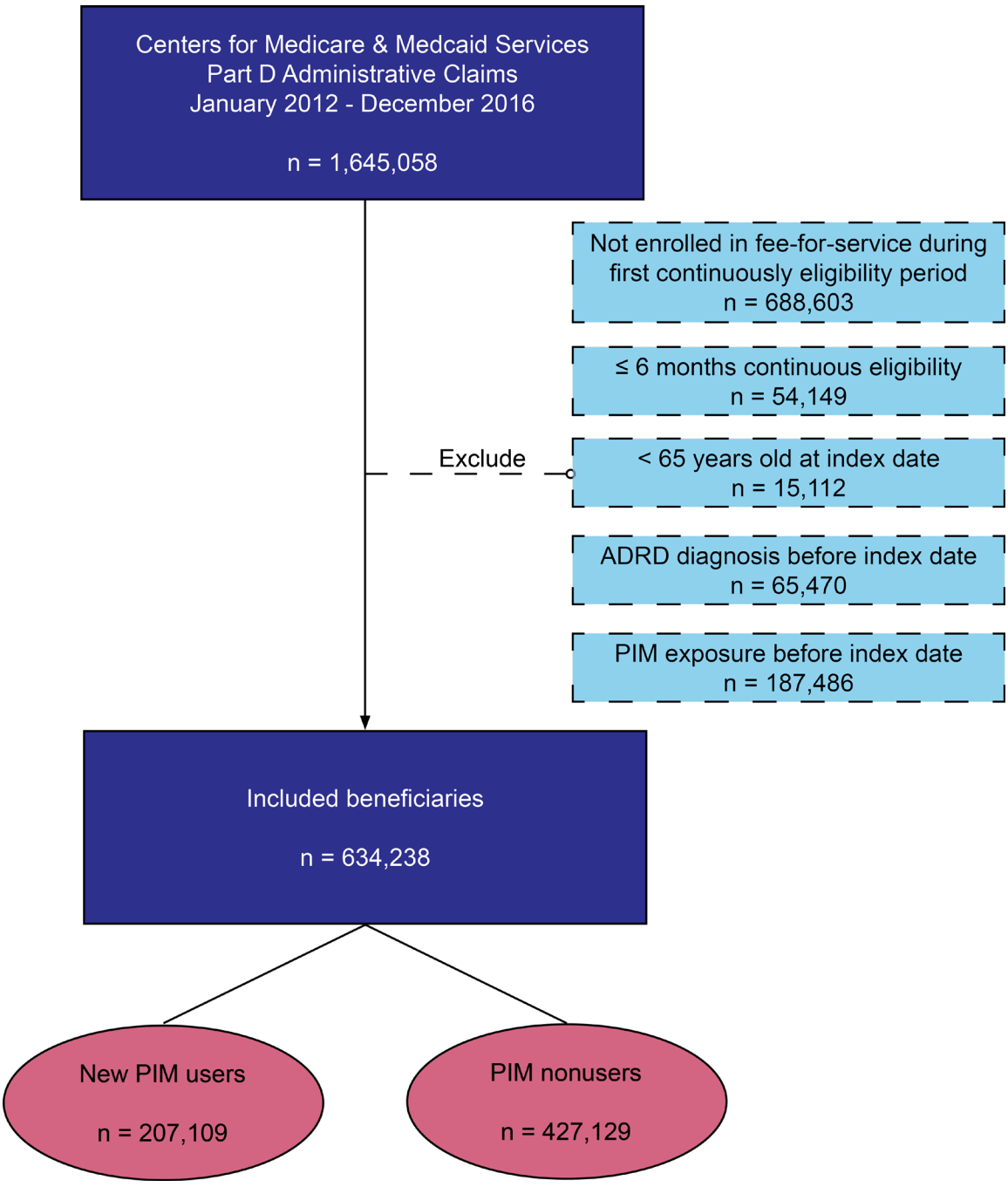
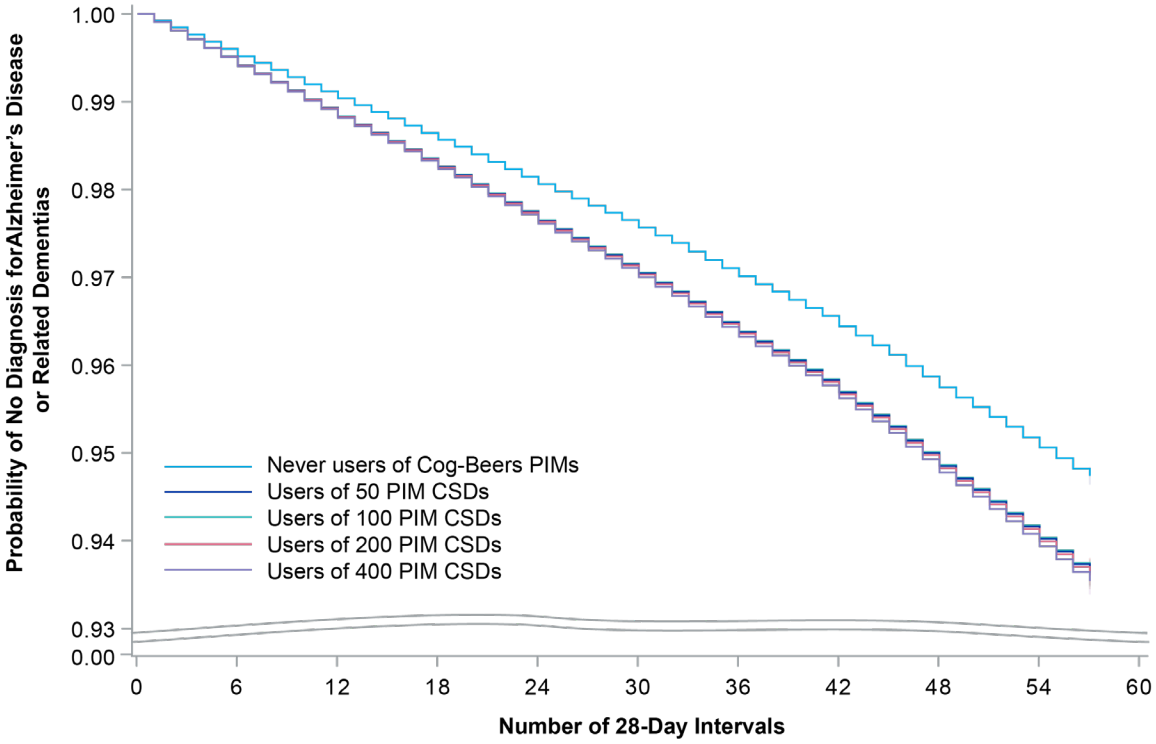


Figure 3.4.3. Probability of ADRD Diagnosis by Cumulative Cog-Beers Use



3.4.6 Supplementary Data

Supplementary Table 3.4.1. Minimum Effective Daily Doses

Medication	MEDD (mg)	Indication
Alprazolam	0.75	Anxiety disorders
Amitriptyline	25	Major depressive disorder
Amoxapine	50	Major depressive disorder
Aripiprazole	2	Major depressive disorder
Asenapine	10	Schizophrenia
Belladonna	45	Peptic Ulcer Disease and GI Motility Disorders
Benztropine	0.5	Parkinsonism
Brexpiprazole	1	Schizophrenia
Brompheniramine	24	Upper respiratory tract conditions
Carbinoxamine	12	Allergies
Cariprazine	1.5	Schizophrenia
Carisoprodol	750	Musculoskeletal conditions
Chlordiazepoxide	15	Anxiety
Chlorpheniramine	24	Allergic symptoms, allergic rhinitis, urticaria, pruritus
Chlorpromazine	40	Nausea and vomiting
Cimetidine	200	GERD
Clemastine	2	Allergic rhinitis
Clidinium	5	Irritable bowel syndrome
Clobazam	5	Lennox-Gastaut
Clomipramine	25	Obsessive-compulsive disorder
Clonazepam	0.5	Panic disorder
Clorazepate	30	Anxiety disorders
Clozapine	12.5	Schizophrenia
Cyclobenzaprine	15	Muscle spasm
Cyproheptadine	12	Allergic conditions
Darifenacin	7.5	Overactive bladder
Desipramine	25	Major depressive disorder
Dexbrompheniramine	2	Common cold/upper respiratory allergies
Dexchlorpheniramine	8	Allergy symptoms
Diazepam	4	Anxiety
Dicyclomine	20	Irritable bowel syndrome-associated abdominal pain
Dimenhydrinate	200	Motion sickness, nausea/vomiting, or vertigo:
Diphenhydramine	100	Common cold symptoms
Doxepin	3	Major depressive disorder
Doxylamine	25	Insomnia
Estazolam	1	Insomnia
Eszopiclone	1	Insomnia
Famotidine	20	GERD
Fesoterodine	4	Overactive bladder
Flavoxate	300	Overactive bladder
Fluphenazine	2.5	Psychosis
Flurazepam	15	Insomnia
Haloperidol	2	Schizophrenia
Hydroxyzine	25	Antiemetic
Hyoscyamine	0.375	Gastrointestinal disorders
Iloperidone	2	Schizophrenia
Imipramine	10	Major depressive disorder
Lithium	600	Bipolar disorder
Loratadine	10	Allergic conditions

Lorazepam	0.5	Insomnia due to anxiety or stress
Loxapine	20	Schizophrenia
Lurasidone	20	Bipolar disorder
Meclizine	25	Motion sickness
Meprobamate	1200	Anxiety
Methscopolamine	5	Peptic ulcer (adjunctive)
Molindone	50	Schizophrenia
Nizatidine	300	GERD
Nortriptyline	30	Major depressive disorder
Olanzapine	5	Schizophrenia
Orphenadrine	200	Muscle spasms
Oxazepam	30	Anxiety, mild to moderate
Oxybutynin	5	Overactive bladder
Paliperidone	6	Schizoaffective disorder
Paroxetine	10	Major depressive disorder
Paroxetine SR	12.5	Major depressive disorder
Perphenazine	8	Schizophrenia
Pimozide	0.5	Delusional infestation
Prochlorperazine	15	Nausea and vomiting
Promazine	30	Bipolar disorder
Promethazine	50	Motion sickness
Propantheline	75	Peptic ulcer
Protriptyline	15	Major depressive disorder
Quazepam	7.5	Hypnotic
Quetiapine	50	Schizophrenia
Ranitidine	150	GERD
Risperidone	2	Schizophrenia
Scopolamine	0.3	Motion sickness
Scopolamine	0.3	Motion sickness
Solifenacin	5	Overactive bladder
Thioridazine	150	Schizophrenia
Thiothixene	6	Schizophrenia
Tizanidine	2	Spasticity
Tolterodine	4	Overactive bladder
Triazolam	0.125	Insomnia
Trifluoperazine	4	Schizophrenia
Trihexyphenidyl	1	Parkinsonism
Trimipramine	50	Major depressive disorder
Triprolidine	10	Upper respiratory allergies
Trospium	20	Overactive bladder
Zaleplon	10	Insomnia
Ziprasidone	40	Schizophrenia
Zolpidem	5	Insomnia
Zolpidem SL	1.75	Insomnia

MED: minimum effective daily dose; TD: transdermal; SL: sublingual

3.4.7 Code Blocks

Code Block 3.4.1. Models Examining Relationship between ADRD and Cog-Beers PIM Use

```
ods graphics on;
title "Only time-updated ever-never term";
proc phreg data = surv4;
       class female (ref = "0") white (ref = "1") everexposed (ref = "0") anxi (ref = "0") dep (ref = "0") schiot (ref = "0") bipl
(ref = "0");
       model (time0, time1) * censor(1) = everexposed female white age_indt anxi dep schiot bipl mcc / rl;
run;
title;

title "Time-updated ever-never term and linear (truncated) term for cumulative exposure (in 100 standardized dose units)";
proc phreg data = surv4 plots(overlay cl)=(survival);
       class female (ref = "0") white (ref = "1") everexposed (ref = "0") anxi (ref = "0") dep (ref = "0") schiot (ref = "0") bipl
(ref = "0");
       model (time0, time1) * censor(1) = everexposed tsdd100_trunc female white age_indt anxi dep schiot bipl mcc /rl;
       baseline covariates=covs100 / rowid=tsdd100_trunc; *generate survival curves at values specified in covs and label curves
based on tsdd_trunc value;
run; title;

title "Categorical cumulative exposure with no exposure as reference (in 100 standardized dose units)";
proc phreg data = surv4;
       class female (ref = "0") white (ref = "1") tsdd100_cat0 (ref = "0") anxi (ref = "0") dep (ref = "0") schiot (ref = "0") bipl
(ref = "0");
       model (time0, time1) * censor(1) = tsdd100_cat0 female white age_indt anxi dep schiot bipl mcc /rl;
run; title;

title "Categorical cumulative exposure with >0 and <= 25 SDDs as reference (in 100 standardized dose units)";
proc phreg data = surv4;
       class female (ref = "0") white (ref = "1") tsdd100_cat1 (ref = "0") anxi (ref = "0") dep (ref = "0") schiot (ref = "0") bipl
(ref = "0");
       model (time0, time1) * censor(1) = tsdd100_cat1 female white age_indt anxi dep schiot bipl mcc /rl;
run; title; ods graphics off;
```

3.5 Discussion

In this section, we have undertaken to investigate the effect of PIM use on cognitive outcomes by utilizing different exposure definitions, outcome measurements, study designs, statistical, and modeling techniques. We defined PIM use broadly as use of any medication considered to be potentially inappropriate in older adults by large consensus bodies. In addition, we applied more stringent cut-offs to these broad criteria to eliminate confounding that may exist with incidental or non-consistent use of PIMs, and in an attempt to quantify the effect of cumulative PIM use. We also defined PIM use as more targeted lists of medications with more evidence supporting their connection to cognitive decline, measuring this exposure dichotomously, ordinally, and continuously. Finally, we calculated standardized doses for all medications considered to be potentially inappropriate in older adults due to negative cognitive effects and use this "Cog-Beers" PIM dose measure to investigate a cumulative effect on rate of dementia diagnosis.

Overall, the studies in this section support the hypothesis that there is an association between PIM use and cognitive decline, but that the way in which PIM use is defined can have vast impact on effect sizes and significance. While none of the estimated effect sizes were grand, many were clinically significant – especially when targeted PIM use definitions were employed.

In addition to the varied PIM use definitions, each study measured the cognitive outcome on a different scale. In the first study, we considered any diagnosis of dementia as well as receipt of memory-enhancing drugs as a proxy for clinically significant cognitive decline, which bypassed the potentially confounding due to missed diagnoses in administrative medical claims. The second study used a more "fine" measure of cognitive decline, the CDR-SOB, which can capture small, sometimes clinically insignificant changes in cognition. In addition to the short follow-up time of this study, the granular outcome may have led one to hypothesize that no effect would be found. Nevertheless, when PIM use was defined using targeted criteria, a clinically meaningful increase in cognitive decline was detected. Finally, using another source of administrative claims data

in a more generalizable population, we explored the relationship between doses of Cog-Beers PIM use and the rate of ADRD diagnosis. Though these claims data may suffer from the same low diagnosis rate as the first study, the strength came from its ability to use a validated algorithm that looked through all claims over 3 years to identify an outcome.

Though all studies in this section utilized observational retrospective study designs, their importance should not be negated. These studies are necessary to identify a valid measure of PIM use targeted to cognitive outcomes before more expensive and rigorous randomized controlled trials can be undertaken. Furthermore, while there are numerous published studies in the literature that attempt to link various PIM assessment tools to cognitive outcomes (see Section One), none of them make use of more modern statistical inference techniques known as causal inference. In this section, we have presented rigorously designed investigations in order to remove a large amount of confounding and bias that is present in the available literature. These investigations have highlighted the importance of a consistent PIM use measurement in the context of cognitive decline, and have shown that broad PIM criteria do not adequately capture a risk that a large body of evidence suggests is present. Nevertheless, it appears that these broad tools can be adapted to target cognitive outcomes, which bodes well for their use in clinical practice.

4 IMPLICATIONS AND RECOMMENDATIONS

4.1 Introduction

Today, adults over the age of 65 represent approximately 16% of the United States population.[26] This is nearly double what this cohort represented a mere 70 years ago, when chronic diseases overtook acute infections as the leading causes of death. As our society ages, medical problems unique to older adults become of higher priority and clinicians, patients, researchers, and policy makers must strive to stay abreast of the ever-evolving knowledge base. Specifically, as multimorbidity and polypharmacy have risen substantially among older adults, the negative health outcomes of potentially inappropriate medication use have reared significant economical and societal consequences.[193,194] Increasing evidence supports the hypothesis that certain medications can have detrimental but preventable adverse effects on mortality, functioning, hospitalization, and cognition. Because dementia is now the fifth leading cause of death among older adults and it continues to lack an effective treatment or cure, it is imperative that we do all that we can do prevent what should be beneficial medication therapy from needlessly negatively impacting cognition.

This area is of concern not only for the clinicians who struggle to optimize often complex medication regimens, but also for their patients who generally lack public access to information on medications that may be potentially inappropriate. However, even if clinicians and their patients do their utmost to maintain current knowledge on the medications that may be increasing cognitive decline, it will be nearly impossible for them to effectively synthesize and apply this knowledge if researchers continue to use unvalidated and inconsistent PIM assessment tools. Without a clear consensus on how to measure PIM use to target cognitive outcomes, systematic reviews will continue to conclude that "more evidence is needed," and the needle will continue to stay where it is. Of course, in order to perform this vital research task, investigators need support from their institutions and government leaders. As we have shown in the first section of this work,

implementation of national and local initiatives and funding to investigate ways to reduce PIM use can have sweeping positive effects.

All stakeholders in this important area have a role to play in furthering the study of how PIM use is impacting cognition in older adults. Before further research can be undertaken, we must pause to clearly define the exposure of interest, or our progress may never bear fruit.

4.2 Using potentially inappropriate medication tools in clinical practice

Optimal medical management of multimorbid complex older adult patients is no small task. Medical providers have continually remarked that their work is so multifaceted that key elements are often missed, such as effectively communicating important information about newly prescribed medications.[195] While it may be true that there is no single "right answer" when it comes to ensuring a medication regimen is appropriate,[22] providing clinicians with simple, validated tools that accurately address their most pressing concerns can alleviate some of the burden associated with taking a holistic approach to medication management.

Though the advent of broad medication appropriateness tools such as Beers and STOPP criteria at the turn of the 21st century was a step in the right direction, these tools are not designed to target specific health outcomes, nor to engage patients in their medical decisions. Both of these factors are essential if clinicians want to address potentially inappropriate medication use and intervene to reduce its negative impact on cognition. Indeed, studies have shown that when patients are active members of their healthcare team, are given options and explanations as to why interventions must be made, uptake is more successful.[196–198] One approach to aid in reducing PIM use in older adults by more actively engaging patients is to adopt a team-based approach to medication management. Pharmacists, whether present at the medical clinic, hospital, or community, can play an integral role in withdrawing or changing inappropriate medications as foremost medication expert in healthcare.[199–201] In addition to providing more patient-clinician facetime, Pharmacists can also reduce the workload of

prescribers by taking responsibility for utilizing medication appropriateness assessment tools.

Regardless of the structure of clinician-patient relationships and who participates as members of the team, this work supports the adoption of targeted PIM use measures when deprescribing in the context of cognitive decline and impairment. This work has shown that new tools need not be developed. Rather, existing sub-lists in already well-known and respected criteria can be used as a starting point to address PIM use. As the Beers Criteria are the most commonly used explicit criteria in the United States, the findings in this work support the adoption of the Cog-Beers PIM measure to target assessment of medications for cognitive outcomes. While the strongest link between these medications and cognitive decline exists among patients who already experience cognitive impairment, this work has shown that there is a significant effect of Cog-Beers PIM use on cognitive decline, even amongst those cognitively normal at baseline. After exploring various other measures of PIM use, this work was not able to find one tool that was meaningfully better-associated with cognitive outcomes than any other. Thus, in the case when a clinician is more comfortable using another PIM assessment tool, we recommend using targeted components of general tools or PIM assessment tools that contain only medication specific to the cognitive context.

4.3 Measuring potentially inappropriate medication use in research

In the thirty years since geriatrician Mark Beers first developed what is known today as the "Beers Criteria," the field of medication appropriateness has grown substantially. As a benchmark for how much research has been produced in the area, there have been at least 13 ***reviews*** published in the last ***eight*** years covering potentially inappropriate medication use in older adults.[16,20,38,105,172,202–209] This flourishing field has led to the development of over forty tools meant to assess various aspects of medication appropriateness. As we have shown in section one, however, only six of these have been used in studies investigating the link of PIM

use as defined with the criteria to cognitive outcomes. While there are certainly other important health outcomes that other PIM assessment tools may address, given the burden of cognitive disease in today's society, it is striking that so few tools have been validated.

This work has investigated only some of these tools – from the most broad to the most specific – to determine whether any was substantially better at predicting cognitive decline when used to measure PIM use in older adults. After review of various definitions of polypharmacy, various applications of the complete 2012 and 2015 Beers Criteria and version 2 of the STOPP criteria, and cumulative use of medications in sub-lists from both aforementioned tools that include only medications supposed to have cognitive effects, this work has not determined that any of the studied tools is meaningfully better at predicting cognitive decline. Nevertheless, we were able to clearly demonstrate that targeted lists of PIMs such as the Cog-Beers list are more highly associated with cognitive declines and that the relationship between diagnosed ADRD and use of these PIMs may be dose-dependent.

Based on these findings, we recommend that other investigators continue the work of validating medication appropriateness tools for their association with cognitive outcomes, with the ultimate goal of reaching a consensus tool that should be used in all future research endeavors that investigate the effect that using these PIMs has on cognitive decline. Should this goal be achieved, more randomized and controlled trials can be undertaken to answer the next most important question of whether reducing use of PIMs can actually prevent or slow the development of cognitive decline. Without first establishing a clear and universal definition for Cog-PIM use, it will be difficult to lead the field forward and make meaningful differences in patients' lives.

4.4 Championing appropriate medication use in society

For the last two decades, governments around the world have recognized that inappropriate medication use in older adults is a critical public health concern, and

have taken steps to implement initiatives and provide funding to alleviate this problem. These steps have made remarkable progress, leading to such feats as the cross-national SIMPATHY project in the European Union,[24] and the "Quality Use of Medicines" national strategic initiative in Australia.[23] However, governments and other large public and private institutions should also consider that medication appropriateness in older adults crosses into the domain of cognitive health quite clearly, and take the opportunity to provide greater access to funding and resources for this important intersection. For example, because Alzheimer's disease is one of the most expensive chronic conditions in the United States, the government has provided special access to increased funding for research into this important condition.[210] However, there are no nationally sponsored funding opportunity announcements for research into the effect of potentially inappropriate medication use of Alzheimer's dementia or any other cognitive disorder.[211] The closest call for research would be classified as a "non-pharmacological interventions," which covers is a wide pool of potential research areas.

This work supports the expansion of available federal and private resources to investigate the impact PIM use has on cognitive outcomes. The first step may be to make available funds for observational work that strives to link a PIM assessment tool to clinically relevant cognitive outcomes, and for further validation studies of that tool in a variety of data sources. Once researchers have taken advantage of this funding and produced evidence, more calls for clinical trials investigating the effect of PIM use reduction on cognitive preservation can be released. Evidence provided herein has demonstrated that the current state of the field of PIM use and cognitive decline is not yet ready to blossom into widespread uptake in the cognitive research community. However, with the proper funding and incentives, governments an large institutions can push forward the work in this important area. Whether it leads to expanded clinical trials into a heretofore under-researched area or leads to the conclusion that reducing PIM use may not be a clinically effective strategy to mitigate cognitive decline, we will never know until we are given the opportunity to investigate.

"If we knew what we were doing, it would not be called research, would it?"
- Albert Einstein

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VITA

ASHLEY I. MARTINEZ, PHARMD, PHD

EDUCATION AND TRAINING

Doctor of Philosophy, Pharmaceutical Sciences Lexington, Kentucky
University of Kentucky Expected May 2020
Dissertation – Meaningful Measurement Matters: Defining Potentially Inappropriate Medication Use to Target Cognitive Outcomes
Advisor – Daniela C. Moga, MD, PhD

Master of Science, Pharmaceutical Sciences Lexington, Kentucky
University of Kentucky 2017
Thesis – Gastrointestinal Bleeding Events and Statin Use: A Large Propensity Score-Matched Retrospective Cohort Study
Advisor – Patricia R. Freeman, RPh, PhD

Doctor of Pharmacy Lexington, Kentucky
University of Kentucky 2017

Bachelor of Arts, Public Policy and Biology Chicago, Illinois
University of Chicago 2013

PROFESSIONAL EXPERIENCE

Graduate Research Assistant Lexington, Kentucky
University of Kentucky College of Pharmacy 2017 – Present

- Assist with patient enrollment into and analysis of clinical trial (R01 AG054130)
- Co-author academic research articles and book chapters
- Perform primary and secondary data analysis for observational study designs
- Mentor Doctor of Pharmacy and Medical Doctor professional students in research projects

Pharmacy Intern Lexington, Kentucky
Walgreens Pharmacy August 2013 – August 2017
Interpreted and fill prescriptions according to state and federal regulations; Counseled patients and prescribers regarding over-the-counter and prescription products; Administered immunizations under provided protocol

Certified Pharmacy Technician Warrenville, Illinois
Walgreens Pharmacy August 2007 – July 2013
Interpreted and filled prescriptions according to state and federal regulations; Communicated with health care professionals and insurance companies

Research Assistant Chicago, Illinois
University of Chicago Bernard-Mitchell Hospital 2009 – 2011

- Explained and administered clinical survey to patients in hospital
- Compiled and input findings into clinical database
-

PUBLICATIONS

Martinez AI, Abner EL, Jicha GA, Rigsby DN, Eckmann LC, Huffmyer MJ, Moga DC. (2020, April) "One-year evaluation of a targeted medication therapy management intervention for older adults." *Journal of Managed Care Pharmacy*. 26(4): 520-28.

Martinez AI, Spencer J, Moloney ME, Badour CL, Reeve E, Moga DC. (2020, March) "Attitudes Toward Deprescribing in a Middle-Aged Health Disparities Population." *Research in Social and Administrative Pharmacy*. [Epub ahead of print.]

Moga DC, Beech B, Abner E, Schmitt F, El Khouli R, **Martinez AI**, Eckmann L, Huffmyer M, George R, Jicha GA. (2019, December) INtervention for Cognitive Reserve Enhancement in delaying the onset of Alzheimer's Symptomatic Expression (INCREASE): Rationale and Study Design. *Trials*. 20(1):806.

Moloney ME, **Martinez AI**, Badour CL, Moga DC. (2019, August) "Internet-Based Cognitive Behavioral Therapy for Insomnia in Appalachian Women: A Pilot Study." *Behavioral Sleep Medicine*. 1-10. [Epub ahead of print]

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Martinez AI, Freeman PR, Moga DC. (2019, February) "Statin Use and Gastrointestinal Hemorrhage: A Large Retrospective Cohort Study." *American Journal of Cardiovascular Drugs*. 19(1):65-74.

Michnick AI. (2014) Pharmacy Policy Issues: Effectively using pharmacists in interprofessional teams to reduce hospital medication errors. *The Kentucky Pharmacist.* 9:38-9.

HONORS AND AWARDS

2020 Walmart Scholar March 2020
American Association of Colleges of Pharmacy

First Place, Elevator Speech Competition October 2019
10th Annual Therapeutics, Outcomes, Discovery, and Delivery Symposium

Best Spotlight Poster Presentation August 2019
International Conference for Pharmacoepidemiology and Therapeutic Risk Management

Pharmaceutical Sciences Excellence in Graduate Achievement Fellowship 2019-2020
University of Kentucky College of Pharmacy

Women and Philanthropy Travel Scholarship May 2019
Sanders-Brown Center on Aging, University of Kentucky Women and Philanthropy Network

Outstanding Poster Award October 2018
Markesbery Symposium on Aging and Dementia

Second Place Winner, Elevator Speech Competition September 2018
9th Annual Therapeutics, Outcomes, Discovery, and Delivery Symposium

Scholarship, Annual Meeting August 2018
International Conference for Pharmacoepidemiology and Therapeutic Risk Management

Registration and Travel Scholarship, Midyear Meeting April 2018
International Society for Pharmacoepidemiology

Dean's List May 2016
University of Kentucky College of Pharmacy

1st Place Poster Presentation, Pharmacy Student Division March 2016
Rho Chi Alpha Xi Chapter at the University of Kentucky College of Pharmacy

National Patient Counseling Competition Local Chapter Winner February 2016
American Pharmacists Association—Academy of Student Pharmacists

Wrightson Memorial Scholarship 2014 – 2017
University of Kentucky College of Pharmacy

Student Enhancement Scholarship 2013 – 2017
University of Kentucky College of Pharmacy