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Utilization and Spending on Potentially Inappropriate Medications by US Older Adults with Multiple Chronic Conditions using Multiple Medications

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ABSTRACT

Background: The utilization of potentially inappropriate medications (PIMs) in older adults can lead to adverse events and increased healthcare costs. Polypharmacy, the concurrent utilization of multiple medications, is common in older adults with multiple chronic conditions.
Objective: To investigate the utilization and costs of PIMs in multimorbid older adults with polypharmacy over time.
Methods: This retrospective cross-sectional study used linked Medicare claims and electronic health records from seven hospitals/medical centers in Massachusetts (2007-2014). Participants were ≥65 years old, had ≥2 chronic conditions (to define multimorbidity), and used drugs from ≥5 pharmaceutical classes for ≥90 days (to define polypharmacy). Chronic conditions were defined using the Chronic Conditions Indicator from the Agency for Health Research and Quality. PIMs were defined using the American Geriatrics Society 2019 version of the Beers criteria. We calculated the percentage of patients with ≥1 PIMs and the percentages of patients using different types of PIMs. We used logistic regression analyses to test the odds of taking ≥1 PIMs. We calculated mean costs spent on PIMs by dividing the costs spent on PIMs by the total medication cost.
Results: ≥69% of patients used ≥1 PIM. After adjusting for healthcare utilization, chronic conditions, medication intake, and demographic factors, female sex (2014: Odds ratio (OR)=1.27, 95%CI 1.25-1.30), age (2014: OR=0.92, 95%CI 0.90-0.93), and Hispanic ethnicity (2014: OR=1.41, 95%CI 1.27-1.56) were associated with PIM use. Gastrointestinal drugs and central nervous system drugs were the most commonly-used PIMs. In patients using ≥1 PIM, >10% of medication costs were spent on PIMs.
Conclusion: The utilization of PIMs in US older adults with multimorbidity and polypharmacy is high.

1. Introduction

Multimorbidity, often defined as coexistence of two or more chronic conditions (Johnston et al., 2019), is highly prevalent in older adults with 55-98% of adults aged ≥65 years being multimorbid as shown by a systematic review (Marengoni et al., 2011). In the United States, the prevalence of multimorbidity has increased in the past few decades; in one recent study, ≥90% of adults aged ≥65 years were multimorbid (King et al., 2018). Due to expected increases in the aging population, multimorbidity is likely to become even more prevalent in the future. With multimorbidity often comes polypharmacy, which is commonly understood as the concurrent utilization of ≥5 medications (Masnoon et al., 2017). In the United States, as of 2011/2012, 39% of adults aged ≥65 years used ≥5 medications (Kantor et al., 2015).

The more medications older adults regularly use, the more likely they are to also use potentially inappropriate medications (PIMs)

Abbreviations: AGS, American Geriatrics Society; AHRQ, Agency for Healthcare Research and Quality; CCI, Chronic Condition Indicator; CMS, Centers for Medicare and Medicaid Services; OR, Odds ratio; PIMs, Potentially inappropriate medications; RPDR, Partners Research Patient Data Registry; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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(Bazargan et al., 2018, Simões et al., 2019, Roux et al., 2020). Potentially inappropriate medications are defined as drugs for which the risk of an adverse event outweighs its clinical benefit (Fu et al., 2004). There are numerous judgment-based (implicit) and criterion-based (explicit) lists to define potentially inappropriate medications (e.g., Beers list, FORTA, STOPP criteria) (Motter et al., 2018, Curtin et al., 2019). The Beers list, published and regularly updated by the American Geriatrics Society (AGS) (American Geriatrics Society, 2015, American Geriatrics Society, 2019, American Geriatrics Society, 2012), are commonly-used in the US.

The utilization of potentially inappropriate medications in older adults can be problematic because it may lead to health problems, such as adverse drug reactions, falls, cognitive decline, and functional impairment (Xing et al., 2019, Masumoto et al., 2018, Koyama et al., 2014, Liew et al., 2019, Fabbietti et al., 2018). This in turn results in greater health service use, in particular hospitalizations and emergency department visits, thus contributing to higher health care costs (Hyttinen et al., 2016, Heider et al., 2018, Lau et al., 2005, Weeda et al., 2020). For now however, the evidence on the association between the use of potentially inappropriate medications and mortality is mixed (Paque et al., 2019, do Nascimento et al., 2017, Huang et al., 2019).

Previous research efforts have largely focused on the utilization of potentially inappropriate medications in older adults more broadly, in patients with specific diseases or in specific settings (e.g. aged ≥65 years, community dwelling vs. older adults in nursing homes, hospitalized older adults, patients with Alzheimer's disease) (Xing et al., 2019, Hyttinen et al., 2016, Cho et al., 2019, Fralick et al., 2020, Tao et al., 2020). Conversely, little is known about the use of potentially inappropriate medications in multimorbid older adults with polypharmacy issues, even though this population may be at even greater risk of adverse health outcomes. Therefore, the goal of this study was to investigate the utilization of and spending on potentially inappropriate medications in older multimorbid men and women with polypharmacy in the US from 2007 to 2014. Exploring these factors could inform interventions and policy discussions on how to optimize pharmacotherapy in this population group.

2. Methods

2.1. Data Source

To perform this retrospective cross-sectional study, we used a linked dataset of patients who were enrolled in the Partners Research Patient Data Registry (RPDR) (Partners Healthcare, 2020) and were beneficiaries of Centers for Medicare and Medicaid Services (CMS), which means that administrative claims for these patients were available in the CMS database. The linked dataset contains data from 569,969 participants from January 1, 2007 through December 31, 2014. The RPDR contains electronic health records from two tertiary medical centers, three community hospitals, a rehabilitation center, and a psychiatric hospital in the Boston metropolitan area. Records include demographics, inpatient and outpatient encounters, labs and results, prescribing and dispensing records, and other medical care. The Medicare claims are from Parts A (inpatient coverage), B (outpatient coverage), and D (drug coverage). These data include information about drugs dispensed, medical diagnoses, and start/end dates of insurance coverage (Desai et al., 2018). The use of pharmacy claims is considered the gold standard for measuring medication utilization (West et al., 1994, West et al., 1995). Therefore, the use of linked data allowed for the complete capture of clinical criteria to define potentially inappropriate medications (e.g., creatinine) and medication utilization by patients.

2.2. Patient Population

2.2.1. Multimorbidity

Chronic conditions were defined using the Chronic Condition Indicator (CCI) of the Agency for Healthcare Research and Quality (AHRQ), which categorizes ICD-9 diagnosis codes as chronic and not chronic (HCUP Chronic Condition Indicator (CCI) 2009). First, we extracted the ICD-9 codes classified as chronic. Then we assigned related codes (e.g. 249.0 secondary diabetes mellitus, 249.1 secondary diabetes mellitus with ketoacidosis, 250.0 diabetes mellitus) to ICD-9 code categories to ensure that people with two closely-related diagnoses were not misclassified as having multiple chronic conditions. We excluded chronic conditions from the CCI related to pregnancy and childbirth due to their non-relevance in our study population. We ended up with 77 categories of chronic conditions (eTable1 in the supplementary materials). This approach allowed us to capture patients with different and more types of chronic conditions, compared to commonly-used lists of comorbidities, such as the Elixhauser comorbidity tool with 30 categories (Elixhauser et al., 1998). We required ≥2 diagnosis codes on separate days for the category to count as a chronic condition to increase the specificity of the underlying condition (Franklin et al., 2019). We considered patients as multimorbid when they had diagnoses from two or more categories, since this cut-off is widely used in the literature (Johnston et al., 2019, Smith et al., 2016, Barnett et al., 2012).

2.4. Polypharmacy

To define polypharmacy, we used information provided by the U.S. Food and Drug Administration on the classification of medications available on the US market into different pharmaceutical classes (e.g., HMG-CoA reductase inhibitors/statins) (U.S. Food and Drug Administration, 2019). Because molecularly-related medications are typically considered interchangeable (e.g., within statins), we measured utilization at the class level (eAppendix1 in the supplementary materials). We defined all pharmaceutical classes with ≥90 days' supply as chronic use (Lauffenburger et al., 2018). To define polypharmacy, days' supply from claims was defined conservatively. First, for fills on the same day, we assumed concurrent utilization and if the recorded durations differed, we selected the medication with the longest supply. Second, for non-concurrent fills, we used a limited shift of supply (30 days) for overlapping utilization. We considered patients as receiving polypharmacy when they had ≥5 pharmaceutical classes with ≥90 days' supply each. This ≥5 medication threshold is commonly used in the literature (Masnoon et al., 2017).

2.5. Inclusion and Exclusion Criteria

Patients were excluded if they did not have any claim (medication, procedure or encounter) from 2007 to 2014 (13,726, 2.4% of total). Second, we restricted the study population to individuals who are ≥65 years of age. Third, we excluded patients if there was missing information on their sex (0.5-3.7% depending on the year). Fourth, we excluded patients if they were enrolled in Medicare for <180 days in the year of the respective analysis. Next, we excluded patients without ≥5 medication classes with ≥90 days' supply each (i.e., long-term use). And finally, we excluded patients who did not have chronic conditions from ≥2 categories as defined above. A cohort flow diagram for each year from 2007 to 2014 can be found in the supplementary materials (eFigure 1).

3. Potentially Inappropriate Medication Use

We identified potentially inappropriate medications using the American Geriatrics Society (AGS) 2019 updated version of the Beers criteria for potentially inappropriate medications use in older adults (American Geriatrics Society, 2019). The Beers criteria contain evidence-based recommendations that are formulated through a consensus panel of experts using the Delphi method (American Geriatrics Society, 2019). We chose to use the 2019 Beers list, rather than previous versions, to inform current clinical decision-making. All

medications dispensed that met any of the drug, dosage, and duration requirements specified in table 2 of the 2019 Beers criteria were identified as potentially inappropriate. Some of the drugs listed in the 2019 Beers criteria are considered as potentially inappropriate only when they are used for more than a certain number of days, together with or without a certain diagnosis, or when certain laboratory values are below a certain level (e.g. creatinine clearance <30mL/min and use of nitrofurantoin). For example, non-cyclooxygenase-selective nonsteroidal anti-inflammatory drugs (NSAIDs) are considered potentially inappropriate when used chronically, which we defined as ≥90 days when no other information was provided (Lauffenburger et al., 2018). We chose to focus on dispensed medications and utilization to confirm that patients actually filled the medications as opposed to just being prescribed them.

3.1. Statistical Analyses

The cohorts were created using the Aetion Evidence Platform (Version: r3.5.20180426_1659), which has previously been validated for a range of studies. (Aetion Evidence Platform®, 2020, Wang et al., 2016) Descriptive analyses were performed with STATA 15.1 (StataCorp, College Station, TX, USA).

We described the demographics and main clinical characteristics of the study participants. We presented a selection of chronic conditions using the Coding Algorithms for Elixhauser Comorbidities by Quan et al. (Quan et al., 2005). We calculated the percentage of patients with ≥1 potentially inappropriate medication in different age groups and in subgroups with different levels of chronic conditions and long-term medication use. We used logistic regression analyses, including multivariable analyses adjusting for measurable covariates (age-continuous, sex-binary, Hispanic ethnicity-categorical, race-categorical, number of chronic conditions-continuous, number of medications dispensed-continuous, number of hospital admissions-continuous, number of emergency department visits-continuous, number of ambulatory visits-continuous, types of comorbidities-categorical), to test the odds of taking ≥1 PIM. We calculated the percentages of men and women using different types of potentially inappropriate medications from 2007 to 2014. We counted the number of unique potentially inappropriate medications in different age groups as well as in subgroups of patients with different levels of chronic conditions and medication utilization. Finally, to capture additional consequences of potentially inappropriate medication utilization, we calculated mean costs spent on PIMs by dividing the costs spent on PIMs by the total medication costs (based on allowed amounts covered by Medicare). We also performed analyses with different thresholds of chronic conditions (<2) and long-term medications (<5, ≥10).

3.2. Ethical approval

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

3.3. Additional information

This research follows the requirements of the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) reporting guideline (von Elm et al., 2008).

4. Results

Of all 569,969 patients in the RPDR-CMS database, between 61,500 and 103,153 met criteria and were defined as multimorbid with polypharmacy for the yearly cross-sectional analyses from 2007 to 2014 (eFigure 1). Their demographics and main clinical characteristics are described in Table 1. The average age (range: 77.3-77.8 years), BMI (range: 28.7-29.1), number of long-term medications (mean: 7.2), and distributions by race/ethnicity stayed fairly similar over time. More differences between years were noted for female sex (decrease from 65.2% in 2007 to 59.3% in 2014), mean number of chronic conditions (increase from 7.2 to 8.4) and certain chronic conditions.

As shown in Table 2, ≥69% of multimorbid older men and women with polypharmacy across all ages used ≥1 potentially inappropriate medication from 2007 to 2014. In addition to differences by sex, there also appeared to be age differences. When we excluded PIM recommendations that had a low quality of evidence (as defined by the AGS Beers criteria themselves), the percentage of patients with ≥1 PIM dropped slightly but remained above 63% in both men and women. The same age and sex differences were observed (eTable2 in the supplementary materials).

Table 3 presents the associations of different sociodemographic and other variables (e.g. health services use, medication count, and chronic conditions count) with the utilization of potentially inappropriate medications in the 2007 and 2014 cohort (first and last year of available data). In both 2007 and 2014, female sex (2007: Odds ratio (OR)=1.14, 95%CI 1.11-1.16; 2014: OR=1.27, 95%CI 1.25-1.30), age (2007: OR=0.94, 95%CI 0.92-0.95; 2014: OR=0.92, 95%CI 0.90-0.93), and Hispanic ethnicity (2007: OR=1.19, 95% CI 1.04-1.36; 2014: OR=1.41, 95% CI 1.27-1.56) were associated with the utilization of potentially inappropriate medications. While significant in 2007, most categories of the race variable were no longer statistically significant in 2014.

Central nervous system (e.g. benzodiazepines, antidepressants, antipsychotics, etc.) and gastrointestinal potentially inappropriate medications (e.g., proton-pump inhibitors) were the most common potentially inappropriate medications in both sexes (Figure 1 and eFigure 2). As shown by eFigure 2 in the supplementary materials, we observed sex differences in commonly used types of potentially inappropriate medications. Cardiovascular potentially inappropriate medications were more common in men than in women, while their utilization along with endocrine potentially inappropriate medications decreased in both sexes over time. Potentially inappropriate anticholinergic medications and pain medications were used in around 10% of patients, with slightly lower use in men than in women.

The number of potentially inappropriate medications per patient remained stable over time (median: 1, IQR: 1-2, eTable3). The average number of PIMs and the percentage of patients with ≥1 potentially inappropriate medication increased as the number of pharmaceutical classes increased, in patients with and without multimorbidity (eTable4 and eTable5).

As shown in Table 4, in older multimorbid patients with polypharmacy using ≥1 PIM, between 11.0% and 12.8% of medication costs were spent on potentially inappropriate medications in women and between 11.0% and 12.2% in men throughout the study period. The average amount spent on PIMs ranged from $392 USD to $719 for women and $395 to $759 for men from 2007 to 2014.

5. Discussion

In this study of US older adults with multiple chronic conditions and polypharmacy medication use, ≥69% in this population use ≥1 PIM, with differences that did not change over time. Meaningful gaps by sex were also observed, as women had a higher likelihood of using potentially inappropriate medications than men. Central nervous system and gastrointestinal medications were the most common PIMs in both men and women. The impact of PIM use is substantial, as >10% of all medication expenses by Medicare were spent on potentially inappropriate medications in patients using ≥1 PIM.

To our knowledge, this is the first study to specifically focus on the utilization of potentially inappropriate medications in older multimorbid adults with polypharmacy. Most previous research has investigated the utilization of potentially inappropriate medications in broader groups of older adults, even though they may be at lower risk of complications from PIM use. A recent meta-analysis of 66 studies from 27

Table 1
Demographics and main clinical characteristics of adults aged ≥65 years with multimorbidity* and polypharmacy**, by year

	2007 n = 61,500	2008 n = 67,816	2009 n = 72,394	2010 n = 75,567	2011 n = 82,030	2012 n = 88,114	2013 n = 102,547	2014 n = 103,153
Mean age (SD), years	77.3 (7.4)	77.5 (7.5)	77.6 (7.6)	77.7 (7.7)	77.7 (7.7)	77.8 (7.7)	77.8 (7.8)	77.8 (7.7)
Female sex (%)	40,088 (65.2)	43,390 (64.0)	45,909 (63.4)	47,405 (62.7)	50,344 (61.4)	53,311 (60.5)	61,408 (59.9)	61,143 (59.3)
Hispanic ethnicity (%)	1,161 (1.9)	1,288 (1.9)	1,431 (2.0)	1,519 (2.0)	1,616 (2.0)	1,684 (1.9)	1,688 (1.7)	1,656 (1.6)
Race*								
White (%)	55,207 (89.8)	60,897 (89.8)	64,851 (89.6)	67,596 (89.5)	73,395 (89.5)	78,845 (89.5)	92,525 (90.2)	92,891 (90.1)
African-American (%)	2,921 (4.8)	3,223 (4.8)	3,413 (4.7)	3,540 (4.7)	3,848 (4.7)	4,086 (4.6)	4,430 (4.3)	4,408 (4.3)
Asian (%)	966 (1.6)	1,047 (1.5)	1,094 (1.5)	1,128 (1.5)	1,169 (1.4)	1,188 (1.4)	1,149 (1.1)	1,123 (1.1)
Native American / Native Hawaiian (%)	°°	°°	53 (0.1)	45 (0.1)	48 (0.1)	45 (0.1)	47 (0.1)	49 (0.1)
Other (%)	2,278 (3.7)	2,515 (3.7)	2,847 (3.9)	3,065 (4.1)	3,285 (4.0)	3,526 (4.0)	3,724 (3.6)	3,765 (3.7)
Missing information (%)	°°	°°	130 (0.2)	194 (0.3)	270 (0.33)	400 (0.5)	643 (0.6)	886 (0.9)
Mean BMI (SD)	28.9 (6.1)	28.7 (6.1)	28.9 (6.2)	29.1 (6.3)	29.1 (6.2)	28.9 (6.2)	28.8 (6.1)	28.9 (6.1)
Number of chronic conditions								
Median (IQR)	7 (4)	7 (4)	7 (4)	7 (5)	7 (4)	8 (4)	8 (4)	8 (4)
Mean (SD)	7.2 (3.0)	7.4 (3.2)	7.5 (3.2)	7.7 (3.3)	8.0 (3.5)	8.1 (3.5)	8.2 (3.6)	8.4 (3.6)
Number of drugs dispensed*								
Median (IQR)	11 (6)	11 (6)	11 (6)	11 (6)	11 (6)	11 (6)	12 (6)	12 (6)
Mean (SD)	11.8 (4.7)	12.0 (4.8)	12.1 (4.8)	12.1 (4.8)	12.3 (4.9)	12.2 (4.9)	12.5 (5.0)	12.5 (5.0)
Number of drugs per patient with ≥90-day supply								
Median (IQR)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)	7 (3)
Mean (SD)	7.2 (2.2)	7.1 (2.2)	7.2 (2.2)	7.2 (2.2)	7.2 (2.2)	7.2 (2.2)	7.3 (2.3)	7.2 (2.3)
Healthcare utilization								
≥1 hospital admission (%)	20,515 (33.4)	24,863 (36.7)	27,137 (37.5)	28,451 (38.7)	30,537 (37.2)	31,541 (35.8)	35,227 (34.4)	34,999 (34)
≥1 ER visit (%)	29,316 (47.7)	32,898 (48.5)	34,713 (48.0)	36,804 (48.7)	40,269 (49.1)	43,591 (49.5)	50,251 (49.0)	50,255 (48.7)
≥1 ambulatory visit (%)	61,159 (99.4)	66,487 (98.0)	70,413 (97.3)	73,317 (97.0)	79,694 (97.2)	85,820 (97.4)	99,920 (97.4)	100,543 (97.5)
Comorbidities***								
Congestive heart failure (%)	12,673 (20.6)	14,613 (21.6)	15,534 (21.5)	16,366 (21.7)	18,402 (22.4)	19,920 (22.6)	23,145 (22.6)	23,793 (23.1)
Cardiac arrhythmias (%)	6,460 (10.5)	7,355 (10.9)	7,483 (10.3)	8,001 (10.6)	8,932 (10.9)	9,550 (10.8)	10,526 (10.3)	10,936 (10.6)
Valvular disease (%)	10,172 (16.5)	11,073 (16.3)	11,689 (16.2)	12,257 (16.2)	14,221 (17.3)	15,439 (17.5)	18,456 (18.0)	19,204 (18.6)
Pulmonary circulation disorders (%)	2,000 (3.3)	2,570 (3.8)	2,900 (4.0)	3,273 (4.3)	4,074 (5.0)	4,559 (5.2)	5,381 (5.3)	5,799 (5.6)
Peripheral vascular disorders (%)	12,601 (20.5)	14,462 (21.3)	15,291 (21.1)	15,828 (21.0)	17,639 (21.5)	19,019 (21.6)	21,684 (21.2)	21,907 (21.2)
Hypertension (%)	49,089 (70.1)	53,845 (79.4)	57,979 (80.1)	60,931 (80.6)	67,096 (81.8)	72,000 (81.7)	84,011 (81.9)	83,992 (81.4)
Other neurological disorders (%)	4,593 (7.5)	5,307 (7.8)	5,833 (8.1)	6,512 (8.6)	7,434 (9.1)	8,380 (9.5)	9,886 (9.6)	10,266 (10.0)
Chronic pulmonary disorders (%)	14,655 (23.8)	16,844 (24.8)	17,966 (24.8)	19,010 (25.2)	21,199 (25.8)	22,956 (26.1)	26,746 (26.1)	27,064 (26.2)
Diabetes (%)	23,205 (37.7)	25,382 (37.4)	27,189 (37.2)	28,650 (37.9)	31,697 (38.6)	33,961 (38.5)	38,305 (38.4)	38,593 (37.4)
Hypothyroidism (%)	12,197 (19.8)	13,783 (20.3)	14,869 (20.5)	16,068 (21.3)	18,404 (22.4)	20,290 (23.0)	24,250 (23.7)	24,892 (24.1)
Renal failure (%)	7,090 (11.5)	8,881 (13.1)	10,257 (14.2)	11,385 (15.1)	14,052 (17.1)	16,254 (18.5)	19,873 (19.4)	21,234 (20.6)
Liver disease (%)	2,218 (3.6)	2,510 (3.7)	2,668 (3.7)	2,879 (3.8)	3,118 (3.8)	3,448 (3.9)	4,201 (4.1)	4,480 (4.4)
Peptic ulcer disease (excluding bleeding) (%)	521 (0.9)	653 (1.0)	658 (0.9)	726 (1.0)	878 (1.1)	970 (1.1)	1,222 (1.1)	1,071 (1.0)
Lymphoma (%)	1,151 (1.9)	1,427 (2.1)	1,589 (2.2)	1,688 (2.2)	1,929 (2.4)	2,297 (2.6)	2,839 (2.8)	3,012 (2.9)
Metastatic cancer (%)	1,425 (2.3)	1,925 (2.8)	2,042 (2.8)	2,305 (3.1)	2,573 (3.1)	2,941 (3.3)	3,573 (3.5)	3,566 (3.5)
Solid tumor without metastasis (%)	9,792 (15.9)	11,213 (16.5)	11,997 (16.6)	12,745 (16.9)	14,195 (17.3)	15,601 (17.7)	18,391 (17.9)	18,862 (18.3)
Rheumatoid arthritis/collagen vascular diseases (%)	4,344 (7.1)	4,849 (7.2)	5,212 (7.2)	5,600 (7.4)	6,341 (7.7)	7,152 (8.1)	8,528 (8.3)	8,848 (8.6)
Coagulopathy (%)	3,059 (5.0)	3,288 (4.9)	3,556 (4.9)	3,822 (5.1)	4,249 (5.2)	4,527 (5.1)	5,331 (5.2)	5,226 (5.1)
Weight loss (%)	2,608 (4.2)	3,264 (4.8)	3,512 (4.9)	3,962 (5.2)	4,555 (5.6)	5,007 (5.7)	6,166 (6.0)	6,201 (6.0)
Fluid and electrolyte disorders (%)	5,045 (8.2)	5,949 (8.9)	6,477 (9.0)	6,888 (9.1)	7,644 (9.3)	8,270 (9.4)	9,422 (9.2)	9,467 (9.2)
Psychoses (%)	2,727 (4.4)	3,301 (4.9)	3,657 (5.1)	3,984 (5.3)	4,293 (5.2)	4,624 (5.3)	5,510 (5.4)	5,571 (5.4)
Depression (%)	19,719 (17.4)	12,542 (18.5)	13,642 (18.8)	15,060 (19.9)	17,345 (21.1)	19,494 (22.1)	23,493 (22.9)	24,275 (23.5)

* multimorbidity defined as chronic conditions from ≥2 chronic condition categories;
** polypharmacy defined as medications with ≥90 days' supply each from ≥5 pharmaceutical classes
*** comorbidities defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥2 ICD-9 codes per category, hypertension categories merged, diabetes categories merged, drug abuse, alcohol abuse, obesity, HIV/AIDS, paralysis, blood loss anemia and deficiency anemia not reported;°° cells with sizes 0-10 suppressed.

Table 2
Percentage of adults aged ≥65 years with multimorbidity* and polypharmacy** who filled ≥1 potentially inappropriate medication*** by year, sex, and age group

	2007	2008	2009	2010	2011	2012	2013	2014
Both sexes (%)								
	n = 61,500	n = 67,816	n = 72,394	n = 75,567	n = 82,030	n = 88,114	n = 102,547	n =103,153
65 – 74	18,353 (75.4)	20,152 (75.9)	21,548 (75.8)	22,378 (74.7)	23,764 (73.5)	25,106 (72.3)	31,761 (78.4)	31,558 (77.6)
75 – 84	18,991 (73.4)	20,395 (73.2)	21,235 (72.5)	21,282 (71.3)	22,622 (70.2)	23,800 (69.0)	29,458 (74.5)	28,996 (73.1)
≥ 85	7,927 (70.3)	9,434 (70.6)	10,286 (70.1)	10,737 (68.1)	11,494 (65.8)	12,443 (65.8)	15,867 (70.5)	15,814 (69.4)
All ages	45,271 (73.6)	49,981 (73.7)	53,069 (73.3)	54,398 (72.0)	57,880 (70.6)	61,349 (69.6)	77,086 (75.2)	76,368 (74.0)
Women (%)								
	n = 40,088	n = 43,390	n = 45,909	n = 47,405	n = 50,344	n = 53,311	n = 61,408	n = 61,143
65 – 74	11,368 (77.3)	12,121 (77.1)	12,905 (77.1)	13,360 (76.5)	13,878 (75.3)	14,747 (74.4)	18,800 (81.6)	18,675 (81.0)
75 – 84	12,599 (74.0)	13,205 (73.6)	13,527 (73.1)	13,405 (72.1)	13,959 (71.1)	14,317 (69.9)	17,677 (76.5)	17,314 (75.6)
≥ 85	5,840 (69.9)	6,808 (70.1)	7,443 (69.8)	7,672 (67.7)	8,044 (65.4)	8,533 (65.6)	10,894 (71.4)	10,690 (70.5)
All ages	29,807 (74.4)	32,134 (74.1)	33,875 (73.8)	34,437 (72.6)	35,881 (71.3)	37,597 (70.5)	47,371 (77.1)	46,679 (76.3)
Men (%)								
	n = 21,411	n = 24,425	n = 26,482	n = 28,155	n = 31,678	n = 34,793	n = 41,128	n = 42,000
65 – 74	6,985 (72.5)	8,030 (74.1)	8,640 (73.8)	9,015 (72.2)	9,880 (71.0)	10,253 (69.5)	12,953 (74.3)	12,878 (73.1)
75 – 84	6,392 (72.3)	7,190 (72.5)	7,708 (71.6)	7,877 (70.1)	8,662 (68.7)	9,482 (67.8)	11,780 (71.6)	11,680 (69.7)
≥ 85	2,087 (71.2)	2,626 (71.7)	2,843 (70.9)	3,065 (69.3)	3,450 (66.8)	3,919 (66.2)	4,973 (68.7)	5,124 (67.1)
All ages	15,464 (72.2)	17,846 (73.1)	19,191 (72.5)	19,957 (70.9)	21,992 (69.4)	23,745 (68.3)	29,706 (72.2)	29,682 (70.7)

* multimorbidity defined as chronic conditions from ≥2 chronic condition categories
** polypharmacy defined as medications with ≥90 days' supply each from ≥5 pharmaceutical classes;
*** Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767.

Table 3
Multivariable logistic regression analyses of the association between the use of potentially inappropriate medications and patient characteristics in 2007 and 2014.

	2007 (n=344,331) Multivariable model[1]		**2014 (n=397,146)** Multivariable model[1]	
	Odds ratio	95% CI	Odds ratio	95% CI
Age (10-year increase)	0.94	0.92-0.95***	0.92	0.90-0.93***
Female sex	1.14	1.11-1.16***	1.27	1.25-1.30***
Hispanic ethnicity	1.19	1.04-1.36**	1.41	1.27-1.56***
Race (ref. White)				
African-American	1.23	1.16-1.31***	0.87	0.83-0.91***
Asian	1.53	1.39-1.68***	1.00	0.93-1.08
Other[2]	1.39	1.27-1.51***	1.01	0.95-1.07
Medication count (1-unit increase)	1.58	1.57-1.58***	1.47	1.46-1.47***
Ambulatory visits (1-unit increase)	0.99	0.99-0.99***	1.00	0.99-1.00***
Emergency room visits (1-unit increase)	1.00	0.99-1.00	1.00	0.99-1.00
Inpatient stays (1-unit increase)	0.91	0.89-0.93***	0.87	0.87-0.90***
Number of chronic conditions (1-unit increase)	1.03	1.03-1.04***	1.04	1.03-1.04***

[1] The models are adjusted for the types of comorbidities. Comorbidities were defined with coding algorithms for defining Elixhauser comorbidities in ICD-9 administrative data (Quan et al. 2005), ≥2 ICD-9 codes per category
[2] Native American, native Hawaiian and 'other' combined.
** $p<0.05$
*** $p<0.001$

countries found that 33% of adults aged ≥65 years used ≥1 PIM, regardless of criteria for defining potentially inappropriate medications (e.g., Beers, FORTA or STOPP/START criteria) (Liew et al., 2020). Similarly, several studies conducted in community-dwelling adults aged ≥65 years found that around 35-40% of them were using ≥1 PIM (defined by Beers criteria) (Morgan et al., 2016, Fick et al., 2008, Huang et al., 2020). Closer to our study population, two studies found that potentially inappropriate medications were used in about 50% of community-dwelling older adults with hypertension or diabetes (Bazargan et al., 2018, Gagnon et al., 2020). Contrasted with these prior studies, our findings suggest that PIM uses is even higher (e.g., ≥69%) in older adults with multiple chronic conditions and multiple long-term medications.

Our findings concerning the most commonly-used potentially inappropriate medications are in line with prior research in this area, which had also identified proton-pump inhibitors, benzodiazepines and other central nervous system drugs, endocrine medications, such as sulfonylureas, and nonsteroidal anti-inflammatory drugs as commonly used potentially inappropriate medications (Bazargan et al., 2018, Simões et al., 2019, Roux et al., 2020, Fralick et al., 2020, Gagnon et al., 2020). Of note, the spike in potentially inappropriate central nervous system drugs in 2013 and 2014 can be explained by the fact that benzodiazepines and barbiturates were covered by Medicare Part D (drug coverage) as of January 1, 2013 (Centers for Medicare & Medicaid Services, 2012). Future efforts should focus on how the prescribing of the most commonly-used potentially inappropriate medications could be optimized and how these drugs, if applicable, could be sustainably deprescribed.

We found that female sex is associated with an increased PIM use, which is in line with findings from studies in other settings and populations (Simões et al., 2019, Roux et al., 2020, Gagnon et al., 2020, Toepfer et al., 2019, Achterhof et al., 2020). However, the mechanisms behind this association remain unclear. The observed sex difference should be interpreted with caution, since it was likely driven by more chronic use of certain medications in women (i.e. benzodiazepines), the fact that because of a lower creatinine clearance in women some medication may have been flagged as potentially inappropriate in women but not in men, or some potentially inappropriate medications listed in the Beers criteria are exclusively used in women (e.g. estrogens). It is beyond the scope of this paper to analyze the effect of sex differences in comorbidities or to examine potential gender biases in the use of potentially inappropriate medications, but future studies could explore this and potentially determine whether sex-based deprescribing interventions may be necessary.

Our results do not suggest clinically-relevant differences by age. In the current literature, there is contradicting evidence on the association between age and the utilization of potentially inappropriate medications. Some studies found that it increases with age (Roux et al., 2020, Morgan et al., 2016, Gagnon et al., 2020) while another one found that there is no age effect (Simões et al., 2019). Despite this, the age effect

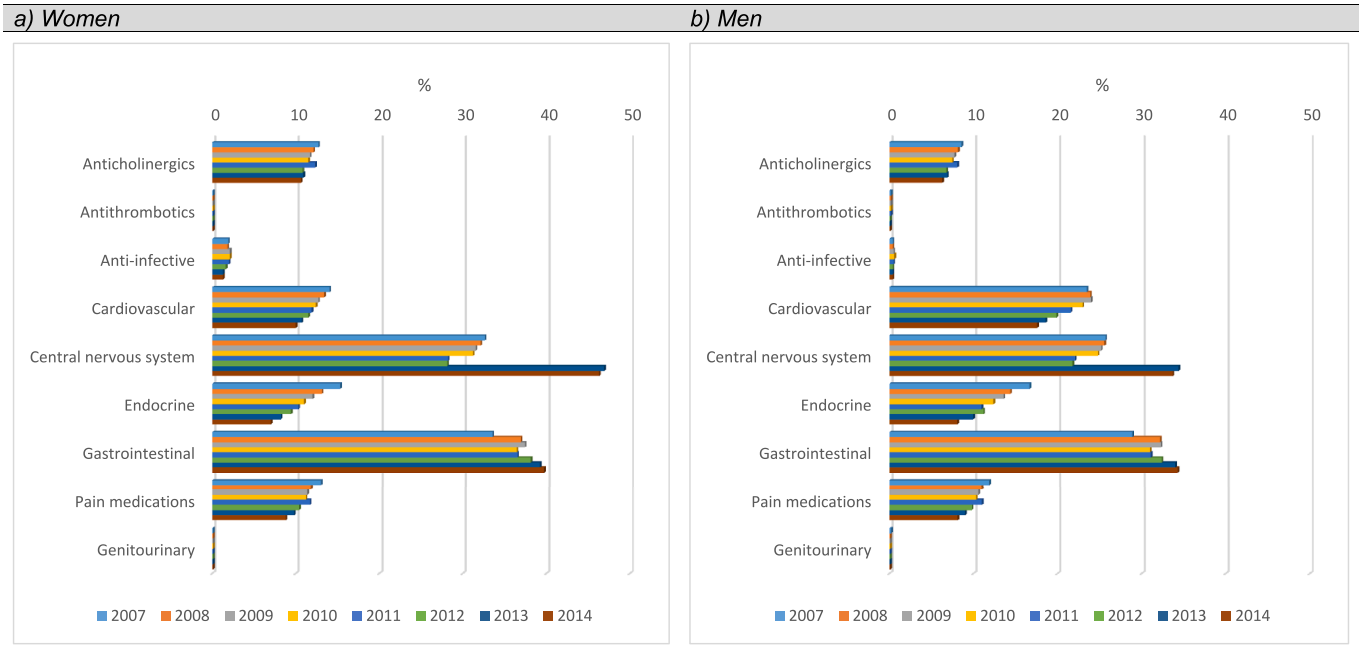

Fig. 1. Different types of potentially inappropriate medications* used in adults aged ≥65 years *with multimorbidity*** *and polypharmacy****, from 2007 to 2014.
Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767– table 2.
** multimorbidity defined as chronic conditions from ≥2 chronic condition categories;
*** polypharmacy defines as medications with ≥90 days' supply each from ≥5 pharmaceutical classes.

deserves to be further studied, to investigate which age group is most likely to benefit from deprescribing interventions.

Further, we observed an association of the utilization of potentially inappropriate medications with Hispanic ethnicity, but our results concerning the association with race were inconclusive. This is in line with previous research, which found that older Hispanics were more likely than older Whites to use potentially inappropriate psychotropic medications (Lim and Jung, 2019). The question of the association between the utilization of PIMs and race and ethnicity deserves to be further studies, as this information may be crucial for tailoring future interventions to optimize medication use and deprescribe.

The high use of potentially inappropriate medications in older adults is not without other consequences. A recent study from the US estimated that 7.3 billion doses of PIMs were dispensed in 2018 to patients who were enrolled in Medicare Part D and that this PIM use corresponded to a reported spending of US$ 4.4 billion (Fralick et al., 2020). Similarly, another study also conducted in the US context also found PIM use to be associated with higher costs (Clark et al., 2020). The fact that >10% are being spent potentially inappropriate medications in patients who use ≥1 PIM means substantial additional and potentially unnecessary spending by Medicare. To our knowledge, this is the first study to investigate the cost associated with the utilization of potentially inappropriate medications in relation to all medication costs in the United States. Average yearly spending on potentially inappropriate medications in this population was higher than in a previous study conducted in Canada (Morgan et al., 2016), which of course could be explained by different drug prices in the US and Canada (Gooi and Bell, 2008, Quon et al., 2005, Kim et al., 2017). Further, we only measured direct costs associated with potentially inappropriate medications (Xing et al., 2019), and indirect costs are likely to be much higher as higher utilization of potentially inappropriate medications is associated with higher total medical costs (Harrison et al., 2018).

In summary, our findings have important implications for clinical care and intervention development (e.g. tailored to what PIMs are most commonly used, based on what patient group is most likely to use PIMs). Due to the high utilization of potentially inappropriate medications in older multimorbid adults with polypharmacy and the potential negative and financial consequences linked to the PIM use, regular screening for PIMs should be incorporated in standard practice (e.g. screenings by pharmacists or primary care physicians) and deprescribing interventions should be explored.

5.1. Limitations

The findings of this study should be interpreted in light of several limitations. First, since the different tools used to define potentially inappropriate medications include different medications, the results of this study may not be comparable to studies using different tools (e.g. STOPP criteria instead of Beers). Different tools result in different proportions of PIM use (Sakr et al., 2018, Ma et al., 2019). Second, the Beers criteria are criterion rather than judgment-based. Despite using diagnoses and clinical criteria to determine PIM use, some medications defined as potentially inappropriate may have been used as a last resort. In other cases, alternative to PIMs might have been more expensive. Regardless, the Beers criteria are the most commonly-used metric for PIM use in the US and excluding medications with a low-level of evidence did not meaningfully change the results. Third, despite using a broad approach for identifying patients with multiple chronic conditions, we cannot rule out some potential misclassification because of the nature of the data. Fourth, we were not able to capture dispensation over-the-counter medications, which may have led to an underestimation of the utilization potentially inappropriate medications. Fifth, the data are from several years ago (owing to an administrative lag in acquisition and linkage); given that we observed no changes over time, these findings should remain relevant. Sixth, we did not account our cost analyses for inflation. Finally, our results might not be generalizable to commercially insured older adults or beyond the Boston metropolitan region. For example, while the demographic makeup of the metropolitan area compared with other urban US regions is similar (Kaiser Family Foundation, 2020), individuals in urban areas could have more access to

Table 4
Average medication costs spent on potentially inappropriate medications* versus all medications in adults aged ≥65 years with multimorbidity**, polypharmacy*** and utilization of ≥1 potentially inappropriate medication, by year and sex

	2007	2008	2009	2010	2011	2012	2013	2014
Women								
	n = 29,807	n = 32,134	n = 33,875	n = 34,437	n = 35,881	n = 37,597	n = 47,371	n = 46,679
PIMs in US$, mean (SD)	719.1 (9,456.9)	418.6 (595.1)	409.3 (461.7)	405.9 (450.7)	400.0 (455.9)	392.1 (434.6)	480.9 (521.1)	472.4 (505.0)
All medications in US$, mean (SD)	6,706.2 (12,9204.6)	3,879.1 (7,109.5)	3,905.5 (3,602.4)	4,003.2 (5,037.0)	4,103.7 (9,123.8)	4,100.7 (5,216.1)	4,186.7 (4,749.7)	4,291.4 (8,564.4)
Average ratio (SD)	12.4 (11.6)	12.2 (11.2)	11.8 (11.1)	11.6 (10.9)	11.2 (10.5)	11.0 (10.4)	12.8 (11.5)	12.6 (11.3)
Men								
	n = 15,464	n = 17,846	n = 19,191	n = 19,957	n = 21,992	n = 23,745	n = 29,706	n = 29,682
PIMs in US$, mean (SD)	758.5 (11,744.1)	423.1 (536.5)	418.8 (461.6)	417.3 (462.1)	403.8 (447.6)	395.9 (430.0)	433.7 (463.2)	423.4 (454.2)
All medications in US$, mean (SD)	7,299.3 (97,622.1)	4,018.5 (6,354.6)	4,033.3 (3,169.1)	4,117.6 (3,545.5)	4,202.3 (5,485.0)	4,191.7 (3,251.8)	4,284.1 (3,926.3)	4,317.6 (5,120.2)
Average ratio (SD)	12.2 (11.1)	12.1 (11.0)	11.8 (10.8)	11.7 (10.7)	11.3 (10.4)	11.0 (10.1)	11.5 (10.5)	11.3 (10.3)

* Reference: (2019), American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 67: 674-694. doi:10.1111/jgs.15767;
** multimorbidity defined as chronic conditions from ≥2 chronic condition categories;
*** polypharmacy defines as medications with ≥90 days' supply each from ≥5 pharmaceutical classes

healthcare and physicians, which could change the prevalence of prescribing of potentially inappropriate medications

6. Conclusions

Based on the findings of this study, we conclude that the utilization of potentially inappropriate medications in older multimorbid US adults with polypharmacy is high and has not changed over time. After adjusting for health services use and types of chronic conditions, female sex, age and Hispanic ethnicity were associated with potentially inappropriate medication use. The utilization of potentially inappropriate medications contributes to >10% of medication spending. These findings demonstrate the continued need for PIM screening and deprescribing interventions in this population group.

Ethics approval

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

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Availability of data and materials

The data that support the findings of this study are available from the Research Data Assistance Center (ResDAC) from the Centers for Medicare and Medicaid Services and from Mass General Brigham (formerly Partners Healthcare). Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may however be available from the authors upon reasonable request and with permission of ResDAC.

Author Contributions

Katharina Tabea Jungo: Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original draft, Project administration, Visualization. **Sven Streit**: Conceptualization, Writing – Review & Editing. **Julie C Lauffenburger**: Conceptualization, Methodology, Formal Analysis, Resources, Writing - Review & Editing, Supervision.

Declarations of Competing Interest

None. The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2020.104326.

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