Potentially inappropriate medication use by level of polypharmacy among US Veterans 49-64 and 65-70 years old

Running title: PIMs among US Veterans

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Ethic statement: This study was approved by the institutional review boards of VA Connecticut Healthcare System and Yale University. It has been granted a waiver of informed consent and is Health Insurance Portability and Accountability Act compliant.

Data availability statement: Due to US Department of Veterans Affairs (VA) regulations and our ethics agreements, the analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol.

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Keywords: Pharmacoepidemiology; Age; Data analysis; Older; Middle-aged; Population health; Polypharmacy; Potentially inappropriate medications; Drug utilization study

Key points (100/100 words):

- Between 2015 and 2016, about 60% of United States (US) Veterans patients aged 49 to 70 years with polypharmacy and 80% with hyperpolypharmacy were exposed to potentially inappropriate medications (PIMs).
- Beers, Laroche and PROMPT criteria provided similar estimation of PIMs prevalence both inside and outside their target age population.
- The prevalence of polypharmacy and hyperpolypharmacy was substantial even among those 49-64 years of age.

- Meaningful differences in PIMs prevalence were observed between patients aged 49 – 64 and patients aged 65 -70 overall, but these were small among those with polypharmacy
- Proton pump inhibitors, antidiabetics, non-steroidal anti-inflammatory drugs, opioids, benzodiazepines and antidepressants represented the most common PIMs.
- Small differences in PIMs prevalence were observed by sex and race/ethnicity.

Plain Language Summary (193/200 words):

Potentially inappropriate medications (PIMs) are medications contra-indicated in particular circumstances. We sought to characterize PIMs by level of polypharmacy by age, sex and race/ethnicity.

We set up a study using electronic health records available through the US Department of Veterans Affairs. We analysed pharmacy fill and refill records between October 1, 2015 – September 30, 2016 for all patients aged 49 to 70. PIMs were defined by lists of medications: the combined Beers and Laroche (henceforth Beers Laroche) criteria used for older patients and the PROMPT criteria used for middle-aged.

2 748 705 patients were included in the study. Among patients with 0-4, 5-9 and ≥10 medications about 14%, 60% and 85%, respectively, had at least one PIMs defined by PROMPT or Beers Laroche criteria. Small differences in prevalence were found by age. Meaningful differences in prevalence were shown by sex and race/ethnicity according to both set of criteria. The most common PIMs were digestive, analgesic, antidiabetic and psychotropic medications.

Prevalence of PIMs was high and increased with polypharmacy. Beers Laroche and PROMPT provided similar estimation inside and outside their target age, suggesting that PIMS are common among those with polypharmacy regardless of age.

Abstract (249/250 words)

Background: Potentially inappropriate medications (PIMs) are medications contra-indicated in particular circumstances. We sought to characterize PIMs by level of polypharmacy by age, sex and race/ethnicity.

Methods: We performed a cross-sectional drug dispensing study using electronic health records available through the US Department of Veterans Affairs. We extracted pharmacy fill and refill records during fiscal year 2016 (i.e., October 1, 2015 – September 30, 2016) for all patients aged 49 to 70 who accessed care in the preceding fiscal year. PIMs were defined by the combined Beers and Laroche (henceforth Beers Laroche) criteria used for older patients and the PROMPT criteria used for middle-aged.

Results: In the 1 499 586 patients aged 49-64, PIMs prevalence by PROMPT in patients with 0-4, 5-9 and ≥10 medications was 14.0%, 62.2% and 86.1%, respectively, and by Beers Laroche was 14.3%, 63.4% and 85.7%, respectively. In the 1 249 119 patients aged 65-70, PIMs prevalence by Beers Laroche was 14.8%, 59.9% and 83.3%, and by PROMPT was 13.9%, 57.4% and 82.0%, respectively. Meaningful differences in prevalence were shown by sex and race/ethnicity according to both set of criteria (e.g. PROMPT in patients with 5-9 medications: 66.1% women vs. 59.3% men; Standardized-mean-differences (SMD) = 0.14; 61.7% of White vs. 54.5% of non-White; SMD= 0.15). The most common PIMs were digestive, analgesic, antidiabetic and psychotropic medications.

Conclusion: Prevalence of PIMs was high and increased with polypharmacy. Beers Laroche and PROMPT provided similar estimation inside and outside their target age, suggesting that PIMS are common among those with polypharmacy regardless of age.

Introduction

Polypharmacy, typically defined as the use of five or more concurrent medications, is common and associated with adverse drug events [1], drug-drug interactions [2], non-adherence [3], cognitive impairment [4], falls [5], hospitalisations [6] and mortality [7]. Potentially inappropriate medications (PIMs) are defined as drugs for which risks outweigh potential benefits [8]. PIMS include specific drugs that should not be used in general, or in patients with multimorbidity, or at a certain age.

Large national healthcare databases offer real-world data, and can help understand the specific mechanisms for harm from polypharmacy [9]. For instance, healthcare databases provide the opportunity to look at trends in prescription drug use. In the United States (US), polypharmacy increased from 8.2% to 15.0% between 1999 and 2012 among adults, aged 20 years and over [10].

Lists of PIMS have been created by experts and may help explain harms associated with polypharmacy [11,12]. Most of these lists focus on patients aged 65 or over because advanced age is associated with altered pharmacokinetics; pharmacodynamics and multiple diseases, which can help trigger these adverse events [13]. The Beers criteria were created in the US in 1991 and regularly updated with the latest version in 2019. The Laroche list was published in 2007 and is an adaptation to the French setting but also provides additional data. PROMPT criteria were developed in 2014 to target specifically middle aged patients (45 to 64 years old) [14]. These criteria overlap and commonalities and differences can help paint a more comprehensive picture of PIMs [14–16].

PIMs lists have been applied in health care databases mainly in Europe and among those over 65 years with few consideration of sex or race [17]. Very little work has been done among those under 65 years of age or according to sex and race/ethnicity. The aim of this study was to measure the prevalence of PIMs by level of polypharmacy using three commonly used PIMs criteria among patients aged 49 to 70 years old in the largest integrated healthcare system in the US, overall and by demographic subgroups.

Methods

Study design and population

We conducted a cross-sectional drug utilization study using data from electronic health records available through the US Department of Veterans Affairs (VA) Corporate Data Warehouse (CDW). The VA provides healthcare benefits to more than 9 million patients annually at over 1200 points-of-care. The CDW includes all pharmacy fills and refills, inpatient and outpatient diagnosis, and demographics. The Veteran Birth Cohort is a subset of CDW and includes patients born between 1945 and 1965, which accounts for approximately 4.5 million patients [18,19]. We extracted data from fiscal year 2016 (i.e., October 1, 2015 – September 30, 2016) on all patients in the Veteran Birth Cohort who were alive on October 1, 2015 and accessed care in the preceding fiscal year. The Veteran Birth Cohort has been approved by the institutional review boards of Yale University (ref #1506016006) and VA Connecticut Healthcare System (ref #AJ0013), granted a waiver of informed consent, and deemed Health Insurance Portability and Accountability Act compliant.

Potentially inappropriate medications (PIMs) and polypharmacy

All drugs were considered regardless of route of administration (systemic or not). Specific therapeutic classes were excluded: antiseptics, soap, deodorants, keratolytics, diagnosis agents, vaccines, immunoglobulins, contact lens, eye washes, dental agents, and devices. Fixed dose combinations were split into active ingredients for systemic and oral drugs. Topical combinations (including dermatological, nasal, optical and otic agents) were not split and counted as one medication.

Chronic medication use was defined as uninterrupted duration of dispensed medication for at least 183 days (6 months), allowing for a grace period of 20% the prescription duration after each fill to account for potential stockpiling. Polypharmacy was defined by the use of five to nine chronic medications on any single day during the study period; hyperpolypharmacy by the use of ten chronic medications or more (Figure 1). We extracted medication data from up to one year prior to the study period, fiscal year 2015, to identify chronic medications that had already started before and continued after the start of the study.

Beers and Laroche criteria were combined (henceforth referred to simply as Beers Laroche) and applied simultaneously and PROMPT criteria were applied separately (Table S1 and S2). We used only the criteria that were applicable in the VA according to clinical (e.g., benign prostatic hyperplasia or heart failure with reduced ejection fraction were not identifiable) and pharmacy data (e.g., aspirin indication could not be identified as antiplatelet or an analgesic). For Beers/Laroche criteria, if a medication was mentioned in both lists with different requirement, when applied to the data, the list applied was the one with the broader criteria (e.g., Benzodiazepines and hypnotics are inappropriate at any dose according to Beers while half dose can be used according to Laroche. The Beers criteria were applied in this case).

PIMs were considered as any drug identified as potentially inappropriate by at least one applicable criterion of either Beers Laroche or PROMPT lists, regardless of age [12,14,20].

Other characteristics

We extracted data on demographic characteristics (e.g., age, sex, and race/ethnicity). We also used inpatient and outpatient ICD-9 diagnostic codes occurring in the year prior to study start to identify a large set of clinical characteristics, including hyperlipidemia, hypertension, mild depression, diabetes, pulmonary disorders, post-traumatic stress disorder (PTSD), alcohol abuse, myocardial infarction, anxiety, major depression, bipolar disorder, chronic seizure, delirium, dementia, helicobacter pylori, heart failure, gastric or duodenal ulcers, falls, fractures, oesophagitidis, pathological hypersecretory condition, Parkinson disease, and schizophrenia (Table S3)

Statistical analysis

Prevalence of polypharmacy/hyperpolypharmacy was defined as the number of patients who had at least one day of polypharmacy/hyperpolypharmacy in fiscal year 2016 out of the number of all eligible patients included in the study (n=2,748,705). Prevalence of PIMs was defined as the number of individuals with at least one day of any chronic PIMs (Figure 1) over patients with 0-4 medications, polypharmacy (5-9 medications) or hyperpolypharmacy (10 or more). All analyses were stratified on age (49 - 64 years old and 65 - 70 years old), sex and race/ethnicity. White and Black patients, were

defined as such if they had no Hispanic ethnicity. Hispanic are defined by ethnicity regardless of other races. Race "other" were patients who were not in any of the above categories. Standardised mean differences (SMDs) were used to estimate differences of PIMs prevalence between age, sex and races groups with a SMD < 0.1 indicating no difference, 0.2 a small difference, 0.5 a moderate difference and 0.8 a large difference [21]. All data management and analyses were performed using SAS software version 9.4 (SAS Institute, North Carolina, USA).

Results

Of 3 923 534 patients in the Veteran Birth Cohort alive on October 1, 2015 who had ever accessed VA care, 808 796 were excluded because they did not access VA care in the preceding fiscal year, and 366 033 were excluded because they initiated VA care in the preceding fiscal year and therefore were unlikely to have established chronic care in the VA before study start. Therefore, 2 748 705 patients with active use and an established clinical history were included in this study. They were mostly men (93.3%) and the mean age was 62 years old, with 45.4% of patients aged 65 -70. They were mostly white (68.7%) or Black (20.3%). The most frequent chronic conditions were hyperlipidemia (66.0%), hypertension (64.8%), depression (34.3%) and diabetes (30.1%). In fiscal year 2016, the prevalence of polypharmacy (5-9 medications) was 23.0% and hyperpolypharmacy (≥ 10 medications) was 7.3%. The prevalence of polypharmacy and hyperpolypharmacy in patients aged 65-70 were 27.0% and 9.1%respectively , and in patients aged 49-64 19.7% and 5.8% respectively. Among men, the prevalence of polypharmacy and hyperpolypharmacy were 23.3% and 7.4%, and among women 18.9% and 5.9%. Prevalence of polypharmacy and hyperpolypharmacy by race were 24.0% and 7.9% in White, 21.6% and 6.1% in Black, 22.3% and 6.7% in Hispanic, and 16.0% and 4.7% in other race (Table 1, Table S4).

We applied PROMPT criteria inside the target age of our population, patients aged 49-64, and we found the prevalence of having at least one PIMs was 14.0% among patients with 0-4 medications, 62.2% in patients with polypharmacy, 86.1% in patients with hyperpolypharmacy. Most common PIMs were proton pump inhibitors (PPIs; respectively 6.2% of patients with 0-4 medications, 30.1%

of patients with polypharmacy, 48.5% with hyperpolypharmacy), non-steroidal inflammatory drugs (NSAIDs, 3.2%, 14.8%, 25.2%), sulfonylureas (1.5%, 12.4%, 19.4%), opioids without concurrent laxatives (1.5%, 7.2%, 13.5%), stimulant laxative (0.5%, 4.9%, 18.0%) and Benzodiazepines (0.9%, 5.4%, 12.7%). When we applied Beers Laroche in this same age group we found PIMs prevalences of 14.3%, 63.4% 85.7% respectively. Similarly, the most common PIMs were PPIs (5.9%, 26.3%, 34.6%), sulfonylureas (1.5%, 12.4%, 19.5%), NSAIDs (2.9%, 11.6%, 15.4%), stimulant laxatives (0.5%, 5.6%, 21.3%) and benzodiazepines (0.6%, 3.6%, 8.7%) (Table 2).

We applied the Beers Laroche criteria inside target age of our population, patients aged 65-70, and we found PIMs prevalences of 14.8% in patients taking 0 -4 medications, 59.9% in patients with polypharmacy, 83.3% in patients with hyperpolypharmacy. The most common PIMs were PPIs (6.9% of patients taking 0-4 medications, 25.6% of patients with polypharmacy, 33.3% of patients with hyperpolypharmacy), sulfonylureas (2.1%, 15.9%, 24.8%), NSAIDs (1.9%,7.3%, 10.4%), stimulant laxatives (0.5%, 4.6%, 18.8%), insulin sliding scale (1.0%, 5.9%, 12.5%), antidepressants (0.8%,4.0%, 8.5%) followed by benzodiazepines (0.6% 2.8%, 7.0%). When we applied the PROMPT criteria in this same age group, we found prevalences of 13.9%, 57.4% and 82.0% respectively. Similar common PIMs were found: PPIs (7.1%, 28.5%, 44.7%), sulfonylureas (2.1%, 15.9%, 24.8), NSAIDs (2.1%, 9.4%, 17.1%), stimulant laxatives (0.4%, 4.2%, 16.6%) and benzodiazepines (0.9%, 4.0%, 9.9%) (Table 2)

Among patients with 0 -4 medications, PIMs prevalence were similar between patients aged 49-64 and patients aged 65 – 70 according to both Beers Laroche (14.3% vs. 14.8%, SMD = 0.01) and PROMPT criteria (14.0% vs. 13.9%, SMD = 0.00). Among those with polypharmacy and hyperpolypharmacy, The Beers Laroche criteria showed no differences in PIMs prevalence according to age (63.4% vs. 59.9%, SMD = 0.07 and 85.7% vs. 83.3%, SMD = 0.07 respectively) but PROMPT criteria showed small differences (62.2% vs. 57.4%, SMD = 0.10 and 86.1% vs. 82.0%, SMD = 0.11, respectively) suggesting that patients aged 49 – 64 had a higher PIMs prevalence than patients aged 65-70. Small differences of PIMs prevalence were observed according to sex with a higher prevalence in women than men in polypharmacy and hyperpolypharmacy according to the Beers Laroche criteria (68.6% vs.

61.1%, SMD = 0.16 and 89.2% vs. 84.1%, SMD = 0.15 respectively) and PROMPT criteria (66.1% vs. 59.3% SMD = 0.14 and 89.0% vs. 83.5% SMD = 0.16). Differences existed according to race/ethnicity: For instance according to PROMPT, White and Black patients had small differences compared to non-White and non-Black, White patients having higher prevalence compared to Black, Hispanic and other race/ethnicity (61.7% vs. 54.5% of patients with polymarmacy, SMD = 0.15; 84.7% vs. 81.0% of patients with hyperpolypharmacy, SMD = 0.10) and Black lower prevalence than White, Hispanic and other race/ethnicity (52.3% vs. 61.4% of patients with polymarmacy, SMD = 0.19; 79.8% vs. 84.6% of patients with hyperpolypharmacy, SMD = 0.13) (Tables 3 – 6, Tables S5 – S8).

Small differences in prevalence of the most common PIMs were observed between age, sex and race/ethnicity. If looking only in patients with polypharmacy or hyperpolypharmacy, patients aged 49 – 64 had higher prevalence of NSAIDs (SMD between 0.15 – 0.20), skeletal muscle relaxants (0.14 – 0.19), opioids (0.17 – 0.18) and lower prevalence of sulfonylureas (0.10 – 0.13) than patients aged 65-70. Similarly, women had higher prevalence of NSAIDs (0.13 – 0.20), PPIs (0.10 – 0.18), skeletal muscle relaxants (0.15 – 0.23), antidepressants (0.14 – 0.19), benzodiazepines (0.10 – 0.12), antihistamines (0.12 – 0.20), stimulant laxatives (0.10 – 0.16) and lower prevalence of sulfonylureas (0.23 – 0.27) and insulin sliding scale (0.17) than men. Similarly, White had higher prevalence of PPIs (0.13 – 0.17) and opioids (0.10) than non-White, and Black lower prevalence of PPIs (0.14 – 0.18), opioids (0.10), antidepressants (0.10) and benzodiazepines than non-Black (0.14 – 0.22) (most frequent PIMs presented in Table 2 - 6, all PIMs are presented in Table S5 – S8).

Discussion

Approximately six in ten patients with polypharmacy and eight in ten patients with hyperpolypharmacy were exposed to PIMs by either Beers Laroche criteria targeting older people or PROMPT criteria targeting middle-aged people. PROMPT criteria showed small differences in PIMs prevalence in patients aged 49 – 64 than patients aged 65 – 70, while no difference existed with Beers Laroche criteria. Women were more exposed to PIMs than men and White more than all other

248 race/ethnicities but these differences were largely driven by number of medications prescribed. Once
249 analyses were stratified by polypharmacy and hyperpolypharmacy, differences were small. Both PIMS
250 criteria identified similar common PIMs such as PPIs, sulfonylureas, NSAIDs, antidepressants and
251 benzodiazepines. Small differences of patterns existed according to age, sex and race.

252 Most previous PIMs research was focused on people of 65 years of age and older. All but four focused
253 on people of 60 years of age and older (Table S9) [15,16,22,23]. In our study we observed that PIMs
254 were as prevalent in people <65 as in older people. The prevalence of PIMs observed in younger
255 individuals should raise concern. It has been seen in other studies such as in Japan where PIMs
256 concerned 71.9% of patients older than 45 and receiving care at home [22] and in a study in the
257 Netherlands that showed that younger patient were subjected to a higher prevalence of PIMs than older
258 patients with polypharmacy between 2012 and 2016 [16]. This suggests that initiation of PIMs in
259 younger patients with polypharmacy is an increasing concern.

260 Most studies used criteria according to the age of the studied population, i.e., Beers and Laroche for
261 older patients and PROMPT for middle-aged patients. Beers criteria were created for individuals aged
262 65 and over, the Laroche list for individuals aged 75 and over, and PROMPT criteria were created for
263 middle-aged people aged 45 to 64. To the best of our knowledge, we are the first to show the use of
264 either Beers Laroche and PROMPT criteria in a population aged 49-70 provides similar estimation
265 regardless of if applied in the target population or not. We observed a high prevalence that increased
266 with polypharmacy and hyperpolypharmacy with any criteria and at any age category. This suggest
267 that these criteria may be used in both middle aged and older people regardless of the initial target
268 population. These criteria also provided close estimations of PIMs prevalence in analysis stratified by
269 sex and race/ethnicity. Another argument is that all these medications may be pharmacologically
270 inappropriate in anyone when used chronically.

271 Previous PIMs research used to be conducted in small samples of patients, often those who visited or
272 were discharged from a single hospital, so may not be generalizable. However, new population-based
273 study such as ours described similar common PIMs. Benzodiazepines, analgesics, NSAID and PPIs
274 were showed in two small sized study in Spain [24,25]. Proportion of the lists that is actually used may

also vary between studies but results stays consistent and similar to ours. Similarly, two studies employing somewhat different applications of Beers criteria used showed that gastrointestinal medications including PPIs were among the most frequent PIMs in older people (≥ 65 years old) in two different hospitals in 2016, one in Jordan [26] and one in Saudi Arabia [27]. PPIs were identified as the major PIMs regardless of the subcategories of Beers criteria use. Studies using PROMPT showed similar results to ours: In the United Kingdom (UK), France and the Netherlands, proton pump inhibitors, benzodiazepines were among the most frequent PIMs[14–16,23]. These similarities suggest that those common PIMs are a feature of polypharmacy.

Identification of inappropriate PPIs according to Beers/Laroche and PROMPT criteria sometimes demands clinical data such as conditions that justified the chronic use of a PPI (esophagitis, Helicobacter pylori) or other drugs. From the VA data we could identify these specific clinical conditions but it was not possible to distinguish antiplatelet aspirin (only low-dose aspirin) from analgesics (either low-dose or high dose). Consequently, we considered PPIs used concurrently with low-dose aspirin (antiplatelet) always appropriate even though they are not, leading to a possible underestimation of PIMs. Despite this, the prevalence of PPIs remains high in our study, similarly to what was observed in France [15], the Netherlands [16] Spain [24] and the UK [23].

Beers Laroche and PROMPT criteria overlap with slight differences which helped us to better understand PIMs use. In addition to oesophagitis and helicocter, PPIs were considered appropriate if used concomitantly with a chronic NSAID or oral corticoids with Beers Laroche criteria but not with PROMPT criteria. Furthermore, Beers Laroche criteria listed specific NSAIDs contrary to PROMPT that would consider NSAIDs overall. The close estimations between our criteria suggested that most people used chronically PPIs without NSAIDs, and vice versa. PPIs and NSAIDs are known to be frequently initiated at the same time, often without following the recommendations, i.e. without gastrointestinal risk factors [28,29]. Once either PPIs or NSAIDs have been discontinued, treatment is probably rarely re-evaluated, leading to chronic and inappropriate use of either treatment.

Benzodiazepines and hypnotics are often reported as the most common PIMs for instance in Korea [30] and in most European countries (Spain [25], France [15,31], the Netherlands [16], Lithuania

[32],Finland [33], Germany [34] and Scotland [35]). Our data allowed the identification of patients with chronic anxiety, a condition for which Beers Laroche criteria considers short acting benzodiazepines appropriate, contrary to the PROMPT criteria [12,14]. Close prevalences between criteria suggest that anxiety cannot explain the high use of these drugs by itself, in our study and in Europe, despite the risks of associated adverse effects [36–39].

The study had limitations largely related to the data source and population. The Veteran Birth Cohort included patients aged 49 to 70 as of October 2015; therefore, our findings may not generalize to patients aged younger than 49 or older than 70. Although the cohort included proportionally few women (~7%), the large nature of our study meant this translated to 185,466 women; though, our findings may not generalize to women in the general population. Given the cohort was mostly men, overall estimates of the prevalence of PIMs is likely to be an underestimate of the prevalence in the general population since medication use is, in part, driven by sex and gender (e.g., estrogens are frequently prescribed PIMs [40]). Importantly, we found a small difference of PIMS prevalence in sex-stratified analyses for medication usually not driven by sex such as a higher prevalence of antidiabetic PIMs in men compared to women, and a higher prevalence of central nervous system PIMs in women compared to men. Dose and indication of treatment were not available which limited full use of some of the Beers Laroche and PROMPT criteria. For instance, PROMPT criteria say that PPIs should not be used at doses above the recommended maintenance dosage for greater than eight weeks, so we only took account of the duration of treatment. In addition, some clinical data might be inconsistently coded (e.g., anxiety is rarely coded using ICD-9 codes so prevalences of Benzodiazepines – short/intermediate acting PIMs might be overestimated). Over-the-counter medications and medications dispensed outside of the VA were not available, which could have resulted in the underestimation of the true prevalence. However, our analysis included patients with active use and an established clinical history in the VA and assumed most patients have received most or all of their medications through the VA, which minimized the potential risk for underestimation.

This study was reported using the observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE; Table S9) [41]. A comparative table with all studies cited in this discussion is available in supplementary materials (Table S10).

Conclusion

PIMs prevalence was high and increased with polypharmacy and hyperpolypharmacy in US veterans aged 49 -70. Beers, Laroche and PROMPT criteria provides very close estimation of PIMs prevalence if they are used either inside or outside their target age (middle age or older patients). Furthermore, regardless of the criteria used, differences in PIMs prevalence between patients aged 49 – 64 and patients aged 65 – 70 were small or absent, suggesting that PIMs exposure should be addressed as well in middle aged people as in older people. The most common PIMs were gastrointestinal such as PPIs and stimulant laxatives, antidiabetics such as sulfonylureas and insulin sliding scale, analgesics and psychotropics such as NSAIDs, opioids, benzodiazepines and antidepressants. These medications should be prioritized for deprescribing interventions, especially among patients with polypharmacy and hyperpolypharmacy. Small differences of patterns were observed according to sex and race ethnicity suggesting that intervention should target every patient with polypharmacy regardless of age, sex and race.

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Figures titles

Figure 1: Figure 1 Definition of exposure to chronic polypharmacy and potentially inappropriate medications (PIMs) in 2016. The example presented defined an individuals who is prevalent of PIMs and polypharmacy in 2016

Tables titles

Table 1 Characteristics of patients aged 49-70 years in 2016 according to age and sex

Table 2 prevalences of most common potentially inappropriate medications (PIMs) defined by either combined Beers and Laroche and prevalances of most common PIMs defined by PROMPT criteria in US veteran patients aged 49-70 years according to polypharmacy in 2016

Table 3 Prevalence of most frequent potentially inappropriate medications (PIMs) defined by combined Beers and Laroche criteria in patients aged 49-70 years according to age, sex and polypharmacy in 2016

Table 4 Prevalence of most frequent potentially inappropriate medications (PIMs) defined by combined Beers and Laroche criteria in patients aged 49-70 years according to race and polypharmacy in 2016

Table 5 Prevalence of most frequent potentially inappropriate medications (PIMs) defined by PROMPT criteria in patients aged 49-70 years according to age, sex and polypharmacy in 2016

Table 6 Prevalence of most frequent potentially inappropriate medications (PIMs) defined by PROMPT criteria in patients aged 49-70 years according to age, sex and polypharmacy in 2016

Supplementary materials titles

Table S1 Drugs identified as potentially inappropriate medications defined by combined Beers and Laroche criteria according to the VA generic name and specific requirement of the definition.

Table S2 Drugs identified as potentially inappropriate medications defined by PROMPT criteria according to the VA generic name and specific requirement of the definition.

Table S3 Codes from the International classification of disease 9th edition (ICD 9th) used to identify most frequent chronic diseases and clinical requirements.

Table S4 Characteristics of included patient aged 49 - 70 according to race/ethnicity

Table S5 Prevalence of potentially inappropriate medications (PIMs) defined by combined Beers and Laroche criteria in patients aged 49-70 years according to age, sex and polypharmacy in 2016

Table S6 Prevalence of potentially inappropriate medications (PIMs) defined by combined Beers and Laroche criteria in patients aged 49-70 years according to race and polypharmacy in 2016

Table S7 Prevalence of potentially inappropriate medications (PIMs) defined by PROMPT criteria in patients aged 49-70 years according to age, sex and polypharmacy in 2016

Table S8 Prevalence of potentially inappropriate medications (PIMs) defined by PROMPT criteria in patients aged 49-70 years according to race and polypharmacy in 2016

Table S9 The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data

Table S10 Prevalences of PIMs defined by Beers, Laroche and PROMPT criteria according to polypharmacy in previous international studies

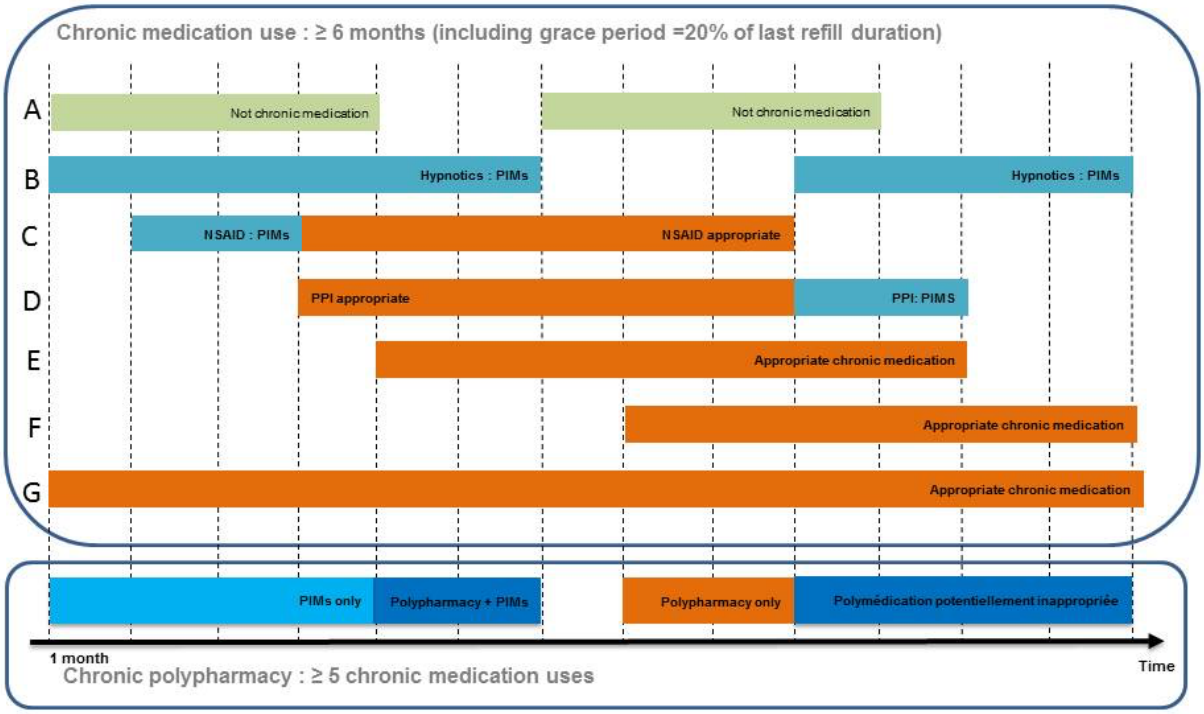

Figure 1 Definition of exposure to chronic polypharmacy and potentially inappropriate medications (PIMs) in 2016. The exemple presented defined an individuals who is prevalent of PIMs and polypharmacy in 2016

PPI: Proton pump inhibitor; NSAID: Non-steroidal Anti-Inflammatory Drug

Potentially inappropriate medication use by level of polypharmacy among US Veterans 49-64 and 65-70 years old

Supplementary material

Supplementary table 2 The RECORD statement for pharmacoepidemiology (RECORD-PE) checklist of items, extended from the STROBE and RECORD statements, which should be reported in non-interventional pharmacoepidemiological studies using routinely collected health data

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	1-4
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	5
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	5
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	6
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	6-8
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	6
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	6-7
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	—	8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	6

(*Continued*)

Supplementary table 2 (*Continued*)

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	6-8
Study size				
10	Explain how the study size was arrived at.	—	—	6
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	6-7
Statistical methods				
12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	7-8
Data access and cleaning methods				
12	—	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. 12.2: Authors should provide information on the data cleaning methods used in the study.	—	6-7
Linkage				
12	—	12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	—	6-7
Results				
Participants				
13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	8
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	8-9
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	8-10
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	NA

Supplementary table 2 (*Continued*)

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	8-10
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	10-11
Limitations				
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	13
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant.	14
Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	10-13
Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	—	—	2
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	2

RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology. This checklist has been duplicated from table 1 in *BMJ* 2018;363:k3532, as a standalone document for readers to print out or fill in electronically.