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Factors associated with potentially inappropriate medication use in community-dwelling older adults in the United States: a systematic review

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Abstract

Objectives Potentially inappropriate medication (PIM) use in older adults is a prevalent problem associated with poor health outcomes. Understanding drivers of PIM use is essential for targeting interventions. This study systematically reviews the literature about the patient, clinician and environmental/system factors associated with PIM use in community-dwelling older adults in the United States.

Methods PRISMA guidelines were followed when completing this review. PubMed and EMBASE were queried from January 2006 to September 2017. Our search was limited to English-language studies conducted in the United States that assessed factors associated with PIM use in adults ≥65 years who were community-dwelling. Two independent reviewers screened titles and abstracts. Reviewers abstracted data sequentially and assessed risk of bias independently.

Key findings Twenty-two studies were included. Nineteen examined patient factors associated with PIM use. The most common statistically significant factors associated with PIM use were taking more medications, female sex, and higher outpatient and emergency department utilization. Only three studies examined clinician factors, and few were statistically significant. Fifteen studies examined system-level factors such as geographic region and health insurance. The most common statistically significant association was the south and west geographic region relative to the northeast United States.

Conclusions Amongst older adults, women and persons on more medications are at higher risk of PIM use. There is evidence that increased healthcare use is also associated with PIM use. Future studies are needed exploring clinician factors, such as specialty, and their association with PIM prescribing.

Introduction

Appropriate prescribing for older adults is challenging. Community-dwelling older adults in high-income countries take on average two to nine prescription medications a day with many studies estimating that over half of older adults are taking at least one medication that is recognized as a potentially inappropriate medication (PIM).[1] A PIM is broadly defined as a medication where the risk associated with its use likely exceeds its benefit.[2] This definition is challenging to operationalize. There are several published criteria including criterion-based measures such as lists of specific drugs and drug classes to avoid (i.e. Beers, Screening Tool of Older Persons Prescriptions)[3] and judgement-based measures such as the Medication Appropriateness Index[4] which asks a series of questions about the appropriateness of the drug in question. These drugs are considered inappropriate because older adults who use PIMs are more likely to experience adverse drug reactions,[5] falls,[6] hospitalization[7] and increased healthcare costs.[8]

The population of older adults globally is projected to more than double by 2050,[9] making it increasingly important to address unsafe medication use in older adults. Six of the 10 American Geriatrics Society's 'Things Patients and Providers Should Question'[10] from the

Choosing Wisely Initiative[11] caution against use of specific medications known to be overused in older adults. There are several published systematic reviews on quantification of PIM use,[12–14] but few have focused on synthesizing the determinants of PIM use. Without knowing what drives the use of potentially harmful medications, it will be challenging to target interventions towards specific factors to reduce this practice. Therefore, we sought to systematically review the literature to identify the determinants of PIM use in older community-dwelling adults in the United States.

Methods

Data sources and searches

This manuscript describes results of one topic from a broader systematic review on determinants of overuse of health services. The protocol of the broader systematic review was registered in Prospero (#42015029482). We completed this systematic review following the guidelines found in the PRISMA-P 2015 checklist (Table S1). MEDLINE® and EMBASE® were searched from January 2006 through July 2016 for published literature about overuse of healthcare services. A heterogeneous body of literature was identified and divided into topics appropriate for in-depth systematic reviews. Additional searches were focused for each topic. An additional search from January 2006 through September 2017 was completed searching terms specific to PIM use. The search terms used were based on MeSH terms and text keywords derived from key articles identified a priori (Appendix S1). The search results were limited to articles about humans that were written in English. Relevant systematic reviews and the reference list from each included article were hand-searched for additional studies.

Study selection

Two reviewers independently screened titles, abstracts and full text for inclusion and came to agreement through consensus adjudication. Articles were included if the authors evaluated factors associated with the use of medications that are considered inappropriate or potentially inappropriate based on defined criteria (i.e. Beers list). The term 'determinant' is used in this article to refer to those factors that were tested for their associations with PIM use, although we recognize that they may not have been tested for their causal associations. Studies included were limited to those examining patients aged 65 and older and those that were not exclusively describing care outside of the United States. The latter geographical restriction was included given the unique healthcare environment in the United States including lack of a single payer system and direct to consumer advertising of pharmaceuticals. Articles were also restricted to those which included data collected in 2006 and onward. This was done given the substantial changes in the United States healthcare system in the last decade including an increased focus on quality of PIM prescribing following publication of the landmark Institute of Medicine report Crossing the Quality Chasm,[15] revision of the Beers criteria[16] and an increasing focus on quality of care.[17] Studies which exclusively evaluated older adults in the hospital or nursing home were excluded as we have previously published a review of studies in these settings.[18] Studies which used large claims or administrative databases that included inpatient hospital care were included as it was felt that the majority of the included claims were generated by community-dwelling adults seeking ambulatory care. Articles testing interventions targeting medication use were also not included.

Data extraction, quality and applicability assessment

Data extraction forms were created and pilot-tested in Excel (Microsoft, Redmond, WA, USA). Reviewers extracted information on the study characteristics, study participant characteristics, the methods of data collection, the criteria used to define PIM, the potential determinants evaluated by the investigators and those identified as being statistically significant ($P \leq 0.05$) in their association with PIM use. The determinants were classified as being related to the patient (e.g. age, sex and comorbidities), the clinician (e.g. years in practice and specialty) or the environment (e.g. region or payer). One reviewer completed data extraction, and the second reviewer confirmed the first reviewer's data extraction for completeness and accuracy. Two reviewers independently assessed the quality of individual studies. The Critical Appraisal Checklist (Center for Evidence-Based Medicine) was used for appraisal of the quality of included cohort studies and surveys.[19] Differences were resolved between reviewer pairs through discussion with the research team.

Data synthesis and analysis

Detailed evidence tables were created containing all information abstracted from eligible studies. Results were synthesized by the type of determinant and summarized in tables. The results were not amenable to quantitative pooling given the heterogeneity in design across studies.

Results from studies which used more restrictive PIM criteria ($n = 8$) (i.e. limiting PIM to sedative hypnotics) were analysed separately to determine whether factors

associated with prescribing these agents differed from factors associated with more general PIM prescribing. There was no appreciable change in trends of statistically significant factors, and so results of studies with restrictive PIM criteria were included.

Role of the funding source

The funders had no role in this project.

Results

A total of 12 768 titles were screened; 730 articles underwent full-text review and 22 were included (Figure S1, Table 1).

Risk of bias

The overall risk of bias was low in 18 studies[20–37] and moderate in four studies (Table 2).[38–41] The deficiencies in the studies that had more than a low risk of bias were potential biases due to confounding, missing information about participants at baseline, and low or unreported response rates in surveys.

Characteristics of included studies

Twenty-two studies evaluated determinants of PIM use in community-dwelling and ambulatory clinic patients.[20–41] Most studies were either cross-sectional analyses of claims data or analyses of large nationally representative surveys such as the Medical Expenditure Panel Survey (MEPS) or the National Ambulatory Medical Care Survey (NAMCS) (Tables 1 and 2). The majority of participants were white women in their 70s and 80s (Table 1). Most studies used a broad definition, such as the Beers criteria, to define PIM but eight included studies used a more restrictive definition of PIM such as anticholinergics[30] or potentially inappropriate medications in patients with cognitive disorders (Table 1).[25,34] Fourteen of the included studies examined actual dispensing data through claims, pharmacy contact or review of actual pill bottles.[20,21,23–25,27,28,30,31,35,37–39,41]

Determinants of PIM use in community-dwelling and ambulatory clinic patients

Patient factors

Nineteen studies evaluated patient factors contributing to PIM use in community-dwelling adults or those attending ambulatory clinics (Table 3). Seventeen used multivariable regression,[21–23,25–34,36–38,41] adjusting for a combination of patient factors,[22,25,33,41] patient and system factors[21,23,26,28–31,34,36–38] or patient system and clinician factors.[27,32] Two studies used bivariate analysis.[20,39]

Demographic characteristics

Being a woman was positively associated with PIM use in 10 studies[21,23,27–30,32–34,37] Among the six studies[20,22,31,36,38,39] which did not report a statistically significant association between sex and PIM use were two that used bivariate instead of multivariate analysis,[20,39] a small (n = 82) study limited to Chinese American older adults in a single city,[36] and two that had a sample that was more than 80% women.[22,38] However, one study using nationally representative MEPS data did not report a statistically significant association with sex and PIM use when their final multivariate model was adjusted for number of medications.[31]

Other demographic factors such as age and race/ethnicity were inconsistently associated with PIM use across studies. Age was examined in 17 studies,[20–23,26–30,33,34,36–39,41] with four reporting that older age[28,29,33,36] and four reporting that younger age[27,30,31,37] were associated with PIM use. Age was most frequently examined categorically with the categories ranging in size from 5 to 20 years. Race and ethnicity were statistically significant in just five of the 13 studies that examined this.[21–23,26,27,30–34,37–39] The specific racial and ethnic categories compared varied widely across studies. No one race or ethnicity consistently was identified as being at higher risk of PIM use. Marital status was examined in six studies[22,26,30,31,36,38] none of which found a statistically significant association with PIM use.

Clinical characteristics

The most consistently observed statistically significant factor associated with PIM use was a higher number of prescribed medications, demonstrated in all 14 studies[20–23,27,31–34,36–39,41] in which it was evaluated.

Two[23,27] of three[41] studies reported that older adults with more prescribers had more PIM use. The study which did not report this association had a moderate risk of bias and small sample size. People who used more health care, as measured by more outpatient visits[27,29,33] or more emergency department visits,[27] were more likely to receive a PIM. The association between hospital admission and PIM use, however, was variable.

Seven studies[22,23,26,28,37,39,41] examined the association between medical comorbidities and PIM use. Assessment of comorbidity varied across studies, with some studies using a comorbidity count[22,23,39] and others using the hierarchical condition category[42] risk adjustment model,[28,37] the Charlson Comorbidity Index[41] or number of organ

Table 1 Study and participant characteristics by data source

Author	Study population[a]	Demographic characteristics of participants Mean age (y ± SD); Sex and race (%)	PIM criteria used			Prevalence of PIM use (%)
			Beers	Zahn	Other	
Administrative data						
Zhang (2010)[27]	Medicare Part D beneficiaries, 2007	Not reported			x[b]	11–44[c]
Woelfel (2011)[20]	Medicare Part D beneficiaries in central and northern California, 2008	76 ± 9.3 40% women 51% white		x		18
Blackwell (2012)[29]	Medicare Part D beneficiaries, 2007	Not reported 63% women 83% white	x			39
Holmes (2013)[31]	Medicare Part D beneficiaries in Texas, 2007–2008	Not reported 65% women 69% white	x			32
Lund (2013)[32]	Veterans with ≥1 outpatient visit, 2007	76 ± 6.4 2% women Not reported	x	x	x	4–18[d]
Jiron (2016)[35]	Fee-for-service Medicare beneficiaries, 2007–2012	78 ± 7.8 66% women 85% white	x			34–37[e]
Kester (2016)[36]	Medicare MCO enrollees with dementia, 2008–2010	81 ± 7.3 61% women Not reported			x[f]	12
Chart review						
Kester (2016)[36]	Outpatients from one of two outpatient sites: Cleveland Clinic and Intermountain Health System, 2006	76 ± 7.2 60% women 84–96% white	x	x		16–23[g]
Hu (2012)[28]	Chinese American home care patients in New York City	82 ± 7.3 55% women 0% white	x			24
Prithviraj (2012)[30]	Newly diagnosed cancer patients at an oncology clinic, 2008–2009	75 ± 6.9 83% women Not reported	x			41
Nightingale (2015)[39]	Newly diagnosed cancer patients at an oncology clinic 2011–2013	80 ± 7.4 64% women 74% white	x		x[h]	51
DiNapoli (2016)[34]	Veterans with a new mental health diagnosis in Pittsburgh 2007–2011	77 ± 6.4 2% women 85% white			x	20
Ie (2017)[40]	Family Medicine physicians >18 y and their patients at five practices, 2016	36 ± 10.6 50% women Not reported	x			Not reported
Nationally representative survey						
Zhang (2011)[21]	Community-dwelling adults who responded to the Medical Expenditure Panel Survey, 2007	Not reported 58% women 80% white		x		14
Kachru (2015)[22]	Community-dwelling adults who responded to the Medical Expenditure Panel Survey, 2009–2010	Not reported 57% women 80% white			x[i]	10
Extavour (2016)[24]	Community-dwelling adults from the National Ambulatory Medical Care Survey, 2010	75 ± not reported 62% women 95% white			x[j]	11
Miller (2016)[23]	Community-dwelling adults who responded to the Medical Expenditure Panel Survey, 2006–2010	Not reported 58% women 80% white	x			31
Swanoski (2017)[37]					x[k]	Not reported

Table 1 Continued

Author	Study population[a]	Demographic characteristics of participants Mean age (y ± SD); Sex and race (%)	PIM criteria used Beers	Zahn	Other	Prevalence of PIM use (%)
	Community-dwelling adults with diabetes who take two or more medications from the National Ambulatory Medical Care Survey, 2012	Not reported 56% women 82% white				
Other						
Weston (2010)[26]	Persons with mild cognitive impairment from Alzheimer's Disease Research Centers of California, 2008–2009	75 ± 9.8 50% women 77% white			x [l]	21
Koyama (2013)[33]	Women enrolled in the Study of Osteoporotic Fractures, 1997–2008	78 ± 3.1 100% women 89% white			x [l]	24
Mattos (2016)[38]	Pennsylvania pharmaceutical assistance programme participants, 2010–2011	79 ± 6.7 89% women 91% white			x[m]	18
Shade (2017)[41]	Patients at a rural clinic who are on three or more medications, 2015	78 ± 7.3 44% women 98% white	x			49

PIM, potentially inappropriate medication; y, year.
[a]All participants are age 65 years and older, unless otherwise stated.
[b]Healthcare Effectiveness Data and Information Set.
[c]Prevalence differed by region.
[d]Prevalence differed by PIM criteria used.
[e]Prevalence differed by year.
[f]Antipsychotics.
[g]Prevalence differed by PIM criteria used.
[h]Healthcare Effectiveness Data and Information Set, Screening Tool of Older Persons Prescriptions.
[i]Anticholinergics.
[j]Antidepressants and sedatives.
[k]Medications inappropriate in diabetes per Beers criteria.
[l]Beers Criteria 2003 inappropriate in cognitive impairment.
[m]Benzodiazepine receptor agonists.

systems involved in chronic disease.[26] Only two studies found that a higher comorbidity score was associated with more risk.[37,39] Eight studies[22,26,28,30,32,34,38,39] specifically examined psychiatric comorbidities and PIM use; seven found that patients with one or more psychiatric comorbidities had more PIM use.[26,28,30,32,34,38,39] Individual comorbidities other than dementia were not consistently associated with PIM use.[27,30–32,34,39] The association of dementia or cognitive impairment with PIM use was assessed in five studies,[22,25,27,30,34] and worse cognition or diagnosis of dementia was statistically significant in two.[25,27] Four studies examined functional status of older patients and risk of PIM use and found no statistically significant association.[22,30,31,34,39]

Clinician factors

Only three studies evaluated clinician factors contributing to PIM use in community-dwelling older adults or those attending ambulatory clinics (Table 3).[27,32,40] Two[27,32] of these studies used nationally representative samples, and one[40] was a survey of five family practice clinics. All three used multivariable analysis with the two nationally representative studies adjusting for some combination of patient, system and clinician factors[27,32] and the smaller survey study adjusting for a combination of clinician factors.[40]

In NAMCS respondents, less time spent with patients was associated with a statistically significant higher risk of potentially inappropriate antidepressant exposure; being seen by a neurologist or psychiatrist compared to someone of another specialty was associated with a statistically significant higher risk PIM prescribing.[32] Amongst a random sample of Medicare beneficiaries,[27] patients seen by geriatricians were less likely to receive a PIM than if they were not seen by a geriatrician.

In the survey conducted in five family practice clinics,[40] clinicians who prescribed fewer PIMs were more

Table 2 Study design, associations of investigated factors with of potentially inappropriate medication (PIM) and risk of bias[a]

Author, year Study design	Criteria used to define PIM	Patient factors	System/Environment factors	Clinician factors	Risk of bias
Administrative data					
Zhang (2010)[27] Cross-sectional	HEDIS medications considered to be high risk and potential drug–disease interactions	None	Adjusted annual gross drug spending per beneficiary and **adjusted annual gross non-drug medical spending [higher non-drug spending]**	None	Low
Woelfel (2011)[20] Cross-sectional	Beers Criteria 1997	Age, sex, self-reported health status, **number of medications per patient [higher]**	None	None	Low
Blackwell (2012)[29] Cross-sectional	Beers Criteria 2003 excluding those with dose requirements or disease requirements	**Age [65–74, ref: 75+], race/ethnicity [white, ref: black/other] sex [female, ref: male], disease burden [low, ref: medium-low], number of medications [higher]**	**Geographic region [midwest, south, west, other, ref: northeast], dual enrollee status [ref: non-dual enrollee]**	None	Low
Holmes (2013)[31] Cross-sectional	Beers Criteria 2003 – excluding drug-disease combinations	Age, **sex [female, ref: male], race/ethnicity [black, ref: white], hospitalization in the year prior to PIM use (2007) [not hospitalized at least once, ref: hospitalized at least once]** nursing home stay in 2008, comorbidity score (Elixhauser), **total number of medications in 2008 [six or more medications, ref: <5 medications], number of different prescribers [two or more prescribers, ref: 1 prescriber]**	**Eligibility for low-income subsidy [eligible, ref: not eligible]**	None	Low
Lund (2013)[32] Cross-sectional	Four methods: Zhan Criteria, modified Fick Criteria, therapeutic duplication, drug–drug interactions	None	Zhan criteria: **rural [ref: urban], midwest, west, south [ref: northeast], Rural northeast [ref: urban northeast], urban midwest [ref: rural midwest], urban west [ref: rural west], rural south [ref: urban south]** Fick criteria: **rural [ref: urban], midwest, west, south [ref: northeast], Rural northeast [ref: urban northeast], rural midwest, urban west [ref: rural west], rural south [ref: urban south]**	None	Low
Jiron (2016)[35] Retrospective cohort	Beers Criteria 2012 – all medications inappropriate and all medications to be used with caution	**Age [66–69 years, ref: 70+], sex [female, ref: male], race [white, ref: Asian, Hispanic], myocardial infarction [absence, ref: presence], CHF [presence, ref: absence]**, peripheral	**Geographic region [south or west, ref: northeast]**	**Prescriber is a geriatrician [is a geriatrician, ref: provider is not a**	Low

Table 2 Continued

Author, year Study design	Criteria used to define PIM	Patient factors	System/Environment factors	Clinician factors	Risk of bias
		vascular disease, **cerebrovascular disease [presence, ref: absence] dementia [presence, ref: absence]**, chronic obstructive pulmonary disease, rheumatic disease, **peptic ulcer disease [presence, ref: absence]** mild liver disease, **diabetes without complications [presence, ref: absence], paraplegia and haemiplegia [presence, ref: absence] renal disease [absence, ref: presence],** diabetes with chronic complications, **cancer [absence, ref: presence], moderate or severe liver disease [presence, ref: absence],** metastatic cancer, AIDS/HIV, polypharmacy, **number of prescription medications filled per month [3 or more, ref: less than 3], number of outpatient visits [13+, ref: >13], number of ED visits [1 or more, ref: none],** number of hospital visits, any hospital admission, any outpatient visits, **number of prescribers per month [2 or more, ref: less than 2],** number of prescriber specialties per month		**geriatrician],** general practitioner/family practice/internist, other specialty	
Kester (2016)[36] Prospective cohort	Antipsychotic medications (1st and 2nd generation)	**Age [higher], sex [female, ref: male],** hierarchical condition category, **diagnosis of depressive disorder [presence, ref: absence], diagnosis of substance use disorder [presence, ref: absence]**	**Geographic region [south, ref: midwest, west], dual eligible status [ref: non-dual eligible]**	None	Low
Chart review					
Buck (2008)[25] Cross-sectional	Beers Criteria 2002 and Zhan Criteria independent of diagnoses	**Age [older], sex [female, ref: male],** **polypharmacy [>6 medications, ref: <6]**, race, **number of primary care clinic visits [more visits]**	None	None	Low
Hu (2012)[28] Cross-sectional	Beers Criteria 2002 excluding disease dependent	**Age [81+, ref: <81]**, sex, education, marital status, post-hospital residence, primary language, English proficiency, Chinese proficiency, **number of medications at discharge [≥ 8 medications, ref: <8],**	Hospitalized on medical unit	None	Low

Table 2 Continued

Author, year Study design	Criteria used to define PIM	Patient factors	System/Environment factors	Clinician factors	Risk of bias
		number of medications at home care admission, **length of hospital stay [≥6 days, <6 days]**			
Prithviraj (2012)[30] Cross-sectional	Beers Criteria 2003 excluding drug–disease interactions	Age, sex, race, marital status, education, living situation, **body mass index [≥19, ref: body mass index <19],** cancer type, cancer stage, receipt of surgery, comorbidity count, Charlson comorbidity index, Eastern Cooperative Oncology Group (ECOG) score, hearing and vision impairment on 5-point scale, patient self-reported falls in the last 6 months, MMSE, **number of medications [≥5 medications, ref: <5 medications],** Geriatric depression scale, medical outcomes study social support survey, composite variable 'geriatric deficits' (≥1 deficit in MMSE, geriatric depression scale, hearing and vision questionnaire, social support survey)	None	None	Low
Nightingale (2015)[39] Cross-sectional	Beers 2012, STOPP 2008 and HEDIS 2011	Age, sex, race, cancer type and stage, **number of comorbidities [higher],** Eastern Cooperative Oncology Group (ECOG) performance status, functional status (fit, vulnerable, frail), **moderate polypharmacy [5–9 medications, ref: <5 medications], excessive polypharmacy [10+ medications, ref: <5 medications], presence of comorbidities [cardiovascular, neurologic, psychiatric, gastrointestinal]**	None	None	Moderate
DiNapoli (2016)[34] Prospective cohort	Online drug database (clinicalpharmacology.com Elsevier Gold Standard) and VA provider input	Age, race, marital status, **two or more mental health diagnoses [ref: 1],** number of chronic organ system diseases	VA service connection status	None	Low
Ie (2017)[40] Cross-sectional	Beers Criteria, 2015	None	None	**Lack of benefit/risk information about deprescribing is a barrier to**	Moderate

Table 2 Continued

Author, year Study design	Criteria used to define PIM	Patient factors	System/Environment factors	Clinician factors	Risk of bias
				deprescribing, number of medications, **proportion of minority patients [low, ref: high], proportion of patients ≥75 [low, ref: high]**, use of the beers list	
Nationally representative survey					
Zhang (2011)[21] Cross-sectional	Zhan criteria	Age, **sex [female, ref: male],** race/ethnicity, **family income [middle, ref: high]**, education level, **self-rated health [fair, poor, ref: excellent]**, **number of prescriptions [higher]**	Medicare status, Medicare part D coverage, metropolitan statistical area, **geographic region [south, ref: northeast]**	None	Low
Kachru (2015)[22] Cross-sectional	Beers Criteria 2012, anticholinergics only	**Age [<74, ref: age>75], sex [female],** race, marital status, **education [<12 years of education, ref: >15 years],** family income, usual source of care, needs help with ADLs, needs help with iADLs, self-reported health, mental health status, comorbidities: epilepsy, dementia, fractures, Parkinson's, benign prostatic hyperplasia, CHF, arrhythmia, mood disorder, **anxiety [presence, ref: absence]**, urinary incontinence	Metropolitan statistical area, **geographic region, [south, ref: northeast]**	None	Low
Extavour (2016)[24] Cross-sectional	Beers Criteria 2012/2015 Sedatives or Antidepressants	**Sedative hypnotics: sex [female, ref: male]**, **race [white, ref: other],** ethnicity, **chronic renal failure [absence, ref: presence], depression [presence, ref: absence]**, **diabetes [absence, ref: presence]**, **obesity [absence, ref: presence]**, chronic obstructive pulmonary disease, **number of medications [higher]**, **household income [40,627–52,387, ref: highest income]** **Antidepressants: race [other, ref: white], depression [absence, ref:**	**Sedative hypnotics:** practice ownership, use of electronic health record **Antidepressants:** metropolitan statistical area, **computer system features prescribing [no, ref: yes]** **payment type [private self-pay, ref: other]**, payment type (Medicare Medicaid)	**Sedative hypnotics: specialty [neurology, ref: other], [psychiatry, ref: other],** physician assistant involvement **Antidepressants: time spent with patient [less time]**, physician specialty	Low

Table 2 Continued

Author, year Study design	Criteria used to define PIM	Patient factors	System/Environment factors	Clinician factors	Risk of bias
		presence], asthma [absence, ref: presence], osteoporosis [absence, ref: presence], annual household income			
Miller (2016)[23] Cross-sectional	Beers Criteria 2012	**Age [65–74 ref: 75–84, 85+],** sex, race, marital status, **education [less than high school, ref: high school graduate or post-graduate education],** income, risk taking, usual source of care, self-rated health status, self-rated mental health status, ADL limitations, iADL limitations, **cardiovascular condition [absence, ref: presence]**, central nervous system condition, mental health disorder, **arthritis [presence, ref: absence],** diabetes; **number of medications [higher]**	geographic region, metropolitan statistical area, health insurance status	None	Low
Swanoski (2017)[37] Survey	Beers 2012 criteria, drugs inappropriate in diabetes	**Age [75+, ref: 65–74], sex [female, ref: male], race/ethnicity [all other races/ethnicities, ref: non-Hispanic Caucasian], visit reason [other, ref: new problem], visit reason [chronic problem, routine, ref: other], visit reason [chronic problem, flare-up, ref: other], visit reason [preventive care, ref: other], two or more visits in year [ref: one or fewer]**	**Geographic region of physician [rural, ref: urban]**	None	Low
Other					
Weston (2010)[26] Cross-sectional	Beers Criteria 2003 inappropriate in cognitive impairment, additional medications per authors' discretion	Age, race/ethnicity, **sex [female, ref: male],** education, living situation, **number of medications [higher]**, functional status, MMSE score, history of hypertension, urinary incontinence, history of diabetes, anti-dementia drug use, history of stroke, history of myocardial infarction, **history of depression [presence, ref: absence]**	Insurance status	None	Low
Koyama (2013)[33] Prospective cohort	Beers Criteria 2003 inappropriate in cognitive impairment, additional medications per authors' discretion	**Cognitive status (dementia versus mild cognitive impairment versus normal) [at 10-year follow-up, dementia>mild cognitive impairment> normal cognition]**	None	None	Low

Table 2 Continued

Author, year Study design	Criteria used to define PIM	Patient factors	System/Environment factors	Clinician factors	Risk of bias
Mattos (2016)[38] Cross-sectional	Benzodiazepine receptor agonists and non-benzodiazepine sleep aids	Age, sex, race, marital status, **depression or anxiety diagnosis [presence, ref: absence], total number of medications [higher],** level of education	**Rural [ref: urban]**	None	Moderate
Shade (2017)[41] Cross-sectional	Beers 2012	Age, comorbidity score, mental component score, total sleep time, wake after sleep onset, wake percentage, PROMIS **Number of medications [higher],** number of prescribers, physical component score, Pittsburgh sleep quality index	None	None	Low

ADL, activities of daily living; CHF, congestive heart failure; ED, emergency department; HEDIS, Healthcare Effectiveness Data and Information Set; iADL, independent activity of daily living; MCO, managed care organization; MDS, minimum data set; MEPS, Medical Expenditure Panel Survey; MMSE, Mini-Mental State Exam; NAMCS, National Ambulatory Medical Care Survey; PIM, potentially inappropriate medications; Ref, reference group; VA, veterans affairs.
[a]Bold – significant factors [positive association with PIM use].

likely to consider risks and benefits of deprescribing and the number of medications on the medication list when making prescribing decisions. Physicians who had a higher proportion of patients >75 years or a higher proportion of minority patients were also less likely to prescribe PIMs. The associations of physician sex, years of clinical experience and prescribing confidence with PIM prescribing were not statistically significant.

System/Environmental factors

Fifteen studies evaluated system-level factors contributing to PIM use (Table 3); all 15 used multivariable analyses.[21,23,24,26–32,34–38]

Geographic region

Seven studies examined the association between geographic region and PIM use with nationally representative data including Medicare claims,[27,28,37] MEPS[21,30,31] and national Veterans Affairs data.[24] The association between geographic region of the United States with PIM use was statistically significant in six studies.[21,24,27,28,30,37] The south was associated with more PIM use in all six, the west in three[24,27,37] and the midwest in two.[24,37] Each used the northeast as a reference group, except for one[28] where the west and midwest were the reference groups. Rural rather than urban site of care was statistically significant in three studies.[24,29,38] Two of the studies that found a statistically significant result used a more restrictive definition of PIM, such as medications inappropriate to use in patients with diabetes,[29] or benzodiazepines and non-benzodiazepine sleep aids.[38] However, one study that reported no statistically significant association between rural site of care and PIM use limited the evaluation to medications inappropriate to use in patients with cognitive impairment or dementia.[30]

Health insurance

Two studies that explored whether dual Medicare–Medicaid enrollee status was associated with PIM use reported that dual enrollees were at higher risk.[28,37] Two[21,34] studies examining insurance type did not report a statistically significant association with PIM use.

Discussion

Potentially inappropriate medication use is heterogeneous across older community-dwelling adults and those attending ambulatory clinics. Based on studies in this review, PIM use is higher in those taking more medications. Women and older adults with more psychiatric comorbidities or

more outpatient and emergency department visits may also be at higher risk. Living in the south is associated with higher PIM use in several studies. The clinician determinants of PIM use have not been well studied.

The association between an increased number of outpatient and emergency department visits and PIM use, as well as the association between receipt of more medications and PIM use, suggests that more frequent contact with the healthcare system may be a risk factor for PIM use. Indeed, a number of the other statistically significant associations identified in our review are associated with increased healthcare utilization. Women are known to be higher utilizers of health care than men[43] as are persons with more psychiatric comorbidities.[44] More frequent interaction with the healthcare system results in more care, which may also result in care that is inappropriate.[45] Although the associations described in our included studies do not prove causality, there is additional evidence to support this hypothesis.[46]

Relatedly, care that is fragmented across providers has been associated with overuse of health care.[47] In this review, we included articles that reported statistically significant associations between having multiple prescribers and higher risk of PIM use. Indeed, older adults frequently receive fragmented care.[48,49] A study from 2007 reported that a Medicare beneficiary will consult two primary care physicians and five specialists working in four different practices in a year.[48] It is plausible that when a patient consults multiple prescribers, no single prescriber feels responsible for review and management of the patient's medication list.

Clinician factors were rarely studied, which seems to be an important omission preventing a full understanding of the phenomenon of PIM use. One study in this review that examined clinician specialty found that geriatricians were less likely to prescribe a PIM than non-geriatricians,[27] while another study found that psychiatrists and neurologists were more likely to prescribe inappropriate sedatives.[32] The latter study did not specifically examine prescribing by geriatricians. Only one study in this review examined individual physician characteristics such as demographics, number of years in practice and confidence in prescribing, but this was not statistically significant.[40]

Although our study was limited to the United States, our findings are consistent with systematic reviews in other high-income countries.[50,51] For example, a systematic review of potentially inappropriate prescribing in community-dwelling elderly in Europe also reported that polypharmacy and depression were risk factors for receiving inappropriate medications.[52] Similarly, a systematic review of risk factors for PIM use amongst community-dwelling elderly from numerous countries, including the United States, reported that female sex and a greater number of medications were most commonly associated with increased risk of PIM use.[50] However, that review was limited to studies that used administrative data to identify PIM use. In addition to confirming those findings, our review expands upon this by including studies which use other sources of data such as survey data and chart review. These data sources provide evidence about clinician- and system-level determinants, in addition to patient-level determinants.

Thinking about these findings in the context of the behavioural model of healthcare use,[53] we can identify potential targets for intervention. This model posits that healthcare use is determined by predisposing factors (e.g. age and gender), enabling factors (e.g. health insurance) and need (e.g. perceived or evaluated need for a treatment). Many of the studies included in this review examined predisposing factors of patients, which are often not modifiable. Similarly, the finding that a higher count of medications is associated with PIM use may reflect that these individuals have high healthcare needs, which also may not be easily modifiable. These determinants, however, might be addressed by educating providers about higher risk of PIM use in certain patient populations. Enabling factors, such as census region and number of healthcare visits, may present opportunities for intervention. Census region is probably capturing variation in provider availability and provider practice patterns that might respond to locally targeted interventions; the number of healthcare visits may be capturing fragmentation of care that might improve with care coordination. Further research is needed to identify precise targets and interventions.

Our review has limitations. Only studies of persons in the United States were included, so our findings may not be transferrable to other countries. However, as noted above our findings are consistent with previous studies in other high-income countries. Although a broad search strategy including a hand search of references was used, studies that focused on a single inappropriate medication or a single class of medications may have been missed. Additionally, included studies focus on *potentially* inappropriate medications, not *certainly* inappropriate medication use. Considering the heterogeneity in ageing, there are patient circumstances where the benefits of a medication classified as a PIM outweigh the risks of that individual. The data sources (large surveys and claims) are typically unable to capture this subjective decision-making, and thus, some of the medication use classified as PIM use may be a misclassification. Additionally, these data sources often fail to capture over the counter medication use, another important source of PIMs. Importantly, most of the studies cannot make strong causal inferences about the studied risk factors and PIM use

Table 3 Associations of commonly investigated factors with potentially inappropriate medication (PIM) use

	Patient factors								
	No. of medications[a]	Increasing age[b]	Female sex[c]	Race and ethnicity[d]	Level of education	Marital status	No. outpatient/ ED visits	No. of hospital admissions	No. of prescribers
Administrative data									
Zhang (2010)[27]g									
Woelfel (2011)[20]	+	0	0						
Blackwell (2012)[29]	+	–	+	+					
Holmes (2013)[31]	+	0	+	+				+	+
Lund (2013)[32]									
Jiron (2016)[35]	+	–	+	+			0	0	+
Kester, 2016)[36]		+	+						
Chart review									
Buck (2008)[25]	+	+	+	0			+		
Hu (2012)[28]	+	–	0			0			
Prithviraj (2012)[30]	+	0	0	0	0	0			
Nightingale (2015)[39]	+	0	0	0					
DiNapoli (2016)[34]		0		0					
Ie (2017)[40]									
Nationally representative survey									
Zhang (2011)[21]	+	0	+	0	0				
Kachru (2015)[22]		–	+	0	–	0			
Extavour (2016)[24]	+		+	0					
Miller (2016)[23]	+	–	0	0	0				
Swanoski (2017)[37]		–	+	+			+		
Other									
Weston (2010)[26]	+	0	+		0				
Koyama (2013)[33]									
Mattos (2016)[38]	+	0	0	0	0	0			
Shade (2017)[41]	+	0							0

No., number; +, positive association with risk of PIM use; –, negative association with risk of PIM use; 0, no statistically significant association with risk of PIM use.

[a]Number of medications examined as a continuous and categorical variable across studies.

[b]Age was examined as a continuous and categorical variable with categories ranging from 5 to 20 years.

[c]Male sex was examined in all 16 studies and was significant in 0 studies.

[d]Results were conflicted with varying reference groups.

[e]Specialties examined varied.

[f]Results were conflicting with studies comparing varying payer types. Two studies, which looked specifically at Medicare–Medicaid dual eligibility, found a significant positive association.

[g]This study did not examine any of the listed characteristics, it examined adjusted gross spending, see Table 1.

given limitations in their methods – these reported 'determinants' might best be considered to be associations.

A number of potential risk factors for PIM use in community-dwelling older adults and those seeking ambulatory care are reported in this review. Our findings add to the literature regarding the risks associated with multiple medications. Studies designed to rigorously assess the causal relationship between multiple medication use and PIM use are needed to determine which factors directly lead to increased PIM use, so these factors can be targeted with an intervention. Similarly, the potential link between increased contact with the healthcare system and risk of PIM use warrants targeted analysis to determine whether the appropriate target of an intervention to curb PIM use is care coordination, continuity or a different point of intervention.

Conclusion

This review supports that the risk of PIM exposure varies amongst community-dwelling older adults and those seen in ambulatory clinics. Patient factors such as sex and the number of medications have been well described; however, more research is needed focusing on prescriber characteristics and the causal relationship between these factors and PIM use.

	Clinician factors								System factors		
	More medical comorbidity	Presence of psychiatric comorbidity	Worse functional status	Cognitive impairment	Clinician age, sex, years of experience	Time spent	Proportion of patients >75 years	Specialty[e]	Geographic region (south)	Rural site of care	Insurance type[f]
	+								+		+
	0										
									+	+	
				+				+	+		
	0	+							+		+
	0	0	0	0							
	+		0								
	0	+									
							+				
									+	0	0
		+	0						+	0	
		+				–		0		0	0
			0						0	0	0
									+		
		+	0	0							
				+							
		+								+	
	0	0									

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

RS and JS developed the search strategy. SN, RS, AO and MJ reviewed and pilot-tested the data extraction tool, and

reviewed and abstracted studies. All authors contributed to, reviewed and provided critical feedback on the manuscript. All Authors state that they had complete access to the study data that support the publication.

Ethical approval

The work in this manuscript did not require ethical approval because it was a systematic review of published literature.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. PRISMA-P 2015 checklist.

Appendix S1. Listing of search terms.

Figure S1. Flow diagram of inclusion and exclusion process.

