

Research Paper

Potentially Inappropriate Medications in Indian Geriatric Patients Visiting Out-patient Departments of Tertiary Care Teaching Hospital

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Abstract

Aim: To investigate the prevalence of potentially inappropriate medications (PIMs) identified by the American Geriatrics Society Beers 2019 criteria in geriatric patients in India. **Materials and Methods:** This cross-sectional study was conducted between October 2018 and October 2019 in the tertiary care teaching hospital of the Gujarat state, India. Patients of either sex attending outpatient departments of age 65 years and above were included. Data including age, gender, department, relevant laboratory investigations, prescribed drugs, dosages, and duration was recorded in the Case Record Form. PIMs identified as per 2019 Beers criteria and analyzed. The association between age, gender, polypharmacy and encounter of PIMs was analyzed. **Results:** A total of 306 patients were analyzed. Mean age of patients was 69.43 (standard deviation = 5.47) years and 185 (60.46%) were male. At least one PIM was prescribed in 46% (140) patients. Two or more PIMs were prescribed in 18.6% of patients. The most frequent PIMs independent of diagnosis and condition (Criteria 1) were first-generation antihistaminics 25.7%, skeletal muscle relaxants 21% and sulfonylureas (glimepiride) 17.4%. The most common drugs to be used with caution (Criterion 3) included tramadol 50.75%, diuretics 25.4%, and antipsychotics 13.5%. Patients who were on polypharmacy were at significantly high ($P < 0.001$) risk of PIM use with an adjusted odds ratio 4.864 (95% confidence interval: 2.95–8.03). **Conclusion:** Our study showed a high prevalence of PIMs use in Indian geriatric patients. There was an association between inappropriate medication use and polypharmacy.

Keywords: Beers criteria 2019, geriatric, polypharmacy, potentially inappropriate medications

INTRODUCTION

According to the Indian Population Census 2011, there are nearly 104 million geriatric persons (aged 60 years or above) in India, 53 million females and 51 million males. The life expectancy at birth during 2009–2013 was 69.3 for females as against 65.8 years for males.^[1] Aging-related physiological alterations such as reductions in kidney, liver, and cardiac activity can significantly change the pharmacokinetic and pharmacodynamic properties of drugs. It predisposes geriatric patients to drug-related problems, such as adverse drug reactions (ADRs), drug–drug interactions, and drug–disease interactions.^[2]

Potentially inappropriate medications (PIMs) can be defined as drugs for which use among geriatric patients should be avoided due to the high risk of adverse reactions for this population and/or insufficient evidence of their benefits when

safer and equally or more effective therapeutic alternatives are available.^[3] PIMs are those that are regarded as being high risk or less effective in geriatric persons when used in the presence of safer and more effective alternatives.^[4] Inappropriate medication prescribing in geriatric patients has become a public health concern due to its high prevalence,^[5] associated negative outcomes, including ADRs, morbidity, hospitalization, health services use, and increased costs.^[6–9]

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Various studies were conducted in many countries using globally developed tools for screening this phenomenon.^[10] Since 2011, the American Geriatrics Society (AGS) has been the steward of the Beers criteria and has produced updates on a 3-year cycle. The criteria were first published in 1991, making them the longest-running criteria for PIMs in the geriatric population. The Beers Criteria is an explicit list of PIMs that are typically best avoided by geriatric patients in most circumstances or under specific situations, such as in certain diseases or conditions. The last updated version of the AGS Beers Criteria was released in January 2019 with nearly 70 modifications to the 2015 AGS Beers Criteria. The goal of the 2019 update of AGS Beers Criteria continues to be refining geriatric care by reducing their exposure to PIMs^[11]

Very few Indian studies have systemically examined PIMs prescribing among geriatric patients. Common PIMs detected by older versions of Beers Criteria in Indian patients include H₂ blockers, proton pump inhibitors, mineral oil, diuretics, benzodiazepines, peripheral α 1 blockers, first-generation antihistamines, digoxin and nonsteroidal anti-inflammatory drugs (NSAIDs).^[12-16] There were many risk factors associated with PIMs use in these studies. One of the most common risk factor was polypharmacy (prescription with five or more medications).^[17]

However to our knowledge; no Indian study has been found which identifies PIMs using the latest updated version (2019) of the AGS Beers Criteria. Therefore, the main objectives of this study were to investigate the prevalence and predictors of PIMs prescribing particularly polypharmacy among Indian geriatric outpatients using the AGS Beers 2019 Criteria.

MATERIALS AND METHODS

This cross-sectional study was conducted at a tertiary care teaching hospital in the Gujarat state of India. Patients of either sex attending outpatient departments of aged 65 years and above were randomly enrolled from October 1, 2018 to October 31, 2019. If a patient had more than one visit for a prescription refill within the study period, only the first occurrence was used in the analysis. Patients without any medications were excluded from the study. This study was approved by the institutional ethics committee.

From case sheets, data including age, gender, department, primary diagnosis, relevant laboratory investigations particularly serum creatinine (if done), prescribed drugs, dosages, and duration and PIMs as per the 2019 AGS-Beers criteria^[11] was recorded in the Case Record Form after getting their informed consent. Creatinine Clearance (CrCl) was calculated using the Modification of Diet in Renal Disease^[18] equation. The entire course of prescribed medications for each case record was entered in the Microsoft Excel sheet.

Evaluation of potentially inappropriate medications

The PIMs were evaluated and grouped under five criteria according to the 2019 AGS-Beers Criteria:

- Criteria 1: Independent of diseases or diagnosis
- Criteria 2: Drug–drug interactions
- Criteria 3: Used with caution
- Criteria 4: Drug-disease/drug-syndrome interactions and
- Criteria 5: Impaired kidney function (reduced CrCl).

Statistical analysis

All analyses were conducted using Microsoft Excel version 2010. The significance and association between age (65–74 years vs. ≥ 75 years), gender and polypharmacy, and encounter of PIMs were analyzed using Chi-square test and odds ratio (OR). Value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 306 geriatric patients were scrutinized in 1 year study period. The age of the patients ranged from 65 to 93 years. The average age of patients reported in this study was 69.43 ± 5.47 years. 185 (60.46%) were male and 121 (39.54%) were female.

In the 306 prescriptions analyzed, there were a total of 1542 medications. On average, each patient was prescribed 5.04 ± 2.44 drugs (range: 1–13).

Out of the total study population, 115 (37.58%) patients belonged to the medicine department, followed by orthopedics department 69 (22.55%) and dermatology department 48 (15.7%). The most common diagnoses observed were hypertension (23%), back and knee pain (19.6%), Type 2 diabetes mellitus (11.8%), ischemic heart disease (8.5%), and Eczema (7.8%).

Frequency of potentially inappropriate medications

Out of 306 geriatric patients, 140 (45.75%) patients received at least one PIM. Total PIMs encountered in 140 patients were 176; so on an average, one patient received 1.26 ± 0.61 PIMs.

The use of multiple PIMs was fairly common. Two patients (1.43%) received the highest 4 PIMs. Seven patients (5%) and 17 (12.14%) patients received 3 PIMs and 2 PIMs, respectively while 114 (81.43%) patients received one PIM in their prescription.

Out of 140 PIMs users, 109 (55.33%) prescriptions satisfied first criteria and 67 (34.01%) satisfied third criteria. Criteria 2, 4 and 5 were satisfied in 6 (3%), 8 (4%) and 7 (3.5%) prescriptions, respectively. The total exceeds 100% as there were patients who were prescribed more than one PIM.

As per Criteria 1 most frequently prescribed PIMs class was first generation antihistaminics (pheniramine and chlorpheniramine) 25.7%, skeletal muscle relaxant (SMRs) (chlorzoxazone and methocarbamol) 21%, sulfonylureas (glimepiride) 17.4% and benzodiazepines (lorazepam and Clonazepam) 11%. Most common drugs used with caution (Criterion 3) included tramadol

50.75%, diuretics (furosemide and spironolactone) 25.4%, and antipsychotics (olanzapine and quetiapine) 13.5% [Table 1].

The most common drug-disease interaction (Criteria 2) being chronic kidney disease combined with offending agents NSAIDs ($n = 5$). The most frequent drug-drug interaction which should be avoided (Criteria 4) was five prescriptions of tramadol and pregabalin. Tramadol was used in 3 patients with impaired kidney function (criteria 5) [Table 2].

Age and gender were not associated with PIM prescription. Patients who were on polypharmacy were at significantly higher ($P < 0.001$) risk of PIM use [Table 3].

DISCUSSION

To our knowledge, there is no study which identifies PIMs as per the latest AGS Beers 2019 criteria as per PubMed and Google scholar search. Hence the data of this study is compared with PIM studies using previous versions of Beers criteria.

The mean age of patients (69.43 ± 5.47 years) of our study was comparable with the study done in the same city (69.34 ± 5.26 years),^[13] South India (73.6 ± 6.7 years),^[15] and Goa (68.88 years).^[16]

In our study, 39.54% of patients were female, which is similar to a study done in a tertiary teaching hospital of Goa (35%).^[16]

Hypertension and diabetes mellitus were similar comorbidities found in an Indian study.^[12,15] This is due to most Indian studies were performed in medicine outpatient units or medicine wards. Our study had many patients from orthopedic and dermatology departments so pain and eczema were other common comorbidities detected.

In our study, 45.75% was the prevalence of PIMs versus According to the Beers criteria 2015, the prevalence of PIMs was 34.0% (95% confidence interval [CI]: 29.4–38.6)^[15] and 66%.^[16] In a study from Jordan outpatients department 62.5% of patients were found to have at least one PIM prescribed by 2015 criteria.^[19] In 2015, Davidoff *et al.* performed a retrospective cohort study and found that 42.6% of geriatric patients were receiving one or more PIM in the United States,^[20] which is similar to our study.

In our study out of total PIM users, 81.43% received one PIMs and highest 4 PIMs in 2 patients while south Indian study^[15] with Beers 2015 criteria shows 108 (79.4%) had one, 23 (16.9%) had two, and 5 (3.7%) had three PIMs and no prescription with 4 PIMs. The majority of patients of Jordan were prescribed one (39.6%) or two (23.3%) PIMs as per Beers 2015 criteria, however, prescribing of three (15.8%) or four (7.6%) PIMs were also common like our study.^[19] The assumption is that hospitals associated with teaching colleges

Table 1: Frequency distribution of the PIMs as per criteria 1 and 3 of Beers 2019

Therapeutic category/class	Drug	Number of patients	Percentage of patients	Strength of recommendation
Criteria 1: PIMs used independent of diagnosis or disease in geriatric patients				
Skeletal muscle relaxants	Chlorzoxazone	20	18.35	Strong
	Methocarbamol	3	2.75	Strong
First-gen antihistamines	Pheniramine	17	15.60	Strong
	Chlorpheniramine maleate	11	10.09	Strong
Sulphonylureas, long acting	Glimepiride	19	17.43	Strong
Benzodiazepines	Lorazepam	8	7.34	Strong
	Clonazepam	4	3.67	Strong
Antispasmodics	Dicyclomine	8	7.34	Strong
	Hyoscine butyl bromide	2	1.83	Strong
Antipsychotics, second generation	Olanzapine	6	5.50	Strong
	Quetiapine	3	2.75	Strong
Mineral oil	Liquid paraffin	4	3.67	Strong
Central alpha-agonists	Clonidine	1	0.92	Strong
Antiparkinsonian agent	Trihexyphenidyl	2	1.83	Strong
Digoxin	Digoxin 0.25 mg	1	0.92	Strong
Criteria 3: PIMs to be used with caution in geriatric patients				
Tramadol	Tramadol	34	50.75	Strong
Diuretics	Furosemide	11	16.42	Strong
	Spironolactone	6	8.96	Strong
Antipsychotics	Olanzapine	6	8.96	Strong
	Quetiapine	3	4.48	Strong
SSRIs	Escitalopram	4	5.97	Strong
	Fluoxetine	1	1.49	Strong
Carbamazepine	Carbamazepine	1	1.49	Strong
Dextromethorphan	Dextromethorphan	1	1.49	Strong

PIMs=Potentially inappropriate medications

Table 2: Frequency distribution of the PIMs as per criteria 2, 4 and 5 of Beers 2019 criteria

Criteria 2: PIMs due to drug-disease/drug syndrome interactions that may exacerbate the disease or syndrome			
Drug (drug class)	Disease and syndrome	Number of patients	Strength of recommendation
Paracetamol (NSAIDs)	Chronic kidney disease stage 4 or higher	3	Strong
Aspirin (NSAIDs)	Chronic kidney disease stage 4 or higher	2	Strong
Quetiapine (antipsychotic drug with strong anticholinergic property)	Dementia or cognitive impairment	1	Strong
Criteria 4: Potentially clinically important drug-drug interactions that should be avoided			
Object drug (class)	Interacting drug (class)	Number of patients	Strength of recommendation
Tramadol (opioids)	Pregabalin	5	Strong
Fluoxetine (selective serotonin reuptake inhibitor-CNS active drug)	Olanzapine (antipsychotic drug - CNS active drug), clonazepam (benzodiazepine - CNS active drug)	2	Strong
Risperidone (anticholinergic)	Trihexyphenidyl (anticholinergic)	1	Strong
Criteria 5: Medications that should be avoided or reduce dosage with varying levels of kidney function in geriatric patients			
Medication	CrCl of patients	Number of patients	Strength of recommendation
Tramadol	Avoid if CrCl is <30	3	Strong
Pregabalin	Reduce dose if CrCl is <60	2	Strong
Ranitidine	Reduce dose if CrCl is <50	2	Strong

PIMs=Potentially inappropriate medications, CrCl=Creatinine clearance, CNS=Central nervous system, NSAID=Nonsteroidal anti-inflammatory drugs

Table 3: Factors associated with encounter of PIMs as per 2019 beers criteria (n=306)

Variables	Category	PIMs, n (%)	Non-PIMs, n (%)	OR (95% CI)	P
Age (years)	65-74	121 (40)	135 (44)	1.46 (0.79-2.72)	0.295
	≥75	19 (6)	31 (10)		
Gender	Male	76 (25)	109 (36)	0.62 (0.39-0.99)	0.056
	Female	64 (21)	57 (19)		
Number of medications	Polypharmacy (≥5)	108 (35)	68 (22)	4.86 (2.95-8.03)	<0.001
	≤4	32 (10)	98 (32)		

PIMs=Potentially inappropriate medications, OR=Odds ratio, CI=Confidence interval

are with the latest evidence-based medical practice. The use of PIMs could be higher in nonteaching institutions.^[21] This study identified some opportunities for interventions.

Most patients are from medicine and orthopedic departments, so first-generation anti-histaminics, SMRs, oral antidiabetic drugs, and tramadol were the most common PIMs in our study.

In our study, first-generation antihistaminics was used as the most often prescribed PIMs Class. They have untoward side effects, particularly notable in the geriatric patient. The geriatric eliminate both first- and second-generation antihistamines more slowly.^[22] They decreased reaction time and produced anticholinergic effects like dryness of the mouth and eyes, blurred vision, urinary retention, and constipation.^[11] Their use is considerably associated with increased risk of injurious falls or fracture among the elderly and should be used with caution as per meta-analysis done by Cho *et al.*^[23] Similarly, antihistamines are used as one of the most common PIM class in a study by Shade *et al.*^[24]

SMRs used in musculoskeletal diseases are very common in geriatric patients. In a nationwide case-control study

in the medicare advantage population, the use of SMRs was associated with a 40% increase in fracture risk (adjusted OR = 1.40; 95% CI, 1.15–1.72, $P < 0.001$).^[25] Similar to other agents in this class, chlorzoxazone can cause central nervous system side effects, such as dizziness, drowsiness, and light-headedness, and use in the geriatric population is generally not recommended.^[26] None of the previous Indian studies documented SMRs as commonly prescribed PIMs detected by older versions of Beers Criteria.

Diabetes mellitus is highly prevalent in geriatric patients so use of oral antidiabetic drugs and sulphonylurea is understandable. Patients can be prescribed safer choices among sulphonylureas and other oral anti-diabetic drugs. Addition of glimepiride (which is responsible for severe, prolonged hypoglycemia in geriatric patients) in 2019 criteria^[11] so such finding is missing in previous studies which have identified PIMs based on Beers 2015 criteria. For those with a contraindication or intolerance to metformin, a short-acting sulphonylurea like glipizide is recommended as initial therapy. Long-acting sulphonylureas such as chlorpropamide, glyburide, and glimepiride are not recommended for geriatric patients

due to increased risk for hypoglycemia.^[27,28] Such kind of more hypoglycemic episodes with glimepiride was noted in an Indian study.^[29]

Tramadol is an analgesic used in many patients with moderate to severe pain. Data from the Healthcare Cost Utilization Project^[30] published in September 2018 showed that between 2005 and 2014, the national rate of opioid-related hospital stays increased 64.1% and the national rate of opioid-related emergency department visits increased 99.4%. Tramadol is a new entry in Beers 2019 criteria as it is associated with Syndrome of inappropriate antidiuretic hormone secretion^[11] and hyponatremia requiring hospitalization.^[31]

In a study by Patel *et al.*,^[32] benzodiazepines were the most prevalent class of PIMs, with 43% of those taking a PIM found to be prescribed a benzodiazepine (12.5% of the entire study sample). Olfson *et al.*^[33] found that 8.7% of geriatric patients used benzodiazepine. In our study population, psychiatric patients were very less in numbers that may be one of the reasons why we have less number of PIMs with benzodiazepines. Further, data regarding the duration of treatment was collected. As a result, proton pump inhibitors and NSAIDs prescribed for very brief period were not considered as PIMs in this study.

The present study underscores the prevalence of PIMs and how they can potentially cause harm to the geriatric population through drug-drug, drug-disease interactions, and harmful drugs in patients with reduced CrCl. NSAIDs used in chronic kidney diseases should be avoided as it may increase risk of acute kidney injury and further decline of renal function.^[11] Concurrent use of opioid and pregabalin can increase risk of severe sedation-related adverse events, including respiratory depression and death.^[34] These adverse effects will further increase with reduced kidney function. Ranitidine can cause mental status changes if used with reduced kidney function.^[35]

Polypharmacy and PIMs: OR of 4.864 (95% CI, 2.946–8.031) and $P < 0.0001$, which indicates that being in the group having medication ≥ 5 increases the chance of getting PIM more than four and half times. Bhatt *et al.*^[15] reported polypharmacy (adjusted OR = 2.11) had independent association with PIM prescription ($P < 0.05$). Korean outpatients' study^[36] found that the risk of PIM use rapidly increased with a prescription of >5 medications (OR: 11.32; 95% CI, 9.38–13.66).

The limitation of the study is the inclusion of a limited number of specialties. This decreases the generalizability of our findings. The study being cross-sectional in nature, the actual impact of the use of PIM could not be evaluated.

The AGS Beers Criteria are a vital evidence-based tool that should be used as a guide for drugs to avoid in geriatric individuals. However, they are not meant to supplant clinical judgment or an individual patient's preferences, values, care goals, and needs, nor should they be used punitively or to excessively restrict access to medications. These criteria were

developed to be used in conjunction with a person-centered team approach to prescribing and monitoring adverse effects.^[37] Regular physician education programs may be effective in preventing the prescription of PIMs.^[38]

CONCLUSION

The use of PIMs in geriatric patients was prevalent (46%). The commonly used PIMs were tramadol, first-generation antihistamines, SMRs, sulfonyleureas, and antipsychotics. First-generation antihistamines were the most prescribed class of inappropriate medications. Chlorzoxazone was the drug most often given inappropriately, and tramadol was the drug which should be used with caution in geriatric. There was a significant association between inappropriate medication use and polypharmacy with OR of 4.864 (95% CI, 2.946–8.031).

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Conflicts of interest

There are no conflicts of interest.

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