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Prevalence and factors influencing inappropriate medication use in elderly patients - a retrospective study using updated beers criteria

Sreedharan Nair Dr

PREVALENCE AND FACTORS INFLUENCING INAPPROPRIATE MEDICATION USE IN ELDERLY PATIENTS -A RETROSPECTIVE STUDY USING UPDATED BEERS CRITERIA

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ACADEMY *of* HIGHER EDUCATION
(Deemed to be University under Section 3 of the UGC Act, 1956)

Under the guidance of:

GUIDE

Dr.Sreedharan, M.Pharm, Ph.D,
Associate Professor,
Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
MAHE,
Manipal, Karnataka576104.

Co GUIDE

Dr.Girish Tunga, M.Pharm, Ph.D,
Associate Professor,
Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
MAHE,
Manipal,Karnataka-576104.

Co GUIDE

Dr.Raviraj.V.Acharya,
Professor and Head,
Department of Medicine,
Kasturba Medical College,
MAHE,
Manipal, Karnataka-576104.

SUBMITTED BY:

SYAM SUNDAR. CHINTHALAPUDI
(Reg No: 150614026)

SRILAKSHMI. CHEETI
(Reg No: 140614032)

ADITI BAJPAI
(Reg No: 140614046)

DEEPIKA .S
(Reg No: 180615003)

Pharm D 5th Year

Department of Pharmacy Practice,

Manipal College of Pharmaceutical Sciences,

Manipal Academy of Higher Education, Manipal-576104.

May 2020

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I recommend this piece of work for acceptance for the partial fulfillment on the completion of the 5th year Pharm.D program of the Manipal Academy of Higher Education, Manipal for the Academic year 2019-2020.

Place: Manipal

Date:

Dr.Sreedharan, M.Pharm, Ph.D,
Associate Professor,
Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
Manipal Academy of Higher Education,
Manipal – 576104

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I recommend this piece of work for acceptance for the partial fulfillment on the completion of the 5th year Pharm.D program of the Manipal Academy of Higher Education, Manipal for the Academic year 2019-2020.

Place: Manipal

Date:

Dr. Mahadev Rao, M Pharm, Ph.D,
Professor and Head,
Department of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
Manipal Academy of Higher Education,
Manipal, Karnataka-576104.

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I recommend this piece of work for acceptance for the partial fulfillment on the completion of the 5th year Pharm.D program of the Manipal Academy of Higher Education, Manipal for the Academic year 2019-2020.

Place: Manipal

Date

Dr. C. Mallikarjuna Rao, M.Pharm, Ph.D
Principal,
Manipal College of Pharmaceutical Sciences,
Manipal Academy of Higher Education,
Manipal, Karnataka-576104.

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I recommend this piece of work for acceptance for the partial fulfillment on the completion of the 5th year PharmD program of the Manipal Academy of Higher Education, Manipal for the Academic year 2019-2020.

Place: Manipal

Date:

Dr. Girish Thunga, M. Pharm, Ph.D,
Associate Professor,
Dept of Pharmacy Practice,
Manipal College of Pharmaceutical Sciences,
Manipal Academy of Higher Education,
Manipal, Karnataka– 576104.

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I recommend this piece of work for acceptance for the partial fulfillment on the completion of the 5th year PharmD program of the Manipal Academy of Higher Education, Manipal for the Academic year 2019-2020.

Place: Manipal

Date:

Dr. Raviraj V. Acharya
Professor and Head,
Department of Medicine,
Kasturba Medical College,
Manipal Academy of Higher Education,
Manipal - 576104

MANIPAL COLLEGE
OF PHARMACEUTICAL SCIENCES
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(A constituent unit of MAHE, Manipal)

Declaration

We hereby declare that the project entitled **"Prevalence and factors influencing inappropriate medication use in elderly patients – A Retrospective study using UPDATED Beers criteria"** was carried out under the guidance of **Dr. Sreedharan,** M.Pharm, Ph.D, Associate Professor, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal. The extent and source of information derived from the existing literature have been indicated throughout the project work at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree purpose for this or any other university.

Place: Manipal

Date:

Syam Sundar. Ch

(Reg No: 150614026)

Srilakshmi Cheeti

(Reg No:140614032)

Aditi Bajpai

(RegNo:140614046)

Deepika.S

(RegNo:180615003)

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LIST OF ABBREVIATIONS

1. ADR- Adverse Drug Reaction
2. AGS- American Geriatric Society
3. CI- Confidence Interval
4. COPD- Chronic Obstructive Lung Disease
5. CrCl- Creatinine Clearence
6. CRF – Case Record Form
7. CVA – Cerebrovascular Diseases
8. CVD – Cardiovascular Diseases
9. DAMA - Discharged Against Medical Advice
10. DDI- Drug-drug interactions
11. NSAIDs- Non-Steroidal Anti-Inflammatory Drugs
12. OR- Odds Ratio
13. PIM- Potentially Inapproprite Medication
14. PPIs - Proton Pump Inhibitors
15. SNRIs- Serotonin Norepinephrine Reuptake Inhibitors
16. SSRIs- Selective Serotonin Reuptake Inhibitors

ABSTRACT

Background:

A major safety concern in elderly population is the use of inappropriate medication. Owing to aging-associated with anatomic and physiologic changes, pharmacokinetic and pharmacodynamics of drugs are prone to alter in these elderlies. Inappropriate drug prescribing and polypharmacy in this population elevates the risk of adverse drug reactions.

Objectives:

To assess the prevalence and factors influencing Potentially Inappropriate Medication (PIM) use in elderly patients according to updated Beers Criteria.

Methodology:

A retrospective observational study was carried out. Case records of 580 patients aged 65 years and above were reviewed. Every case record was identified for at least one PIM based on the American Geriatric Society 2019 Updated Beers Criteria for PIM use in elderly patients. Analysis of collected data was done using Statistical Package for Social Sciences (SPSS) software.

Results:

A total of 580 elderly general medicine patients were reviewed amongst them, 301 were identified as test group with the age of mean 73.7±6.4 years and 101 patients as control group with the age of mean 70.5±5.5 years. Most of the study population were males 59.1% in test and 63.4% in control groups. The prevalence of PIMs to be used with caution were 54% and PIMs to be avoided were 45% the most prescribed PIMs were aspirin (23.51%), diuretics (15.56%), long acting sulphonylureas (12.75%) and Proton Pump inhibitors(PPIs) (11.92%). Increasing age polypharmacy, number of drugs in medication history, certain Chronic diseases were associated with high probability of PIM's use among elderly patients. Risk of developing serious, moderate drug-drug interactions (DDIs) was high in elderly patients with PIMs.

Conclusion:

Potentially inappropriate medication use poses a sizable health safety hazard in elderly patients. After evaluating the potentially inappropriate medications of elderly patients using the updated Beers Criteria 2019.Prevalence of PIMs that should be used with caution (54%) was found to be highest followed by PIMs to be avoided (45%) and recommendation for reduce dose to be (1%) .Age, gender, comorbidities, and polypharmacy were identified as risk factors leading to PIM use. It was also observed that patients with PIMs are at a higher risk of developing DDIs. A significant increase in the older population and the need to reduce preventable harm calls for more multidisciplinary strategies to account for the use of high-risk medications. Prescribers can use this data to determine patients at a higher risk for PIMs and be attentive to

them while prescribing. Continuous medication and prescription review done by a clinical pharmacist can aid in reducing the occurrence of PIMs.

INTRODUCTION

INTRODUCTION

Potentially inappropriate medication (PIM) is a drug or drug class which should be avoided in patients aged 65years or above (geriatrics) as their risk of causing potential adverse event outweighs their clinical benefit [1]. Due to advancing age, multiple chronic problems and comorbidities can result in complex therapeutic regimens, which in turn lead to polypharmacy [2]. Increased number of drugs prescribed leads to an increased prevalence of interactions between the drugs. Higher risk of use of PIMs is attributed to the direct independent relation with increased number of medications. [3].

Multiple studies have identified a high prevalence of PIMs in older adults [4]. Geriatrics account for 4.8% of the total population in India according to the 2011 Census. With the availability of better health care facilities and an increase in life expectancy, the elderly population has increased from the year 1991 to 2011. Increased life expectancy poses a need for better patient care in all sets of population, particularly in vulnerable populations like geriatrics. In elderly people, medication-related problems increase due to increasing age-dependent physiological changes that affect the pharmacokinetics and pharmacodynamics of the drugs [5].

A research carried out in The USA revealed that unplanned hospitalization in older adults is majorly due to adverse drug reactions (ADRs). These ADRs are manageable and preventable with further studies. Implementation of population-based results, while also stressing on the need for reducing inappropriate prescribing can certainly help prevent these ADRs. [6].

With rising PIM use in geriatrics, American Geriatric Society (AGS) Beers Criteria 2019, which is an explicit list of PIMs, supposed to be typically best avoided in older adults aged 65 years has the potential to become a mandatory tool in providing better health care services for the elderly [7].

It is known amongst health care professionals as AGS - Beers Criteria® 2019. Research on 2012 publish of Beers Criteria documented that at least 40% of patients had minimum one PIM whereas, approximately 30% PIMS were seen according to the 2003 publishing of the same. [8]

Another study from the Netherlands concluded that more than half of the participants with a history of cardiovascular disease (CVD) or/and cerebrovascular disease (CVA) had at least one PIM. About 40% of the test participants with identified PIMs posed a potential risk of Major Adverse Cardiac and cerebrovascular events [9].

Geriatrician Mark H. Beers, with a panel of his expert colleagues, formulated this criterion in 1991. In 2011 after the demise of Dr.Beers, the criterion was transferred to the American Geriatric Society, which is a non-profit organization working towards providing better geriatric care. The development of this criterion was

intended to provide an efficient and comprehensive tool to help assess the prescribing quality in older adults despite their debility and demographics.

A team of 13 interdisciplinary experts reviewed more than 1,400 research studies and clinical trials between 2017 and the last Beers Criteria update in 2015 on geriatric care and pharmacotherapy to formulate Beers Criteria 2019 using Delphi's method [10].

Drugs included in the Beers list are classified under three brackets: 1) drugs to be avoided in elderly, 2) drugs that overshoot a maximum daily dose 3) drugs to be avoided in the presence of specific comorbidities. In specific cases, these tabulated medications might be suitable for specified off label use. This is also a helpful tool in drug utilization studies.

70 changes were released in this update. Addition of 30 drugs or drug classes to be avoided in old people along-with 40 drug or drug classes to be used with caution or avoid when someone lives with diseases or conditions. These amendments also included outright removal of 25 previously identified potentially inappropriate medications. Similarly, several other drugs were re-categorized with the help of stronger evidence [10].

Now, AGS Beers Criteria 2019 comprises five lists of nearly 100 medications and classes of medicines that are supposed to be avoided or used with caution in the older adult population. It offers itself as a broad tool to help the clinicians, nurses, and caregivers have a better chance at geriatric healthcare [10].

Critical care units serve a pivotal role in patient care through lifesaving and life-preserving treatments. Assessing a patient's health status and carrying out a medication evaluation to alter the medication regimen to provide safer alternatives for older adults is important. Beers Criteria is not a clinical rule; instead, it is a clinical guideline with recommendations to support a clinician's judgment of the therapy given to the patient. Keeping in mind the safety and efficacy of geriatric prescriptions the Beers Criteria is updated to keep up with the best practices in the present world scenarios like avoiding prolonged use of PPIs, non-benzodiazepines, benzodiazepine receptor agonist, hypnotics regardless of the duration of exposure. Tables with updated information on the list of drugs to avoid or reduce dosage based on kidney function along with updated tables of DDIs are provided which add to its benefits [11].

An average of at least four drugs is seen which goes up to 10 and more than 10 in some cases. It highlights the need for periodic assessment of prescriptions to minimize polypharmacy which has been identified as a sizable factor leading to high inappropriate medication use [12]. Moreover, there is a need to subsume Beers Criteria into the electronic prescribing system to forewarn the medical service providers at the time of prescribing, in turn, enabling them to mitigate potential harm [13]. A high number of patients presented with acute ailments end up taking PIMs at discharge or during admission. This high prevalence appears to increase by nearly 20% after hospitalization. Even after the PIMs presented in the prescriptions on admission were emended, 45% of these patients received other PIMs during the hospital stay. Given the

harmful effects that these PIMs might lead to, it is important to address this problem and incorporate this tool for providing better geriatric care. [14] It also highlights the need for practicing geriatrics as a specialty in our country. (14)

To the best of our knowledge, this new criterion has not been employed in any studies in the country so far. Therefore, we have carried out a study based on elderly patients in a tertiary care hospital of Karnataka to estimate prevalence of PIM use, factors influencing their use and impact of PIMs leading to drug-drug interaction using updated AGS Beers Criteria 2019

NEED FOR THE STUDY

NEED FOR THE STUDY

Older adults differ from younger adults in several ways that put them at risk of harm by drug interactions and ADR. Aging is often being accompanied by chronic diseases, comorbidities, disabilities, and social isolation leading older adults to have more illnesses. Hence, geriatrics are most often the main group that needs to get hospitalized for their illnesses. It is not surprising that aging progressively increases the number of drugs taken by each elderly patient. [10] Factors like aging, female gender, polypharmacy, multiple prescribers, poor health quality, chronic diseases like hypertension, diabetes, CVD, CVA and depression were seen to be associated with higher risk for PIM use.[4]

Thus, the need to pre-evaluate elderly prescriptions at the time of prescribing in acute, ambulatory, or institutional settings, in the case of polypharmacy and patients with multiple comorbidities is warranted.

PIM use has become a worldwide concern among geriatrics. The use of PIMs leads to the risk of medication misadventure in geriatrics. AGS Updated Beers Criteria 2019 is the most recently updated criteria that is nowadays being widely used across the globe to assess and evaluate PIM use in geriatrics. Beer Criteria provide a comprehensive list of probable PIMs with proper rationales for their off label uses if any. In India however, a couple of studies have highlighted the contribution of polypharmacy and drug interactions among geriatrics.[10]. No systematic study has been documented examining PIMs prescribing done previously among elderly patients in this locality. Hence the main objective of this study was to assess prevalence of PIM use and factors associated with their use in elderly patients using the AGS 2019 Updated Beers Criteria.

OBJECTIVES

OBJECTIVES

- To assess the prevalence of PIM use in elderly patients according to updated Beers Criteria.
- To assess factors influencing PIM use in elderly patients according to updated AGS Beers Criteria 2019.

METHODOLOGY

METHODOLOGY

An observational study was retrospectively conducted in a tertiary care hospital located in Karnataka, South India. Ethical Clearance from Institutional Ethics Committee, MAHE (IEC-562/2019) was obtained before the start of the study. Patients of both genders aged 65 years or older and admitted under the Department of Medicine between June 2018 -June 2019. A total of 580 files were reviewed and 402 files were considered for the study. Out of 402 files subjects with at least one PIM (according to AGS 2019 Updated Beers Criteria) in their discharge prescription were included as test group. Subjects with no PIMs in the discharge prescription were included as control group. Patients discharged against medical advice and expired were excluded. PIM was identified for each patient from the medical record and classified according to 2019 AGS Updated Beers Criteria. These PIMs were categorized according to their recommendations as, avoid (avoid using the medication or medication class) caution (medication or medication classes to be regularly monitored), and reduce dose (medications for which a dose reduction is needed if identified as PIM). Demographical details like age, gender, weight, height, BMI, and personal history were also obtained.

Presence of any medication or medical history related to the pre-hospitalization period, complaints present during the admission and the diagnosis with comorbidities were recorded. The brand name, generic name, strength, dose, frequency, and duration of the discharge medications were also recorded. Patient's serum creatinine was noted and creatinine clearance was calculated in patients using the age-adjusted standard formula: [133-(0.64*age)] for males and 93% of the value for females [19], and for the patients with kidney diseases creatinine clearance (CrCl) was taken from the medical record. Medications prescribed at the time of discharge were retrospectively screened for potential DDIs, using IBM Micromedex and Medscape. The interactions were divided into serious, moderate and, minor according to their indicated severity. Drug-disease interactions were also studied according to the Beers list.

A pre-designed case report form (CRF) was used to enter the captured data. Outcome measures were categorized the primary outcome: prevalence of inappropriate medication uses in patients above or equals to 65years of age secondary outcomes: factors influencing inappropriate medication use.

Statistical Package for the social sciences version 22.0 was used for data entry and statistical analysis. Continuous data were analyzed using mean ± SD and categorical variables were analyzed using frequency and percentage. Factors associated with the PIM use(outcome), to predict the risk of serious, moderate, and minor drug-drug interactions(outcome) in patients with PIMs were evaluated by performing Binary logistic regression analysis.

RESULTS

RESULTS

DEMOGRAPHICS OF THE STUDY POPULATION:

Medical charts of 580 patients were reviewed. 178 patients unfit according to the study criteria were excluded. Amongst them 301were identified as the test group (≥1 PIMs) and 101 Patients were identified as the control group (no PIMs). The mean age of the study population was found to be 73.7±6.4 years in test, 70.5±5.5 years in control. Most patients were male in the test population. The test group was found to have history of medication use ≥3 (53.8%) as shown in Table 1.

Variable		**Test**	**Control**
Age		73.7±6.4 years	70.5±5.5 years
Gender	Female	123(40.9%)	37(36.6%)
	Male	178(59.1%)	64(63.4%)
Number of Drugs in medication history			
No. of drugs in medication history	0	76(25.2%)	52(51.5%)
	1	32(10.6%)	18(17.8%)
	2	31(10.3%)	13(12.9%)
	≥3	162(53.8%)	18(17.9%)

Table 1. Patient demographics

Majority of the test population had three or more comorbidities, whereas in control mostly one comorbidity was prevalent. Hypertension followed by type 2 diabetes mellitus were found to be common as shown in Table 2.

VARIABLE		**TEST**	**CONTROL**
Number of Comorbidities	0	25(8.3%)	29(28.7%)
	1	53(17.6%)	36(35.6%)
	2	93(30.9%)	22(21.8%)
	≥3	130(43.2%)	14(13.9%)
Hypertension		225(74.8%)	47(46.5%)
Type 2 Diabetes Mellitus		181(60.1%)	26(25.7)
Asthma		28(9.3%)	13(12.9%)
Chronic Obstructive Lung Disease (COPD)		40(13.3%)	8(7.9%)
Cardiovascular Disease		106(35.2%)	11(10.9%)
Cerebrovascular Disease		36(12.0%)	7(6.9%)
Hypothyroidism		29(9.6%)	7(6.9%)
Kidney Disease	Acute Kidney Disease	13(4.3%)	2(2.0%)
	Chronic Kidney Disease	31(10.3%)	
Liver Disease	Acute Liver Disease		1(1.0%)
	Chronic Liver Disease	9(3.0%)	3(3.0%)

Table 2. Frequency and percentage of comorbidities.

PREVALENCE OF PIMS:

Our study found a high prevalence of PIMs to be used with Caution (n=348)(54%) than the PIMs to be Avoided (n= 291)(45%) and recommendation to prescribe drug at Reduce dose (n= 9)(1%) as highlighted in Fig 1.

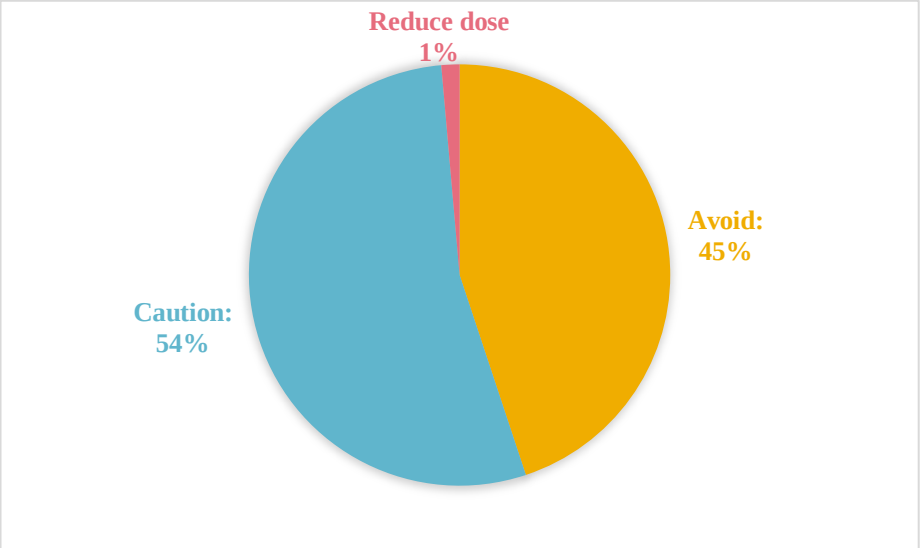

Fig 1. Prevalence of PIMs

The four most prescribed PIMs in our study population were found to be aspirin, diuretics (furosemide, torsemide, spironolactone), long-acting sulphonylureas (glimepiride, glibenclamide), proton pump inhibitors (PPIs) as per AGS 2019 updated Beers Criteria (Table 3).

DRUGS	PERCENTAGE
Aspirin	23.51%
Diuretics	15.56%
Long acting sulphonylureas	12.75%
PPIs	11.92%
Tramadol	4.97%
Prazosin	2.81%
Levetiracetam	0.50%
Benzodiazepines	4.47%
Dextromethorphan	1.99%
Dicyclomine	0.17%
Non-steroidal anti-inflammatory drugs (NSAIDs)	0.83%
Digoxin	0.50%
Antipsychotics	4.64%
Anticholinergics	3.48%
Selective Serotonin Reuptake Inhibitors (SSRI)	1.82%
Pregabalin	0.66%
Serotonin Norepinephrine Reuptake Inhibitors (SNRI)	0.17%

Gabapentin	0.17%
Dabigatran	1.66%
Amiodarone	1.49%
Ranitidine	0.17%
Non-Dihydropyridines	0.17%
Nitrofurantoin	0.33%
Anti-Parkinson's	0.17%
Barbiturates	0.50%
Mineral Oil	3.15%
Mirtazapine	1.16%
Antiepileptics	0.17%
Duloxetine	0.17%

Table 3. Percentage of PIMs

Comparison of gender and PIMs: Comparing Gender with PIMs (only in Test group), out of 178 males, 67 were observed to have one PIM, 62 had 2 PIMs and 49 had 3 or more PIMs. Similarly, out of 123 females, 41 were observed to have one PIM. (Fig 2).

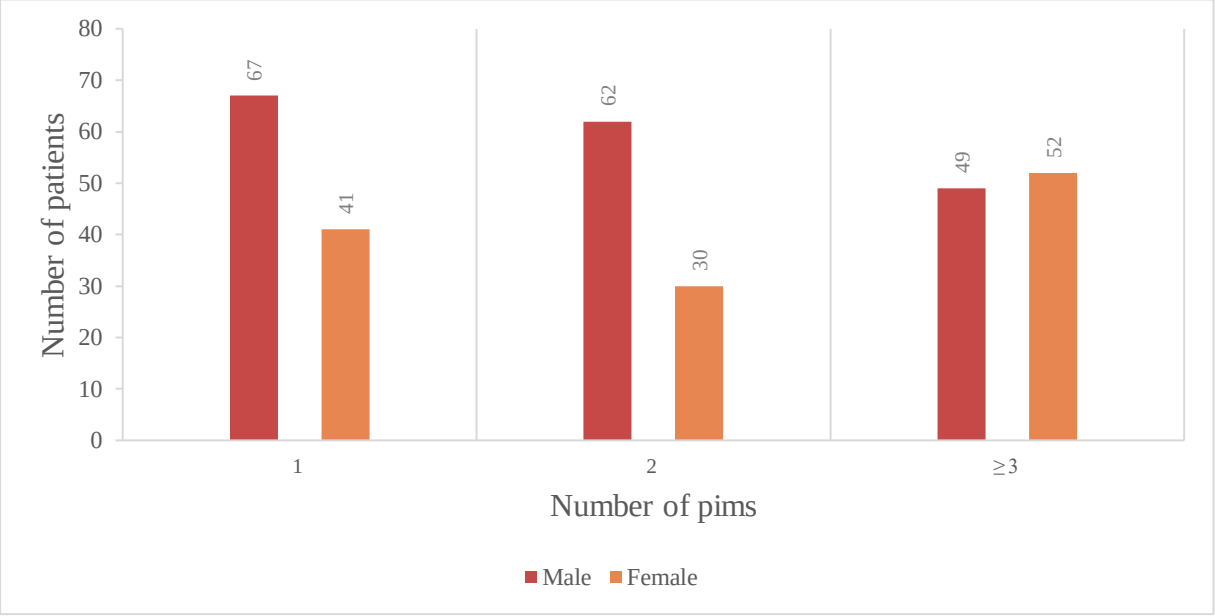

Fig 2. Comparison of Gender and Number of PIMs

Comparison of co-morbidities and PIMs: Comparing the number of comorbidities with the number of PIMs, out of 54 patients with zero comorbidities, 29 had zero PIMs. Out of 89 patients who had one comorbidity, 36 had zero PIMs. Out of 115 patients with 2 comorbidities 39 had one PIM. Out of 144 patients with ≥ 3 comorbidities, 51 had ≥3 PIMs as highlighted in Fig3.

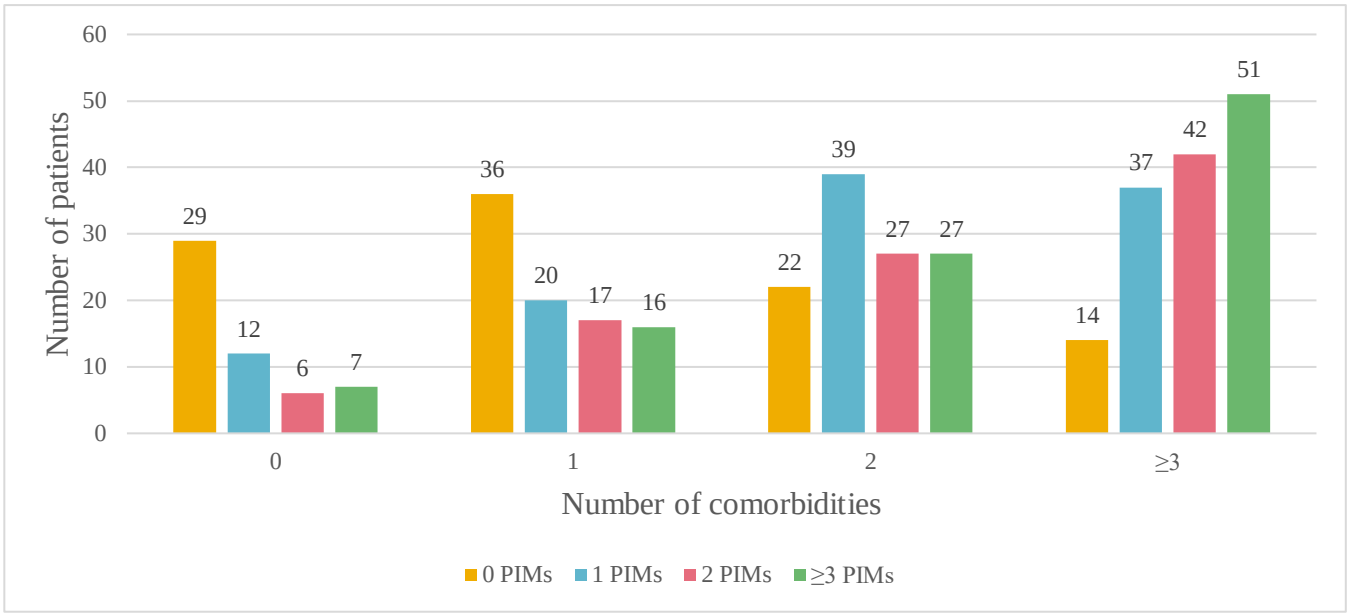

Fig 3. Comparison of PIMs and Comorbidities

Comparison of the number of drugs in medication history and PIMs: As highlighted in Fig 4 while comparing the number of drugs in medication history and PIMs 76 patients with 0-3 drugs in medication history had single PIM usage,33 patients with 4 to 7 drugs in medication history prescribed with two PIMs and 3 PIMs were mostly observed in patients with more than 7 drugs in medication history.

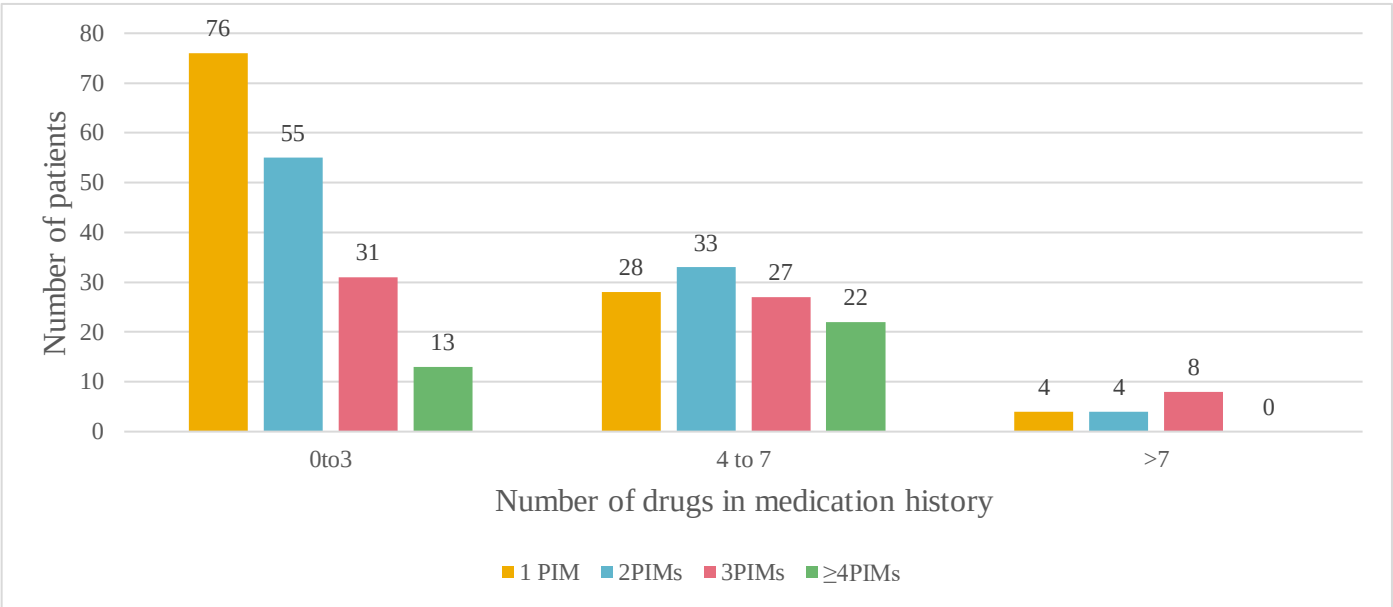

Fig 4. Comparison of number of drugs in medication history and PIMs

Comparison of the total number of discharge drugs and PIMs: The total number of drugs prescribed at discharge were grouped as 1-5drugs,6-10drugs and ≥10 drugs and PIMs as 0(control),1,2,3 and ≥4 as depicted below in fig 5. Out of 93 patients prescribed with 1-5drugs, 55 were observed to have no PIMs. Out of 119 patients prescribed with >10 drugs, zero PIMs were seen in only 8 patients and mostly have ≥4 PIMs.

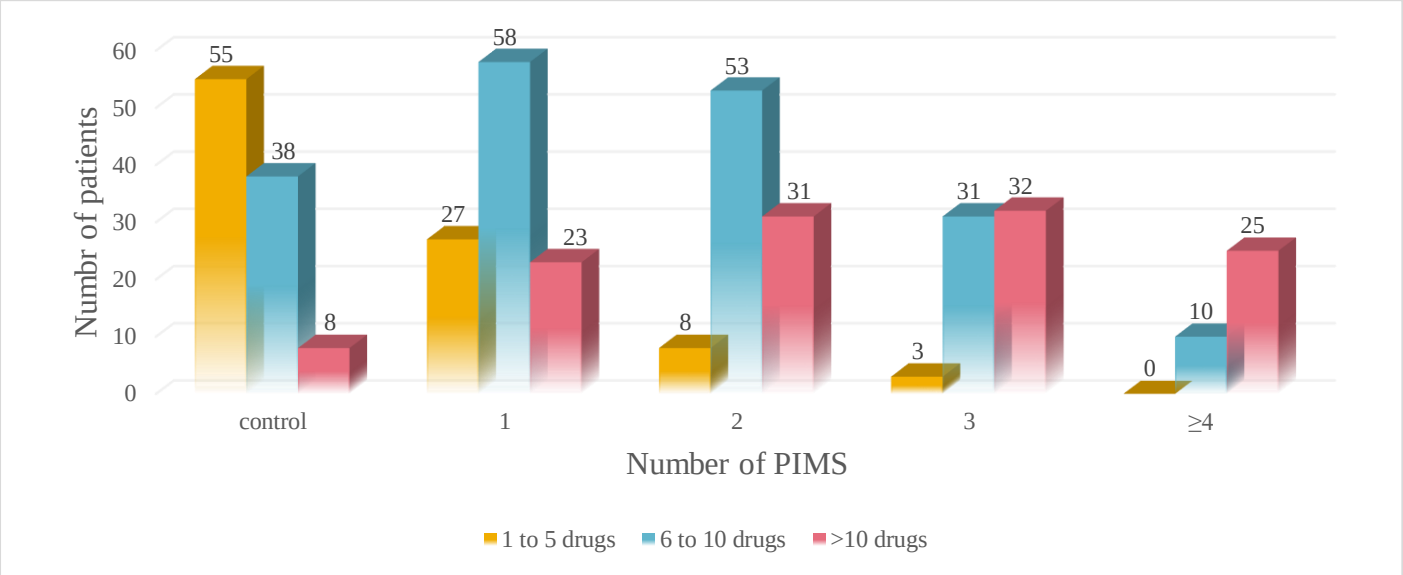

Fig 5. Comparison of Number of Drugs in discharge and PIMs in both Test and Control

Comparison of age and PIMs: On comparing age with the number of PIMs it was observed that elderly patients of age 85 years and above had a greater number of PIMs (≥3). Zero PIMs were more prevalent in the age group between 65 to 69 as depicted in Fig 6.

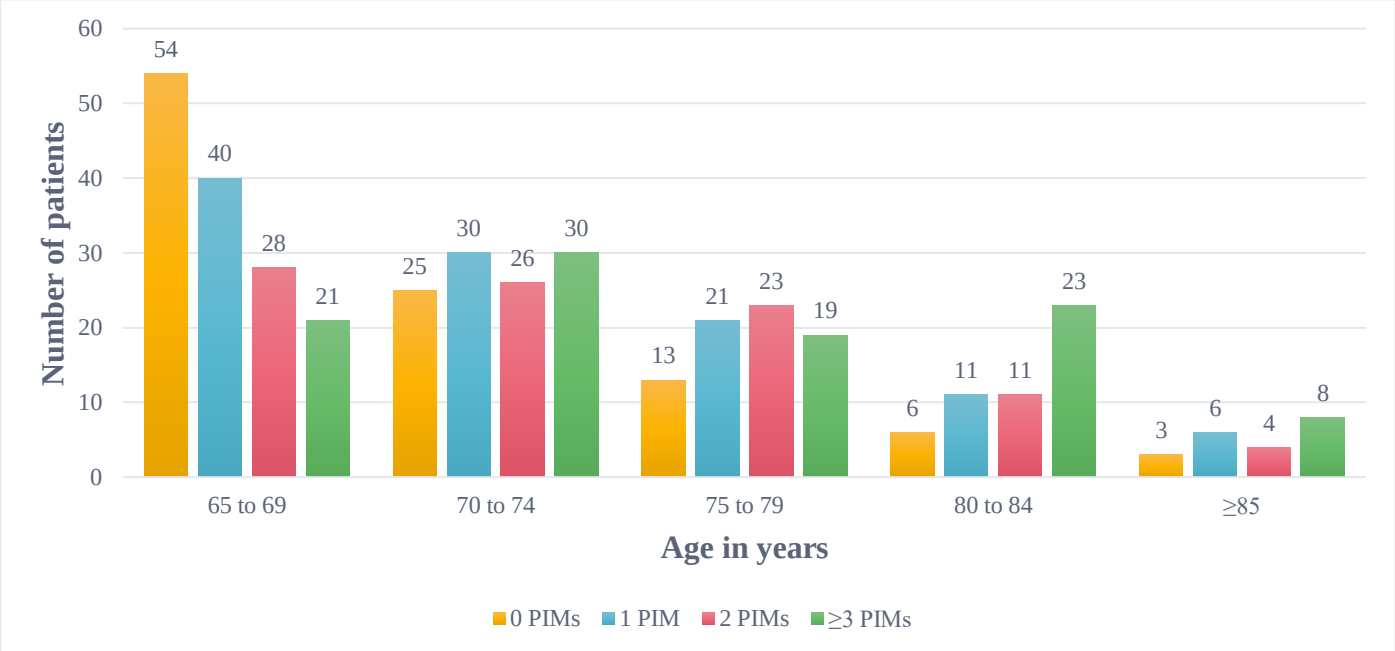

Fig 6. Comparison of age and PIMs

Drug-drug interaction in test and control: When compared for drug interactions in test and control, serious and moderate drug interactions were found to be very high in test population as depicted in Fig.7.

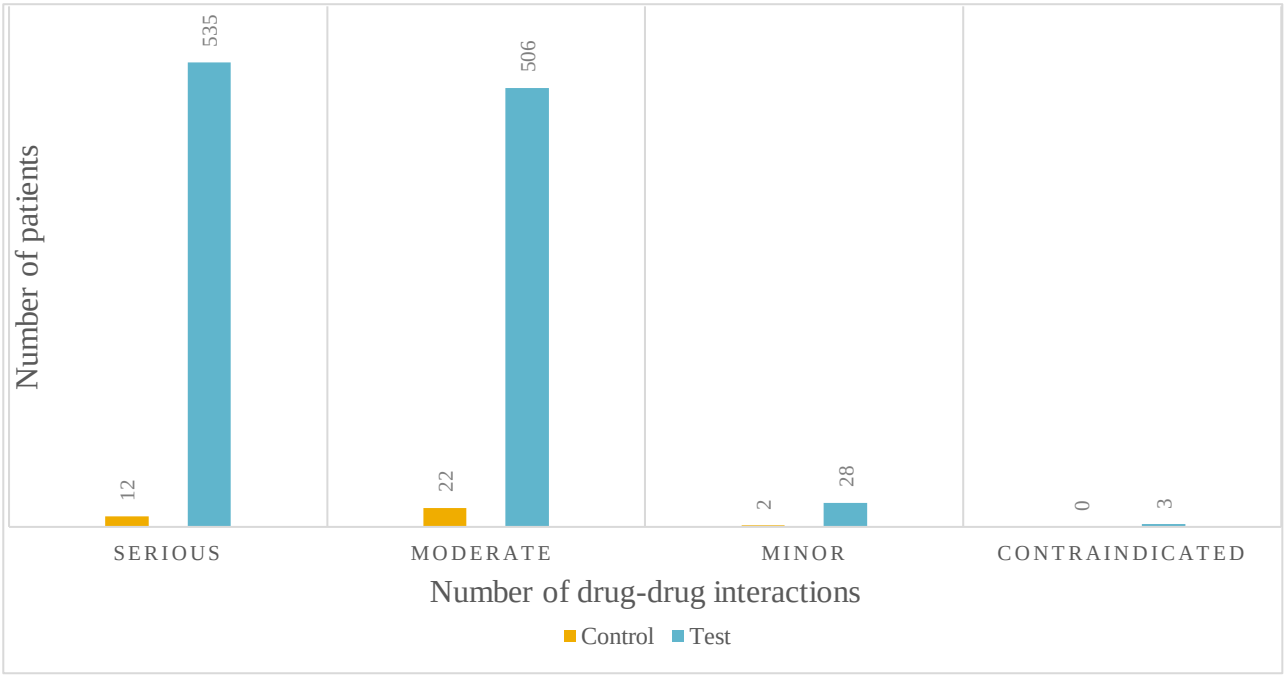

Fig 7. Comparison of drug-drug interactions in test and control

RISK FACTORS ASSOCIATED WITH PIM USE IN LOGISTIC REGRESSION ANALYSIS

On performing regression analysis, PIM use was found to be more likely in elderly patients. Male patients were at fewer odds of having PIMs compared to females. Elderly patients with a history of ≥3 drugs and polypharmacy were observed to have a significant risk of having PIMs. It was also observed that elderly patients with hypertension, type2 diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, and acute kidney disease were at more odds to have PIMs in contrast to patients with asthma, Chronic Obstructive Lung Disease (COPD), thyroid disease and chronic liver disease. An increase in the number of comorbidities is also seen to be associated with a significant prevalence of PIMs. The Odds ratio (OR), 95% Confidence Interval (95% CI) and p-value are depicted in Table.4.

VARIABLE	OR (95%CI)	p-value
Age		
65yrs-69yrs(n=143)	1	NA
70yrs-74yrs(n=111)	3.157 (1.533-6.502)	0.002 *
75yrs-79yrs(n=76)	4.983 (1.949-12.744)	0.001 *
>80yrs (72)	4.088 (1.547-10.804)	0.005 *
Gender		
Male (242)	0.671 (0.360-1.252)	0.21
Female (160)	1	NA
Hypertensive		

Yes(n=272)	1.135 (0.372-3.464)	0.824
No(n=130)	1	NA
Type 2 Diabetes Mellitus		
Yes(n=207)	1.830 (0.641-5.221)	0.259
No (n=195)	1	NA
Acute kidney disease		
Yes(n=15)	2.250 (0.264-19.180)	0.458
No(n=387)	1	NA
Asthma		
Yes(n=41)	0.326 (0.091-1.166)	0.085
No(n=361)	1	NA
Cardiovascular		
Yes(n=117)	1.225 (0.417-3.594)	0.712
No(n=285)	1	NA
COPD		
Yes(n=48)	0.870 (0.243-3.120)	0.831
No(n=354)	1	NA
Thyroid disease		
Yes(n=36)	0.744 (0.187-2.955)	0.674
No (n=366)	1	NA
Chronic Liver disease		
Yes (n=12)	0.746 (0.121-4.603)	0.752
No (n=390)	1	NA
Cerebrovascular disease		
Yes(n=43)	1.873 (0.482-7.271)	0.365
No (n=359)	1	NA
Medication history		
0 Drugs(n=128)	1	NA
1 Drug(n=50)	1.248 (0.529-2.945)	0.613
2 Drugs(n=44)	1.380 (0.542-3.511)	0.499
≥3 Drugs(n=180)	2.836 (1.262-6.373)	0.012 *
Number of Comorbidities		
0(n=54)	1	NA
1(n=89)	0.917 (0.276-3.053)	0.888
2(n=115)	1.399 (0.214-9.124)	0.726
≥3(n=144)	1.579 (0.094-26.488)	0.751
Number of drugs prescribed at discharge		
0-3 drugs (n=32)	1	NA
4-7 drugs(n=110)	5.988 (1.940-18.487)	0.002 *
>7 drugs(n=260)	31.875 (9.786-103.822)	0.000 *

*p-value<0.05, CI-Confidence Interval, >3 drugs prescribed at discharge defined as polypharmacy

Table.no.4 Regression analysis for risk factors

DRUG-DRUG INTERACTIONS:

On regression analysis, the test group was observed to be at more odds to develop Serious and moderate drug-drug interactions (DDIs). The Odds ratio, 95% Confidence Interval, and p-value are depicted in Tables 5,6 and 7 for Serious DDIs, Moderate DDIs, and Minor DDIs, respectively.

Variable	OR (CI 95%)	p-value
Test group (n=301)	19.069(8.929-40.725)	0.000
Control group (n=101)	1	NA

Table.No5 Predicting the risk of serious drug-drug interactions in patients prescribed with PIMs

Variable	OR (CI 95%)	p-value
Test group (n=301)	11.502(6.031-21.937)	0.000
Control group (n=101)	1	NA

Table.No6 Predicting the risk of moderate drug-drug interactions in patients prescribed with PIMs

Variable	OR (CI 95%)	p-value
Test group (n=301)	4.289(0.995-18.479)	0.051
Control group (n=101)	1	NA

Table.No7 Predicting the risk of minor drug-drug interactions in patients prescribed with PIMs

DISCUSSION

DISCUSSION

In the elderly patients, age-dependent physiological changes of the drugs lead to an increase in medication-related problems due to changes in drug's pharmacokinetics and pharmacodynamics. While observing the demographics of the study population the mean age of the study population was found to be 73.7 ±6.4years in the test, and 70.5±5.5 years in control. It was further grouped into 4 categories, 65-69, 70-74, 75-79, ≥80. Using binary logistic regression as the statistical method it was seen that patients aged between 65-69 years were at lesser odds of receiving a PIM than those falling in the other 3 higher categories. This suggests that as the age increases the risk of having a PIM in the patient's therapy also increases. Similarly, earlier studies have also been successful in establishing an association between age and PIM use [21]. Due to advancing age and deteriorating health status [4], there is an increase in predisposing factors that lead to chronic diseases which act as comorbidities over a period making PIM use (including off label use) more prominent.

On comparing Gender in the study population out of a total of 301 test population 178(59.1%) were male and 123(40.9%) were female patients. Whereas in Control group males were 64(63.4%), and females were 37(36.6%). Male patients were observed to be higher in number in both Test and control. Male patients were observed to have a lesser risk of having a PIM when compared to females with odds of 0.671 but statically not significant as the p-value is 0.210. An earlier study from Brazil also associated the male gender with fewer PIMs. This difference may be attributed to likeliness of women to visit the doctor and express their problems over men. [16].

Regarding the comorbidities, many studies suggest that PIMs are strongly associated with several comorbidities [9,18,20,22,25]. In our study, most of the test population (patients with a minimum of 1 PIM) have 3 comorbidities. We also observed that patients having 2 or ≥3 comorbidities have a significantly higher risk when compared to the patients with no comorbidities but was not statistically significant as the p-value is not less than 0.05.

We found that patients with asthma, thyroid, chronic liver disease, and COPD may have a lesser risk of causing PIMs. This can be explained by the fact that drugs used as first-line therapy for these diseases are not included as PIMs in updates 2019 AGS Beers Criteria.

Whereas cerebrovascular disease, acute kidney disease, hypertension, cardiovascular, and type 2 diabetes mellitus were observed to have more risk of causing PIMs in this study population, justifiable with an odds ratio greater than 1, although not statistically significant as the p-value was not less than 0.05. A study carried out in the Arab population using bivariate regression analysis found PIM use to be more likely in patients with comorbidities like diabetes, CVD, CKD, osteoarthritis, osteoporosis, and anxiety [9]. As this study population includes ambulatory care patients, comorbidities like osteoporosis, osteoarthritis, anxiety

were observed to be more. Drug therapy for these conditions include antipsychotics, NSAIDs which are PIMs as per updated 2019 AGS Beers Criteria.

Hypertension was observed to be the most common comorbidity in the control as well as the test group. Anti-hypertensives used as PIMs were diuretics, prescribed mostly as combinations of one loop or thiazide diuretic with one potassium-sparing diuretic and Prazosin. Other antihypertensive drugs are not included in the PIM list as per updated 2019 AGS Beers Criteria which explains the high prevalence of Hypertension in the control group as well. Type 2 diabetes mellitus was observed as the second most prevalent comorbidity in both test and control group as most of the anti-diabetic drugs were not recognized as PIMs, but long-acting sulphonylureas (included in updated 2019 AGS Beers Criteria)which were commonly prescribed drugs for type 2 diabetes mellitus resulted in more odds of presence of a PIM.(Having a PIM)

The 2019 updated AGS Beers Criteria categorized PIMs into three types namely, drugs to be avoided, used with caution, and drugs to be used with reduced dose. In our study, we found that the drugs to be used with caution have high prevalence at 54% and the drugs to be avoided were 45% with reduce dose standing at 1%. A similar study done in Saudi Arabia revealed the prevalence of drugs to be avoided was more than the drugs used with caution [9]. The study was done in an ambulatory care setting where most of the drugs used were gastrointestinal agents which should be avoided in elderly patients. In our study, we observed that gastrointestinal agents were given as per the rationale (which is <8weeks).

A study in India done in the cardiac OPD of a tertiary care hospital to evaluate PIM found that Spironolactone was the most used PIM in the elderly patients [24]. In our study, it was found that diuretics were the second most used PIM amongst elderly patients as diuretics are the most common drugs used in heart failure patients. In other studies, NSAIDs and antipsychotics were the most prevalent PIMs to be used in the geriatric population [15,9,17] as these studies have taken the patient population from ambulatory care and mostly involve anxiety and osteoarthritis.

Elderly patients with medication history 3 or more drugs had a higher odds of having PIMs (OR:2.836, p-value:0.012). Higher number of drugs in medication history can be due to the presence of co-morbidities which have been identified as a risk factor for having PIMs. Therefore, higher number of drugs in medication history can be indirectly linked to the prevalence of PIMs.

Significant amount of research consistently states polypharmacy as a major risk factor for PIMs [4,5,9,16,17,23]. In this study, the total number of discharge drugs was categorized into three groups 0-3drugs, 4-7drugs, and >7 drugs. Elderly patients with >7drugs were more prevalent and at highest odds of having PIMs (OR:31.875, p-value:0.00) followed by 4-7drugs (OR:5.988, p-value: 0.002).

Possible risk of developing DDIs due to inappropriate medication use was also identified in this study. We observed the test group to have a higher risk of serious (OR:19.06), moderate (OR:11.50) DDIs.

The role of caregivers including prescribers and clinical pharmacists should scale up, accommodating necessary measures to manage elderly patients. Providing better healthcare by minimizing PIM use, in turn, minimizing the related adverse events and improving the quality of life is essential.

LIMITATIONS

LIMITATIONS

- Bodyweight in most of the subjects was not recorded as this study was conducted in the geriatric population, where majority of the patients were unable to stand.
- Medication history, personal and social history of the subjects like diet, history of smoking and alcohol consumption was not available for all the patients in the patient records which led to a lot of missing data.
- Most of the time, when the patients did not get their current medications to hospital, he/she is recorded to have no medication history.
- Creatinine clearance levels were not available in all CKD patients.
- ADR because of PIM was not recorded as the study was retrospective in nature.

CONCLUSION

CONCLUSION

Potentially inappropriate medication use poses a sizable health safety hazard in elderly. After evaluating the potentially inappropriate medications of elderly patients using the updated Beers Criteria 2019. Prevalence of PIMs that should be used with caution (54%) was found to be highest followed by PIMs to be avoided (45%) and recommendation for reduce dose to be (1%).

Elderly patients with polypharmacy and higher age are at more odds to have PIMs. Similarly, patients with a history of ≥3 drugs are at higher risk to have PIMs. Furthermore, we observed that patients with PIMs are at higher risk of having serious and moderate DDIs.

A significant increase in the older population and the need to reduce preventable harm calls for more multidisciplinary strategies to account for the use of high-risk medications. Prescribers can use this data to determine patients at a higher risk for PIMs and be attentive to them while prescribing. Continuous medication and prescription review done by a clinical pharmacist can aid in reducing the occurrence of PIMs.

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FUTURE DIRECTIONS

FUTURE DIRECTIONS:

- Studies with a larger sample size should be carried out to investigate the justification for PIM use.
- Studies to evaluate association between readmissions and PIMs.
- Studies to evaluate the association between comorbidity and PIM association in a more elaborate manner.
- A prospective study on the comparison between PIMs and drug-drug interactions and PIMs leading to ADRs.

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APPENDICES

Appendix - I

KASTURBA HOSPITAL
MANIPAL
(An associate Hospital of MAHE, Manipal)

Kasturba Medical College and Kasturba Hospital
Institutional Ethics Committee
(Registration No. ECR/146/Inst/KA/2013/RR-16)

Communication of the decision of the Institutional Ethics Committee

Saturday 02nd November 2019 **IEC : 562/2019**

Project title	:	Prevalence and Factors influencing inappropriate medication use in elderly patients- A retrospective study using Beers criteria.
Principal Investigator	:	Mr. Syam Sundar Chinthalapudi
Guide/ Co Guide/ Co Investigators	:	Dr. Sreedharan Nair, Dr. Girish Thunga, Cheeti Srilakshmi, Aditi Bajpai, Deepika.S, Dr. Raviraja V. Acharya
Name & Address of Institution	:	Department of Pharmacy Practice, MCOPS, Manipal, Dept. of Medicine, KMC, Manipal.
Status of review	:	New
Date of review	:	13.08.2019
Amendment	:	Modified on 02.11.2019
Decision of the IEC	:	Approved for the study period from 13.08.2019 to 12.03.2021 with the changes in data collection proforma.
Endorsement of continuation of approval : (due date 12.08.2020)	:	Signature and Seal

- The PI and all members of the project shall ensure compliance to current regulatory provisions (as per Schedule Y of Drugs and Cosmetics Act and ICH-GCP), Ethical Guidelines for Biomedical Research on Human Participants by ICMR, and the SOP of IEC including timely submission of Interim Annual Report and Final Closure Report
- Participant Information Sheet and a copy of signed Informed Consent shall be given to every research participant
- Inform IEC in case of any proposed amendments (change in protocol / procedure, site / Investigator etc)
- Inform IEC immediately in case of any Adverse Events and Serious Adverse Events.
- Members of IEC have the right to monitor any project with prior intimation.

Dr. Rajeshkrishna Bhandary P
MEMBER SECRETARY - IEC

IEC Secretariat, Room No. 22, Ground Floor, Faculty Room Complex, Kasturba Medical College Premises,
Kasturba Medical College, Manipal - 576104, Karnataka, India. Phone : +91 - 0820 - 2933522, Fax : +91 - 0820 - 2571927. Email : iec.kmc@manipal.edu

(Yoga and Ayurveda services are excluded from the scope of NABH accreditation)

Appendix – II

CASE REPORT FORM

STUDY: Prevalence and factors influencing inappropriate medication use in elderly patients – A retrospective study using Beers criteria

Hospital No: **IP. No:** **Age:** **Gender: M/F** **Weight:** **BMI:**	**Date of admission:** **Date of discharge:**
Complaints on admission: **Medical history:** **Medication history:** **Personal history:**	
Diagnosis with comorbidities:	
Lab data: **Serum creatinine:** **Creatinine clearance:**	

Brand name	**Generic name**	**Strength**	**Dose/Dosage form**	**Frequency**	**Duration**

Syam Thesis

by Sreedharan Nair

PREVALENCE AND FACTORS INFLUENCING INAPPROPRIATE MEDICATION USE IN ELDERLY PATIENTS -A RETROSPECTIVE STUDY USING UPDATED BEERS CRITERIA

Background:

A major safety concern in elderly population is the use of inappropriate medication. Owing to aging-associated with anatomic and physiologic changes, pharmacokinetic and pharmacodynamics of drugs are prone to alter in these elderlies. Inappropriate drug prescribing and polypharmacy in this population elevates the risk of adverse drug reactions.

Objectives:

To assess the prevalence and factors influencing Potentially Inappropriate Medication (PIM) use in elderly patients according to updated Beers Criteria.

Methodology:

A retrospective observational study was carried out. Case records of 580 patients aged 65 years and above were reviewed. Every case record was identified for at least one PIM based on the American Geriatric Society 2019 Updated Beers Criteria for PIM use in elderly patients. Analysis of collected data was done using Statistical Package for Social Sciences (SPSS) software.

Results:

A total of 580 elderly general medicine patients were reviewed amongst them, 301 were identified as test group with the age of mean 73.7±6.4 years and 101 patients as control group with the age of mean 70.5±5.5 years. Most of the study population were males 59.1% in test and 63.4% in control groups. The prevalence of PIMs to be used with caution were 54% and PIMs to be avoided were 45% the most prescribed PIMs were aspirin (23.51%), diuretics (15.56%), long acting sulphonylureas (12.75%) and Proton Pump inhibitors(PPIs) (11.92%). Increasing age polypharmacy, number of drugs in medication history, certain Chronic diseases were associated with high probability of PIM's use among elderly patients. Risk of developing serious, moderate drug-drug interactions (DDIs) was high in elderly patients with PIMs.

Conclusion:

Potentially inappropriate medication use poses a sizable health safety hazard in elderly patients. After evaluating the potentially inappropriate medications of elderly patients using the updated Beers Criteria 2019.Prevalence of PIMs that should be used with caution (54%) was found to be highest followed by PIMs to be avoided (45%) and recommendation for reduce dose to be (1%) .Age, gender, comorbidities, and polypharmacy were identified as risk factors leading to PIM use. It was also observed that patients with

PIMs are at a higher risk of developing DDIs. A significant increase in the older population and the need to reduce preventable harm calls for more multidisciplinary strategies to account for the use of high-risk medications. Prescribers can use this data to determine patients at a higher risk for PIMs and be attentive to them while prescribing. Continuous medication and prescription review done by a clinical pharmacist can aid in reducing the occurrence of PIMs.

INTRODUCTION

Potentially inappropriate medication (PIM) is a drug or drug class which should be avoided in patients aged 65years or above (geriatrics) as their risk of causing potential adverse event outweighs their clinical benefit [1]. Due to advancing age, multiple chronic problems and comorbidities can result in complex therapeutic regimens, which in turn lead to polypharmacy [2]. Increased number of drugs prescribed leads to an increased prevalence of interactions between the drugs. Higher risk of use of PIMs is attributed to the direct independent relation with increased number of medications. [3].

Multiple studies have identified a high prevalence of PIMs in older adults [4]. Geriatrics account for 4.8% of the total population in India according to the 2011 Census. With the availability of better health care facilities and an increase in life expectancy, the elderly population has increased from the year 1991 to 2011. Increased life expectancy poses a need for better patient care in all sets of population, particularly in vulnerable populations like geriatrics. In elderly people, medication-related problems increase due to increasing age-dependent physiological changes that affect the pharmacokinetics and pharmacodynamics of the drugs [5].

A research carried out in The USA revealed that unplanned hospitalization in older adults is majorly due to adverse drug reactions (ADRs). These ADRs are manageable and preventable with further studies. Implementation of population-based results, while also stressing on the need for reducing inappropriate prescribing can certainly help prevent these ADRs. [6].

With rising PIM use in geriatrics, American Geriatric Society (AGS) Beers Criteria 2019, which is an explicit list of PIMs, supposed to be typically best avoided in older adults aged 65 years has the potential to become a mandatory tool in providing better health care services for the elderly [7].

It is known amongst health care professionals as AGS - Beers Criteria® 2019. Research on 2012 publish of Beers Criteria documented that at least 40% of patients had minimum one PIM whereas, approximately 30% PIMS were seen according to the 2003 publishing of the same. [8]

Another study from the Netherlands concluded that more than half of the participants with a history of cardiovascular disease (CVD) or/and cerebrovascular disease (CVA) had at least one PIM. About 40% of the test participants with identified PIMs posed a potential risk of Major Adverse Cardiac and cerebrovascular events [9].

Geriatrician Mark H. Beers, with a panel of his expert colleagues, formulated this criterion in 1991. In 2011 after the demise of Dr.Beers, the criterion was transferred to the American Geriatric Society, which is a non-profit organization working towards providing better geriatric care. The development of this criterion was intended to provide an efficient and comprehensive tool to help assess the prescribing quality in older adults despite their debility and demographics.

A team of 13 interdisciplinary experts reviewed more than 1,400 research studies and clinical trials between 2017 and the last Beers Criteria update in 2015 on geriatric care and pharmacotherapy to formulate Beers Criteria 2019 using Delphi's method [10].

Drugs included in the Beers list are classified under three brackets: 1) drugs to be avoided in elderly, 2) drugs that overshoot a maximum daily dose 3) drugs to be avoided in the presence of specific comorbidities. In specific cases, these tabulated medications might be suitable for specified off label use. This is also a helpful tool in drug utilization studies.

70 changes were released in this update. Addition of 30 drugs or drug classes to be avoided in old people along-with 40 drug or drug classes to be used with caution or avoid when someone lives with diseases or conditions. These amendments also included outright removal of 25 previously identified potentially inappropriate medications. Similarly, several other drugs were re-categorized with the help of stronger evidence [10].

Now, AGS Beers Criteria 2019 comprises five lists of nearly 100 medications and classes of medicines that are supposed to be avoided or used with caution in the older adult population. It offers itself as a broad tool to help the clinicians, nurses, and caregivers have a better chance at geriatric healthcare [10].

Critical care units serve a pivotal role in patient care through lifesaving and life-preserving treatments. Assessing a patient's health status and carrying out a medication evaluation to alter the medication regimen to provide safer alternatives for older adults is important. Beers Criteria is not a clinical rule; instead, it is a clinical guideline with recommendations to support a clinician's judgment of the therapy given to the patient. Keeping in mind the safety and efficacy of geriatric prescriptions the Beers Criteria is updated to keep up with the best practices in the present world scenarios like avoiding prolonged use of PPIs, non-benzodiazepines, benzodiazepine receptor agonist, hypnotics regardless of the duration of exposure. Tables with updated information on the list of drugs to avoid or reduce dosage based on kidney function along with updated tables of DDIs are provided which add to its benefits [11].

An average of at least four drugs is seen which goes up to 10 and more than 10 in some cases. It highlights the need for periodic assessment of prescriptions to minimize polypharmacy which has been identified as a sizable factor leading to high inappropriate medication use [12]. Moreover, there is a need to subsume Beers Criteria into the electronic prescribing system to forewarn the medical service providers at the time of prescribing, in turn, enabling them to mitigate potential harm [13]. A high number of patients presented with

acute ailments end up taking PIMs at discharge or during admission. This high prevalence appears to increase by nearly 20% after hospitalization. Even after the PIMs presented in the prescriptions on admission were emended, 45% of these patients received other PIMs during the hospital stay. Given the harmful effects that these PIMs might lead to, it is important to address this problem and incorporate this tool for providing better geriatric care. [14] It also highlights the need for practicing geriatrics as a specialty in our country. (14)

To the best of our knowledge, this new criterion has not been employed in any studies in the country so far. Therefore, we have carried out a study based on elderly patients in a tertiary care hospital of Karnataka to estimate prevalence of PIM use, factors influencing their use and impact of PIMs leading to drug-drug interaction using updated AGS Beers Criteria 2019

NEED FOR THE STUDY

Older adults differ from younger adults in several ways that put them at risk of harm by drug interactions and ADR. Aging is often being accompanied by chronic diseases, comorbidities, disabilities, and social isolation leading older adults to have more illnesses. Hence, geriatrics are most often the main group that needs to get hospitalized for their illnesses. It is not surprising that aging progressively increases the number of drugs taken by each elderly patient. [10] Factors like aging, female gender, polypharmacy, multiple prescribers, poor health quality, chronic diseases like hypertension, diabetes, CVD, CVA and depression were seen to be associated with higher risk for PIM use.[4]

Thus, the need to pre-evaluate elderly prescriptions at the time of prescribing in acute, ambulatory, or institutional settings, in the case of polypharmacy and patients with multiple comorbidities is warranted.

PIM use has become a worldwide concern among geriatrics. The use of PIMs leads to the risk of medication misadventure in geriatrics. AGS Updated Beers Criteria 2019 is the most recently updated criteria that is nowadays being widely used across the globe to assess and evaluate PIM use in geriatrics. Beer Criteria provide a comprehensive list of probable PIMs with proper rationales for their off label uses if any. In India however, a couple of studies have highlighted the contribution of polypharmacy and drug interactions among geriatrics.[10]. No systematic study has been documented examining PIMs prescribing done previously among elderly patients in this locality. Hence the main objective of this study was to assess prevalence of PIM use and factors associated with their use in elderly patients using the AGS 2019 Updated Beers Criteria.

OBJECTIVES

- To assess the prevalence of PIM use in elderly patients according to updated Beers Criteria.

- To assess factors influencing PIM use in elderly patients according to updated AGS Beers Criteria 2019.

METHODOLOGY

An observational study was retrospectively conducted in a tertiary care hospital located in Karnataka, South India. Ethical Clearance from Institutional Ethics Committee, MAHE (IEC-562/2019) was obtained before the start of the study. Patients of both genders aged 65 years or older and admitted under the Department of Medicine between June 2018 -June 2019. A total of 580 files were reviewed and 402 files were considered for the study. Out of 402 files subjects with at least one PIM (according to AGS 2019 Updated Beers Criteria) in their discharge prescription were included as test group. Subjects with no PIMs in the discharge prescription were included as control group. Patients discharged against medical advice and expired were excluded. PIM was identified for each patient from the medical record and classified according to 2019 AGS Updated Beers Criteria. These PIMs were categorized according to their recommendations as, avoid (avoid using the medication or medication class) caution (medication or medication classes to be regularly monitored), and reduce dose (medications for which a dose reduction is needed if identified as PIM). Demographical details like age, gender, weight, height, BMI, and personal history were also obtained.

Presence of any medication or medical history related to the pre-hospitalization period, complaints present during the admission and the diagnosis with comorbidities were recorded. The brand name, generic name, strength, dose, frequency, and duration of the discharge medications were also recorded. Patient's serum creatinine was noted and creatinine clearance was calculated in patients using the age-adjusted standard formula: [133-(0.64*age)] for males and 93% of the value for females [19], and for the patients with kidney diseases creatinine clearance (CrCl) was taken from the medical record. Medications prescribed at the time of discharge were retrospectively screened for potential DDIs, using IBM Micromedex and Medscape. The interactions were divided into serious, moderate and, minor according to their indicated severity. Drug-disease interactions were also studied according to the Beers list.

A pre-designed case report form (CRF) was used to enter the captured data. Outcome measures were categorized the primary outcome: prevalence of inappropriate medication uses in patients above or equals to 65years of age secondary outcomes: factors influencing inappropriate medication use.

Statistical Package for the social sciences version 22.0 was used for data entry and statistical analysis. Continuous data were analyzed using mean ± SD and categorical variables were analyzed using frequency and percentage. Factors associated with the PIM use(outcome), to predict the risk of serious, moderate, and minor drug-drug interactions(outcome) in patients with PIMs were evaluated by performing Binary logistic regression analysis.

RESULTS

DEMOGRAPHICS OF THE STUDY POPULATION:

Medical charts of 580 patients were reviewed. 178 patients unfit according to the study criteria were excluded. Amongst them 301were identified as the test group (≥1 PIMs) and 101 Patients were identified as the control group (no PIMs). The mean age of the study population was found to be 73.7±6.4 years in test, 70.5±5.5 years in control. Most patients were male in the test population. The test group was found to have history of medication use ≥3 (53.8%) as shown in Table 1.

Variable		**Test**	**Control**
Age		73.7±6.4 years	70.5±5.5 years
Gender	Female	123(40.9%)	37(36.6%)
	Male	178(59.1%)	64(63.4%)
Number of Drugs in medication history			
No. of drugs in medication history	0	76(25.2%)	52(51.5%)
	1	32(10.6%)	18(17.8%)
	2	31(10.3%)	13(12.9%)
	≥3	162(53.8%)	18(17.9%)

Table 1. Patient demographics

Majority of the test population had three or more comorbidities, whereas in control mostly one comorbidity was prevalent. Hypertension followed by type 2 diabetes mellitus were found to be common as shown in Table 2.

VARIABLE		**TEST**	**CONTROL**
Number of Comorbidities	0	25(8.3%)	29(28.7%)
	1	53(17.6%)	36(35.6%)
	2	93(30.9%)	22(21.8%)
	≥3	130(43.2%)	14(13.9%)
Hypertension		225(74.8%)	47(46.5%)
Type 2 Diabetes Mellitus		181(60.1%)	26(25.7)
Asthma		28(9.3%)	13(12.9%)
Chronic Obstructive Lung Disease (COPD)		40(13.3%)	8(7.9%)
Cardiovascular Disease		106(35.2%)	11(10.9%)
Cerebrovascular Disease		36(12.0%)	7(6.9%)
Hypothyroidism		29(9.6%)	7(6.9%)
Kidney Disease	Acute Kidney Disease	13(4.3%)	2(2.0%)
	Chronic Kidney Disease	31(10.3%)	
Liver Disease	Acute Liver Disease		1(1.0%)
	Chronic Liver Disease	9(3.0%)	3(3.0%)

Table 2. Frequency and percentage of comorbidities.

PREVALENCE OF PIMS:

Our study found a high prevalence of PIMs to be used with Caution (n=348)(54%) than the PIMs to be Avoided (n= 291)(45%) and recommendation to prescribe drug at Reduce dose (n= 9)(1%) as highlighted in Fig 1.

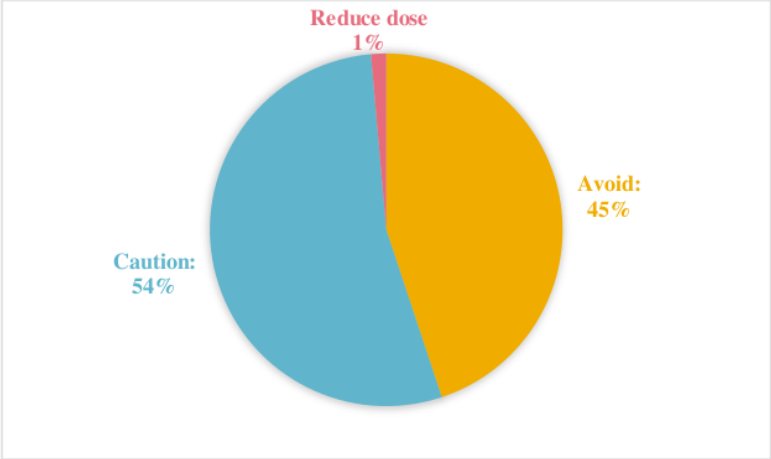

Fig 1. Prevalence of PIMs

The four most prescribed PIMs in our study population were found to be aspirin, diuretics (furosemide, torsemide, spironolactone), long-acting sulphonylureas (glimepiride, glibenclamide), proton pump inhibitors (PPIs) as per AGS 2019 updated Beers Criteria (Table 3).

DRUGS	PERCENTAGE
Aspirin	23.51%
Diuretics	15.56%
Long acting sulphonylureas	12.75%
PPIs	11.92%
Tramadol	4.97%
Prazosin	2.81%
Levetiracetam	0.50%
Benzodiazepines	4.47%
Dextromethorphan	1.99%
Dicyclomine	0.17%
Non-steroidal anti-inflammatory drugs (NSAIDs)	0.83%
Digoxin	0.50%
Antipsychotics	4.64%
Anticholinergics	3.48%
Selective Serotonin Reuptake Inhibitors (SSRI)	1.82%
Pregabalin	0.66%
Serotonin Norepinephrine Reuptake Inhibitors (SNRI)	0.17%

Gabapentin	0.17%
Dabigatran	1.66%
Amiodarone	1.49%
Ranitidine	0.17%
Non-Dihydropyridines	0.17%
Nitrofurantoin	0.33%
Anti-Parkinson's	0.17%
Barbiturates	0.50%
Mineral Oil	3.15%
Mirtazapine	1.16%
Antiepileptics	0.17%
Duloxetine	0.17%

Table 3. Percentage of PIMs

Comparison of gender and PIMs: Comparing Gender with PIMs (only in Test group), out of 178 males, 67 were observed to have one PIM, 62 had 2 PIMs and 49 had 3 or more PIMs. Similarly, out of 123 females, 41 were observed to have one PIM. (Fig 2).

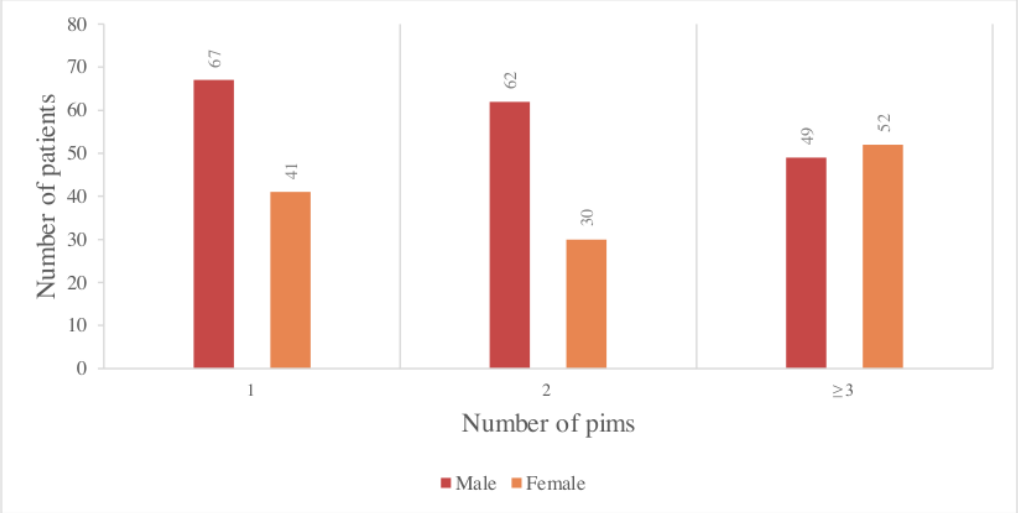

Fig 2. Comparison of Gender and Number of PIMs

Comparison of co-morbidities and PIMs: Comparing the number of comorbidities with the number of PIMs, out of 54 patients with zero comorbidities, 29 had zero PIMs. Out of 89 patients who had one comorbidity, 36 had zero PIMs. Out of 115 patients with 2 comorbidities 39 had one PIM. Out of 144 patients with ≥ 3 comorbidities, 51 had ≥3 PIMs as highlighted in Fig3.

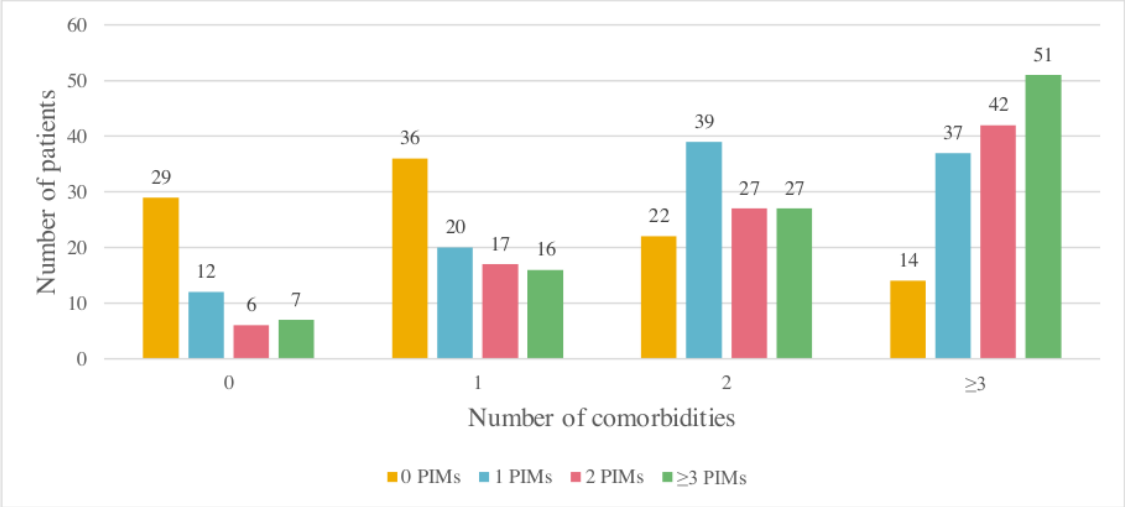

Fig 3. Comparison of PIMs and Comorbidities

Comparison of the number of drugs in medication history and PIMs: As highlighted in Fig 4 while comparing the number of drugs in medication history and PIMs 76 patients with 0-3 drugs in medication history had single PIM usage,33 patients with 4 to 7 drugs in medication history prescribed with two PIMs and 3 PIMs were mostly observed in patients with more than 7 drugs in medication history.

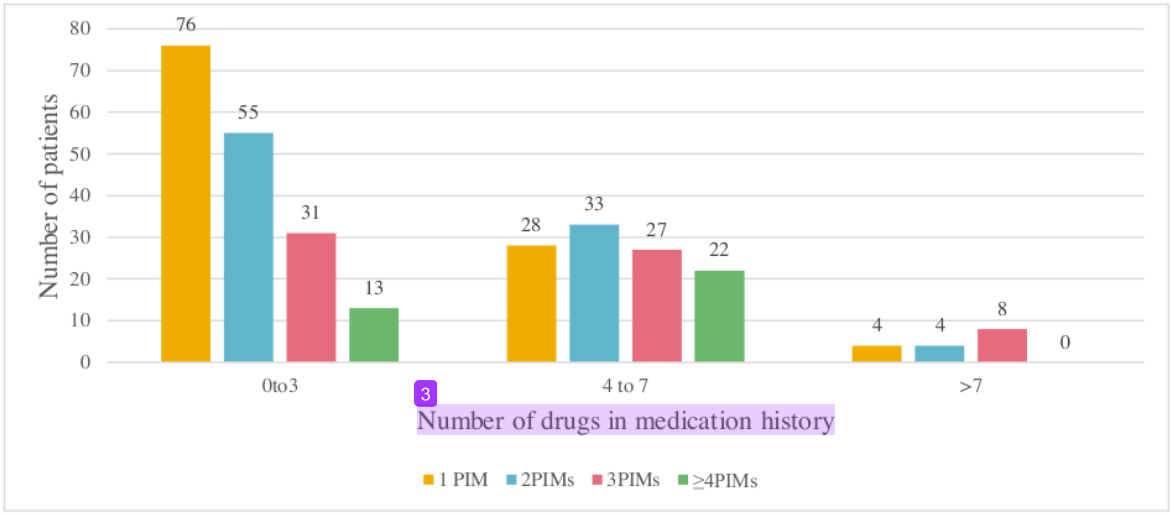

Fig 4. Comparison of number of drugs in medication history and PIMs

Comparison of the total number of discharge drugs and PIMs: The total number of drugs prescribed at discharge were grouped as 1-5drugs,6-10drugs and ≥10 drugs and PIMs as 0(control),1,2,3 and ≥4 as depicted below in fig 5. Out of 93 patients prescribed with 1-5drugs, 55 were observed to have no PIMs. Out of 119 patients prescribed with >10 drugs, zero PIMs were seen in only 8 patients and mostly have ≥4 PIMs.

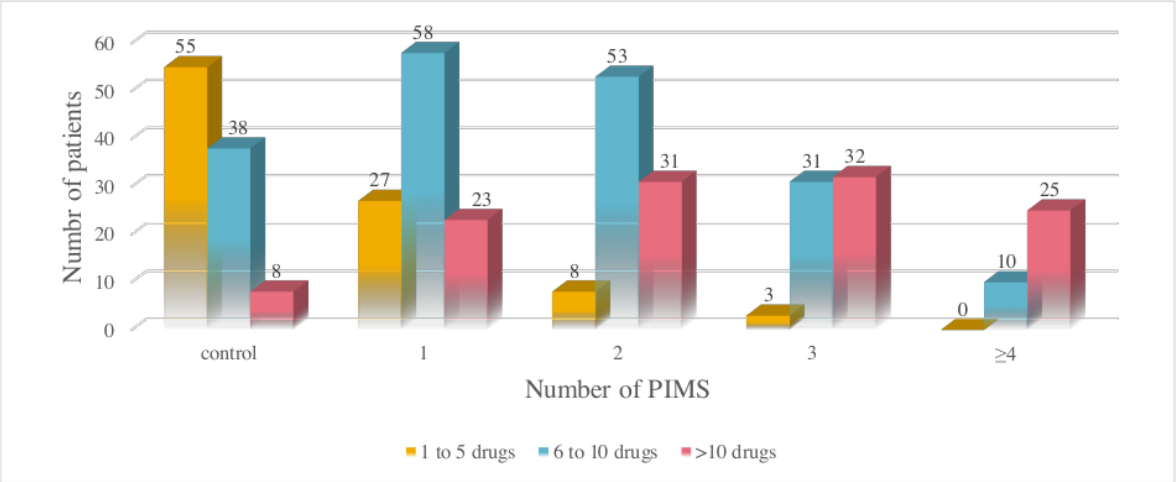

Fig 5. Comparison of Number of Drugs in discharge and PIMs in both Test and Control

Comparison of age and PIMs: On comparing age with the number of PIMs it was observed that elderly patients of age 85 years and above had a greater number of PIMs (≥3). Zero PIMs were more prevalent in the age group between 65 to 69 as depicted in Fig 6.

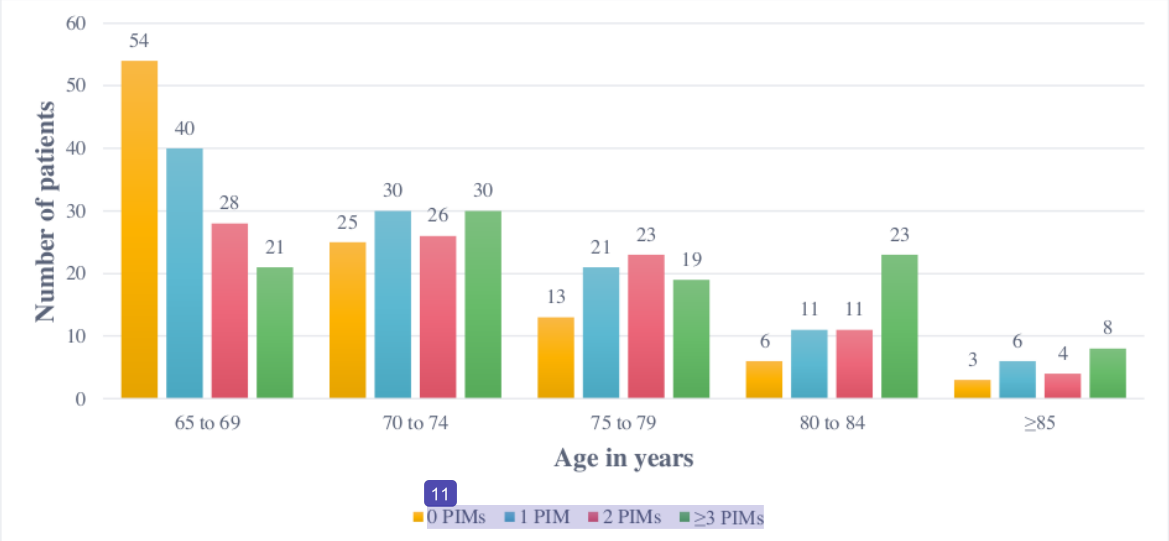

Fig 6. Comparison of age and PIMs

Drug-drug interaction in test and control: When compared for drug interactions in test and control, serious and moderate drug interactions were found to be very high in test population as depicted in Fig.7.

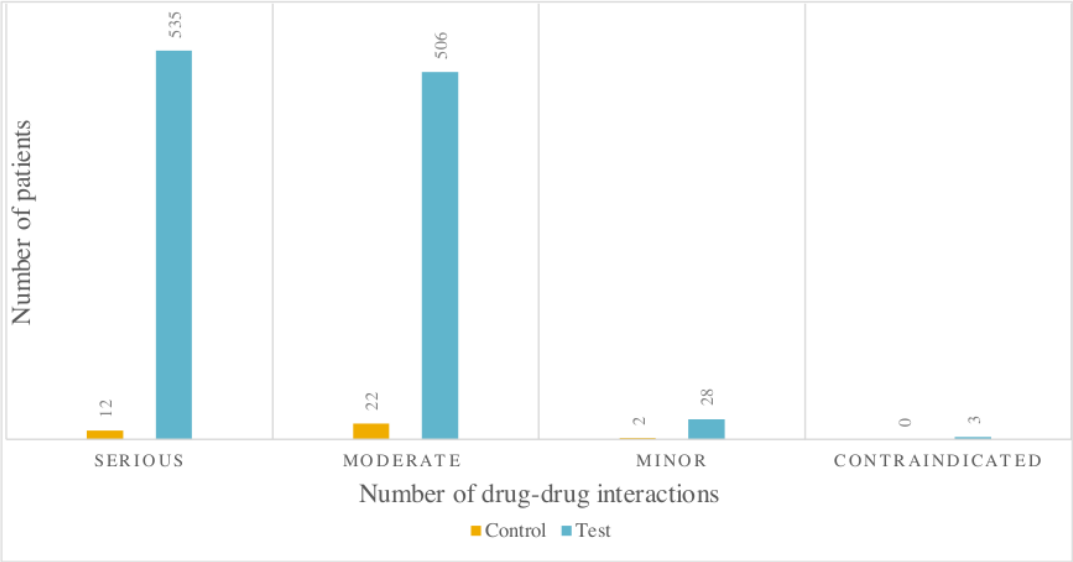

Fig 7. Comparison of drug-drug interactions in test and control

RISK FACTORS ASSOCIATED WITH PIM USE IN LOGISTIC REGRESSION ANALYSIS

On performing regression analysis, PIM use was found to be more likely in elderly patients. Male patients were at fewer odds of having PIMs compared to females. Elderly patients with a history of ≥3 drugs and polypharmacy were observed to have a significant risk of having PIMs. It was also observed that elderly patients with hypertension, type2 diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, and acute kidney disease were at more odds to have PIMs in contrast to patients with asthma, Chronic Obstructive Lung Disease (COPD), thyroid disease and chronic liver disease. An increase in the number of comorbidities is also seen to be associated with a significant prevalence of PIMs. The Odds ratio (OR), 95% Confidence Interval (95% CI) and p-value are depicted in Table.4.

VARIABLE	OR (95%CI)	p-value
Age		
65yrs-69yrs(n=143)	1	NA
70yrs-74yrs(n=111)	3.157 (1.533-6.502)	0.002 *
75yrs-79yrs(n=76)	4.983 (1.949-12.744)	0.001 *
>80yrs (72)	4.088 (1.547-10.804)	0.005 *
Gender		
Male (242)	0.671 (0.360-1.252)	0.21
Female (160)	1	NA
Hypertensive		

Yes(n=272)	1.135 (0.372-3.464)	0.824
No(n=130)	1	NA
Type 2 Diabetes Mellitus		
Yes(n=207)	1.830 (0.641-5.221)	0.259
No (n=195)	1	NA
Acute kidney disease		
Yes(n=15)	2.250 (0.264-19.180)	0.458
No(n=387)	1	NA
Asthma		
Yes(n=41)	0.326 (0.091-1.166)	0.085
No(n=361)	1	NA
Cardiovascular		
Yes(n=117)	1.225 (0.417-3.594)	0.712
No(n=285)	1	NA
COPD		
Yes(n=48)	0.870 (0.243-3.120)	0.831
No(n=354)	1	NA
Thyroid disease		
Yes(n=36)	0.744 (0.187-2.955)	0.674
No (n=366)	1	NA
Chronic Liver disease		
Yes (n=12)	0.746 (0.121-4.603)	0.752
No (n=390)	1	NA
Cerebrovascular disease		
Yes(n=43)	1.873 (0.482-7.271)	0.365
No (n=359)	1	NA
Medication history		
0 Drugs(n=128)	1	NA
1 Drug(n=50)	1.248 (0.529-2.945)	0.613
2 Drugs(n=44)	1.380 (0.542-3.511)	0.499
≥3 Drugs(n=180)	2.836 (1.262-6.373)	0.012 *
Number of Comorbidities		
0(n=54)	1	NA
1(n=89)	0.917 (0.276-3.053)	0.888
2(n=115)	1.399 (0.214-9.124)	0.726
≥3(n=144)	1.579 (0.094-26.488)	0.751
Number of drugs prescribed at discharge		
0-3 drugs (n=32)	1	NA
4-7 drugs(n=110)	5.988 (1.940-18.487)	0.002 *
>7 drugs(n=260)	31.875 (9.786-103.822)	0.000 *

*p-value<0.05, CI-Confidence Interval, >3 drugs prescribed at discharge defined as polypharmacy

Table.no.4 Regression analysis for risk factors

DRUG-DRUG INTERACTIONS:

On regression analysis, the test group was observed to be at more odds to develop Serious and moderate drug-drug interactions (DDIs). The Odds ratio, 95% Confidence Interval, and p-value are depicted in Tables 5,6 and 7 for Serious DDIs, Moderate DDIs, and Minor DDIs, respectively.

Variable	OR (CI 95%)	p-value
Test group (n=301)	19.069(8.929-40.725)	0.000
Control group (n=101)	1	NA

Table.No5 Predicting the risk of serious drug-drug interactions in patients prescribed with PIMs

Variable	OR (CI 95%)	p-value
Test group (n=301)	11.502(6.031-21.937)	0.000
Control group (n=101)	1	NA

Table.No6 Predicting the risk of moderate drug-drug interactions in patients prescribed with PIMs

Variable	OR (CI 95%)	p-value
Test group (n=301)	4.289(0.995-18.479)	0.051
Control group (n=101)	1	NA

Table.No7 Predicting the risk of minor drug-drug interactions in patients prescribed with PIMs

DISCUSSION

In the elderly patients, age-dependent physiological changes of the drugs lead to an increase in medication-related problems due to changes in drug's pharmacokinetics and pharmacodynamics. While observing the demographics of the study population the mean age of the study population was found to be 73.7 ±6.4years in the test, and 70.5±5.5 years in control. It was further grouped into 4 categories, 65-69, 70-74, 75-79, ≥80. Using binary logistic regression as the statistical method it was seen that patients aged between 65-69 years were at lesser odds of receiving a PIM than those falling in the other 3 higher categories. This suggests

that as the age increases the risk of having a PIM in the patient's therapy also increases. Similarly, earlier studies have also been successful in establishing an association between age and PIM use [21]. Due to advancing age and deteriorating health status [4], there is an increase in predisposing factors that lead to chronic diseases which act as comorbidities over a period making PIM use (including off label use) more prominent.

On comparing Gender in the study population out of a total of 301 test population 178(59.1%) were male and 123(40.9%) were female patients. Whereas in Control group males were 64(63.4%), and females were 37(36.6%). Male patients were observed to be higher in number in both Test and control. Male patients were observed to have a lesser risk of having a PIM when compared to females with odds of 0.671 but statically not significant as the p-value is 0.210. An earlier study from Brazil also associated the male gender with fewer PIMs. This difference may be attributed to likeliness of women to visit the doctor and express their problems over men. [16].

Regarding the comorbidities, many studies suggest that PIMs are strongly associated with several comorbidities [9,18,20,22,25]. In our study, most of the test population (patients with a minimum of 1 PIM) have 3 comorbidities. We also observed that patients having 2 or ≥3 comorbidities have a significantly higher risk when compared to the patients with no comorbidities but was not statistically significant as the p-value is not less than 0.05.

We found that patients with asthma, thyroid, chronic liver disease, and COPD may have a lesser risk of causing PIMs. This can be explained by the fact that drugs used as first-line therapy for these diseases are not included as PIMs in updates 2019 AGS Beers Criteria.

Whereas cerebrovascular disease, acute kidney disease, hypertension, cardiovascular, and type 2 diabetes mellitus were observed to have more risk of causing PIMs in this study population, justifiable with an odds ratio greater than 1, although not statistically significant as the p-value was not less than 0.05. A study carried out in the Arab population using bivariate regression analysis found PIM use to be more likely in patients with comorbidities like diabetes, CVD, CKD, osteoarthritis, osteoporosis, and anxiety [9]. As this study population includes ambulatory care patients, comorbidities like osteoporosis, osteoarthritis, anxiety were observed to be more. Drug therapy for these conditions include antipsychotics, NSAIDs which are PIMs as per updated 2019 AGS Beers Criteria.

Hypertension was observed to be the most common comorbidity in the control as well as the test group. Anti-hypertensives used as PIMs were diuretics, prescribed mostly as combinations of one loop or thiazide diuretic with one potassium-sparing diuretic and Prazosin. Other antihypertensive drugs are not included in the PIM list as per updated 2019 AGS Beers Criteria which explains the high prevalence of Hypertension in the control group as well. Type 2 diabetes mellitus was observed as the second most prevalent comorbidity in both test and control group as most of the anti-diabetic drugs were not recognized as PIMs, but long-

acting sulphonylureas (included in updated 2019 AGS Beers Criteria)which were commonly prescribed drugs for type 2 diabetes mellitus resulted in more odds of presence of a PIM.(Having a PIM)

The 2019 updated AGS Beers Criteria categorized PIMs into three types namely, drugs to be avoided, used with caution, and drugs to be used with reduced dose. In our study, we found that the drugs to be used with caution have high prevalence at 54% and the drugs to be avoided were 45% with reduce dose standing at 1%. A similar study done in Saudi Arabia revealed the prevalence of drugs to be avoided was more than the drugs used with caution [9]. The study was done in an ambulatory care setting where most of the drugs used were gastrointestinal agents which should be avoided in elderly patients. In our study, we observed that gastrointestinal agents were given as per the rationale (which is <8weeks).

A study in India done in the cardiac OPD of a tertiary care hospital to evaluate PIM found that Spironolactone was the most used PIM in the elderly patients [24]. In our study, it was found that diuretics were the second most used PIM amongst elderly patients as diuretics are the most common drugs used in heart failure patients. In other studies, NSAIDs and antipsychotics were the most prevalent PIMs to be used in the geriatric population [15,9,17] as these studies have taken the patient population from ambulatory care and mostly involve anxiety and osteoarthritis.

Elderly patients with medication history 3 or more drugs had a higher odds of having PIMs (OR:2.836, p-value:0.012). Higher number of drugs in medication history can be due to the presence of co-morbidities which have been identified as a risk factor for having PIMs. Therefore, higher number of drugs in medication history can be indirectly linked to the prevalence of PIMs.

Significant amount of research consistently states polypharmacy as a major risk factor for PIMs [4,5,9,16,17,23]. In this study, the total number of discharge drugs was categorized into three groups 0-3drugs, 4-7drugs, and >7 drugs. Elderly patients with >7drugs were more prevalent and at highest odds of having PIMs (OR:31.875, p-value:0.00) followed by 4-7drugs (OR:5.988, p-value: 0.002).

Possible risk of developing DDIs due to inappropriate medication use was also identified in this study. We observed the test group to have a higher risk of serious (OR:19.06), moderate (OR:11.50) DDIs.

The role of caregivers including prescribers and clinical pharmacists should scale up, accommodating necessary measures to manage elderly patients. Providing better healthcare by minimizing PIM use, in turn, minimizing the related adverse events and improving the quality of life is essential.

LIMITATIONS

- Bodyweight in most of the subjects was not recorded as this study was conducted in the geriatric population, where majority of the patients were unable to stand.

- Medication history, personal and social history of the subjects like diet, history of smoking and alcohol consumption was not available for all the patients in the patient records which led to a lot of missing data.
- Most of the time, when the patients did not get their current medications to hospital, he/she is recorded to have no medication history.
- Creatinine clearance levels were not available in all CKD patients.
- ADR because of PIM was not recorded as the study was retrospective in nature.

CONCLUSION

Potentially inappropriate medication use poses a sizable health safety hazard in elderly. After evaluating the potentially inappropriate medications of elderly patients using the updated Beers Criteria 2019. Prevalence of PIMs that should be used with caution (54%) was found to be highest followed by PIMs to be avoided (45%) and recommendation for reduce dose to be (1%).

Elderly patients with polypharmacy and higher age are at more odds to have PIMs. Similarly, patients with a history of ≥3 drugs are at higher risk to have PIMs. Furthermore, we observed that patients with PIMs are at higher risk of having serious and moderate DDIs.

A significant increase in the older population and the need to reduce preventable harm calls for more multidisciplinary strategies to account for the use of high-risk medications. Prescribers can use this data to determine patients at a higher risk for PIMs and be attentive to them while prescribing. Continuous medication and prescription review done by a clinical pharmacist can aid in reducing the occurrence of PIMs.

FUTURE DIRECTIONS:

- Studies with a larger sample size should be carried out to investigate the justification for PIM use.
- Studies to evaluate association between readmissions and PIMs.
- Studies to evaluate the association between comorbidity and PIM association in a more elaborate manner.
- A prospective study on the comparison between PIMs and drug-drug interactions and PIMs leading to ADRs.

Syam Thesis

ORIGINALITY REPORT

%5	%1	%4	%1
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Abstracts", Pharmacoepidemiology and Drug Safety, 2019 Publication	%1
2	Submitted to University of Warwick Student Paper	%1
3	Pieter Cornu, Stephane Steurbaut, Tinne Leysen, Eva De Baere, Claudine Ligneel, Tony Mets, Alain G Dupont. "Effect of Medication Reconciliation at Hospital Admission on Medication Discrepancies During Hospitalization and at Discharge for Geriatric Patients", Annals of Pharmacotherapy, 2012 Publication	<%1
4	Vanida Prasert, Manabu Akazawa, Aiko Shono, Farsai Chanjaruporn et al. "Applying the Lists of Risk Drugs for Thai Elderly (LRDTE) as a mechanism to account for patient age and medicine severity in assessing potentially inappropriate medication use", Research in Social and Administrative Pharmacy, 2018 Publication	<%1

5	Tamas A. Szabo. "Anesthetic Implications of Chronic Medications", Geriatric Anesthesiology, 2008 Publication	<%1
6	Ha-Lim Jeon, Juhee Park, Euna Han, Dong-Sook Kim. "Potentially inappropriate medication and hospitalization/emergency department visits among the elderly in Korea", International Journal for Quality in Health Care, 2018 Publication	<%1
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8	www.frontiersin.org Internet Source	<%1
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