IJBPAS, August, 2018, 7(8): 1500-1511

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

STUDY ON DRUG UTILIZATION EVALUATION IN GERIATRIC MEDICAL IN-PATIENTS IN A QUATERNARY CARE HOSPITAL

BASIL JOSE[1], RAJUDIVYA[2], ELJO JOHNSON[3] AND DR. SRINIVASAN R[4*]

1: Pharm D intern, Department of Pharmacy Practice, PES College of Pharmacy, Bengaluru, Karnataka, India

2:, Pharm D intern, Department of Pharmacy Practice, PES College of Pharmacy, Bengaluru, Karnataka, India

3: Pharm D intern, Department of Pharmacy Practice, PES College of Pharmacy, Bengaluru, Karnataka, India

4: Head, Department of pharmacy practice, PES College of Pharmacy, Bengaluru, Karnataka, India

***Corresponding Author: Dr R. Srinivasan, E- Mail: basiljose1993@gmail.com**

Received 4th Feb. 2018; Revised 25th March. 2018; Accepted 25th April 2018; Available online 1st August 2018

https://doi.org/10.31032/IJBPAS/2018/7.8.4502

ABSTRACT

Background

In recent years, various Drug Utilization Evaluation (DUE) studies have been carried out to determine the quality of services provided in the health care system. Such studies mainly focus on factors relating to drug prescription, dispensing, administration, the related outcomes and what impact these outcomes can have on the quality of life of the patient. DUE in geriatrics is an area of focus due to various complications that arise with age and changes in their physiological functions.

Objective

To analyse Drug Utilization patterns, occurrence of Potentially Inappropriate Medications (PIM's), Adverse Drug Reactions (ADR's), Drug Interactions (DI) and Medication errors in patients and to provide suggestions for better healthcare.

Methodology

A retro-prospective qualitative study was carried at a quaternary care hospital over a period of 6 months. All the relevant data was recorded in the data collection form and analysed statistically.

Results

Of the 329 cases collected, male preponderance was observed (65.34%). Most patients admitted belonged to the age group of 65-69 (36.77%).Cardiology (30.39%) was the system most affected, with Hypertension (HTN) (32) and Diabetes Mellitus (DM) (19) being the most common co-morbidities. Most prescriptions hada total of 5-9 (43.76%) drugs, Pantoprazole (266) being the most prescribed drug.73 (22.18%) PIM's, 273 Medication Errors, 5 ADR's and 2 Drug-Disease interactions were found in the prescriptions.

Conclusion

From this study, a conclusion can be drawn that more care needs to be directed towards patient care and also towards improving the quality of life of geriatrics.

Keywords: Geriatrics, drug utilization evaluation, AGS Beer's Criteria, Medication Errors, ADR's

INTRODUCTION

Elderly is the chronological age above 65years.India is the third country after China and USA with large elderly population in the world. Though elderly are reported to be responsible for half the total drug usage, very few trials have been designed for them. Physiological and pharmacological function varies in elderly population. Presence of co-morbidities in elderly people require use of multiple medications which increase the irrational prescription patterns, use of inappropriate medications, noncompliance, economic burden, ADR's, and Drug Interactions.

Occurrence of ADR's in elderly population is 2-3 times higher than the rest of the population.[1,2]In geriatrics, ADR's occur due to multiple co-morbidities and has become increasingly significant in the last 2-3 decades. According to World Health Organization's (WHO) definition "an ADR is a response to a drug that is noxious and unintended, and occurs at doses normally used in human for the prophylaxis, diagnosis and treatment of diseases, or for modification of physiological function."[3]ADR also occurs due to decreased hepatic metabolism, progressive deterioration of renal function[9], altered pharmacokinetics and pharmacodynamics, slower homeostatic responses, inappropriate prescription like wrong doing, incorrect frequency of administration, prescribing ineffective medication and duplicate

therapy. About one fourth of the ADR's are due to inappropriate medication use.[4,5]

The use of PIM's among the elderly is a serious public health problem because it is directly linked to increased morbidity and mortality, causing high costs to the public. Patients taking a large number of medications are more likely to have potentially inappropriate prescriptions, making the patients more vulnerable to undesirable drug-related problems. The AGS Beer's criteria for PIM in older adult is an explicit list of drug that should be avoided in certain disease or syndrome, prescribed at reduced dosage or with caution or closely monitored.[6]

Medication Error is another area of concern seen with respect to prescriptions. Although it is observed in all age groups, it is more prevalent in geriatric population due to the high number of medications prescribed. The NCC MERP defines Medication Error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedure and systems, including prescribing, order communication, product labelling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use."[7]

Thus, DUE is carried out in elderly to analyse the occurrence of medical, social and economic well being. DUE is defined by World Health Organization (WHO) as "marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences."

MATERIALS AND METHODS

A 6 months retro-prospective study was conducted at a quaternary care hospital with permission from the Institutional Review Board. Information of 329 patients (age ≥65 years) admitted into medical wards was collected from the patient case files and recorded into the data collection form. Patients admitted into day-care and ICU were excluded from the study. Collected data consisted of age, sex, current complaints, diagnosis, past medical and medication histories, all known allergies, the given treatment and the documented ADR's.

The collected data was analyzed for age and gender distribution, common diagnosis and systems involved, days of hospital stay, number of drugs per prescription, co-morbidities, medication errors, drug interactions, ADR's and PIM's. Medication errors were NCC MERP classified. ADR's were assessed with Naranjo's Algorithm,

severity by Modified Hartwig and Siegel Scale, and preventability by Modified Schumock and Thornton criteria.[8,9,10] PIM's and DI were classified using AGS Beer's Criteria 2015.[11]

STATISTICAL ANALYSIS

All the collected data was subjected to descriptive statistical analysis using Microsoft Excel 2007.

RESULTS

A retro-prospective study was conducted over a period of 6 months at a quaternary care hospital in Bengaluru. The summary of the results is given in Table 1.

The total number of subjects enrolled in this study were 329, out of which 215(65.34%) were found to be male and 114(34.65%) were found to be female. The average age of the patients admitted was 72.07 years. A total of 121 (36.77%) patients admitted belonged to the age group of 65-69 years. This age group had the maximum patients, followed by 108 (32.82%) patients in the age group of 70-74 years. The average stay in the hospital was 4.72 days. The maximum number of patients were admitted for a period of 1- 4 days, having a total admission of 195 (59.27%) cases, followed by 5-9 days (33.43%), 10-14 days (5.16%) and≥15 days (1.85%) admissions.

Cardiovascular system was found to be the major system involved with a total of 30.29%, followed by Respiratory system (13.98%), Oncology (10.33%), Gastro-intestinal system (9.72%), Central nervous system (8.81%),Orthopaedic (6.38%), Genito-urinary system (4.86%), Haematology (3.95%) and Nephrology (2.43%). The major 5 conditions observed in the study was Hypertension (20.13%), followed by Diabetes Mellitus (15.6%), Ischemic Heart Disease(11.74%), Carcinoma (5.87%) and Cerebrovascular Accident (4.36%).

In all the cases analysed, 93 (28.26%) patients presented with 1 co-morbid condition, followed by 90 (27.35%) patients with 2 co-morbid conditions and 81 (24.62%) patients with 3 or more co-morbid conditions. HTN and DM were most common comorbid conditions seen in the patients.

Out of 329 patients, 198 patients had non-invasive treatment procedures while 131 patients had invasive treatment procedures. Most of the patients were administered with 5-9 drugs (43.76%) , followed by 10-14 drugs (29.78%) and greater than 15 drugs (16.11%) throughout the hospital stay. A total of 3338 drugs were prescribed, with 51.1% of the drugs given through parenteral route and 48.49% through central route. A total of 257 different types of drugs were prescribed, with 43.7% in generic names and 56.3% in various brand names. Average

number of drugs prescribed per patients was 9.56.

The most commonly prescribed drugs were Gastrointestinal (16.26%), Antimicrobials (15.87%), Cardiovascular (15.63%), Respiratory (11.83%) and Blood and Blood forming agents (9.64%). Pantoprazole (80.8%), Paracetamol (41.33%), Atorvastatin (32.5%), Salbutamol (32.5%) were the most commonly prescribed drugs. Salbutamol+ Ipratropium bromide (35.86%), Piperacillin+ Tazobactam (16%) and Multivitamins (13.9%) were commonly prescribed Fixed Dose Combinations (FDC's). Atleast one antimicrobial agent was prescribed in 266 (80.8%) patients. Ceftriaxone, Cefixime, Metronidazole, Cefotaxime and Ciprofloxacin were most commonly prescribed antimicrobial drugs.

ADR's were documented in 5 (1.51%) patients. Description of ADR's, causative drugs, causality, severity and preventability assessment are mentioned in Table 2.

The prescriptions were thoroughly checked for Potentially Inappropriate Medications using AGS Beer's Criteria 2015. There were 73 medications which were found to be inappropriate, accounting for 22.18% inappropriateness of all the prescriptions. Alternatives have also been suggested for the PIM's based on various studies that have been carried out as given in Table 3.

Drugs to be used with caution are:

- Aspirin, Dabigatran (Increased Bleeding)
- Diuretics, Carboplatin, Carbamazepine (Exacerbate Hyponatremia)
- Vasodilators (Exacerbate Episodes Of Syncope).

Benzodiazepine (32.8%), alpha blockers (16.43%) and CNS (12.32%) are the most commonly prescribed inappropriate medications.

Table 4 shows Drug-Disease interactions according to AGS Beer's Criteria 2015. 2 interactions were found in the study.

Medication errors (Figure 1) were classified according to NCCMERP classification. 273 errors were found in total, of which 128 were of no harm and 5 were of harm.

Table 1: Various parameters analysed

Sex (Male/Female)	**65.34%/34.65%**
Age (Mean)	**72.07 Years**
Major Diagnosis	**Cardio-Vascular System (30.29%), Respiratory System (13.98%), Carcinoma (10.33%)**
Average Length Of Stay	**4.72 Days**
Co-Morbidities	**1 (28.26%), 2 (27.35%), >3 (24.62%)**
Common Co-Morbidities	**Hypertension, Diabetes Mellitus, Ischemic Heart Disease**
Treatment Procedure	**Non-Invasive (60.18%), Invasive (39.81%),**
Average Number Of Drugs Per Patient	**9**
Most Common Drug Class	**Gastrointestinal (16.26%), Antimicrobial (15.87%), Cardio-Vascular (15.63%)**
Most Common Drug (N=3338)	**Pantoprazole (266), Paracetamol (136), Atorvastatin**

	(107)
Route Of Administration	Parenterals (51.51%), Enterals (48.49%)
Adverse Drug Reaction	5
Potentially Inappropriate Medications Prescribed	22.18%
Drug-Disease Interactions	3

Table 2: Adverse Drug Reaction With Causative Drugs, Causality , Severity And Preventability Assessment

Description Of ADR	Causative Drug	Causality Assessment (Naranjo Algorithm)	Severity Assessment (Modified Hartwig And Siegel Scale)	Preventability Assessment (Modified Schumock And Thornton)	Interventions
Itching And Rash (N=2)	Ciprofloxacin, Piperacillin And Tazobactam	Score 6 (Probable)	Level 2	Definitely Preventable	Discontinued Drug.Inj.Avil and Hydrocort Administered
Breathing Difficulty, Rash, Cardiopulmonary Arrest (N=1)	Ondansetron	Score 6 (Probable)	Level 2	Definitely Preventable	Inj.Avil and Hydrocort
Systematic Hyponatremia (N=1)	Pantoprazole	Score 7 (Probable)	Level 3	Definitely Preventable	Discontinued Drug
Anaphylaxis (N=1)	Diclofenac, Pencillin	Score 7 (Probable)	Level 3	Definitely Preventable	Hydrocort and Fexofenadine

Table 3: Potentially Inappropriate Medications using AGS Beer's Criteria 2015

Medication		Indication	Number	Alternative
Class	Drug			
Anti cholinergic	Pheniramine	Reduced clearance with age, increased risk of confusion, dry mouth, constipation and other cholinergic effect	4	Intranasal NS[19]
	Hydroxyzine		2	2nd generation anti histamines (cetrizine, fexofenadine) and intranasal steroid (beclomethasone, fluticasone)[19]
Alpha blocker	Prazosin	High risk of orthostatic hypotension	12	Thiazide diuretics, ACEI, ARB, CCB[20]
Centrally acting anti hypertensives	Clonidine	High risk of orthostatic hypotension, bradycardia,CNS effect	8	ACEI, ARB ,thiazide diuretics [19]
Anti arrhythmic	Amiodarone	Associated with thyroid diseases,pulmonary disorders and QT interval prolongation	4	Dronedarone[21]
Sympathomimetic	Digoxin	Increased risk of toxicity and no additional benefit with high dose	2	Captopril[22]
CCB	Nifedipine	Risk of precipitating myocardial ischmeia	2	Amlodipine[19]
CNS	Amitriptyline	Sedative and orthostatic hypotension	9	For depression SSRI (except paroxetine), SNRI,bupropion, for neuropathic pain SNRI,gabapentin,pregabalin and lidocaine patch[19]

Anti epileptics	**Phenobarbital**	**High rate of physical dependancy,tol erance to sleep benefits**	**1**	**Other anticonvulsants (lamotrigine, levetiracetam)[19]**
Benzodiazepines	**Alprazolam**	**Increased sensitivity to BZD, increased risk of deliriium, falls, fractures**	**17**	**Ramelteon and low dose doxepin[20]**
	Lorazepam		**3**	
	Clonazepam		**4**	
NSAIDS	**Ketorolac**	**Increased risk of gastric bleeding, PUD**	**1**	**Acetaminophen, ibuprofen, naproxen[19]**
Opioids	**Pentazocine**	**Confusion, hallucinationit is also a mixed agonist and antagonist**	**4**	**For acute moderate to severe tramadol, morphine, oxycodone[19]**

Table 4: Drug-Disease Interactions according to AGS Beer's Criteria 2015

Sr. No	Disease/ Syndrome	Medication CLASS	DRUG	Number	Rationale	Recommendation
1	**Fracture**	**TCA** **Anti-Psychotic**	**Dosulepin** **Quetiapine**	**1** **1**	**If One Of The Drug Used , Consider Reducing Use Of Other CNS Medication That Increase Risk Of Fracture Or Falls**	**Avoid Unless Other Alternatives Are Not Available.**
2	**Heart Failure**	**NSAID's**	**Etoricoxib**	**1**	**Potential To Promote Fluid Retention And Exacerbate Heart Failure**	**Avoid.**

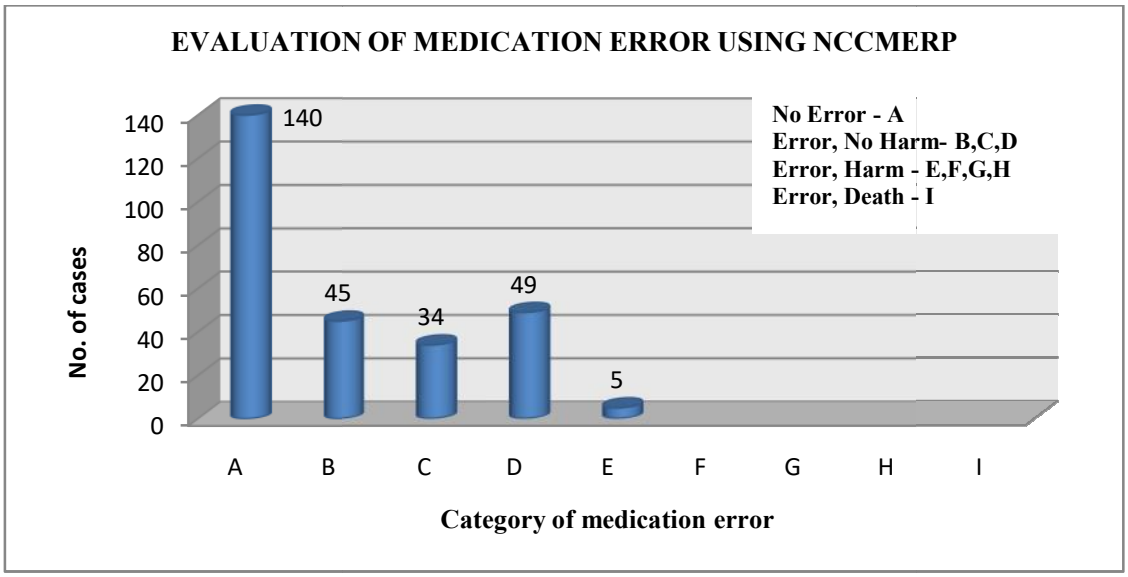

Figure 1: Evaluation of Medication Error using NCCMERP

DISCUSSION

The geriatric population worldwide is prone to many drug related problems, thus having increased the need to conduct studies for the same. We undertook this study to analyse geriatric drug use patterns and other related problems.

Of the 329 patients enrolled in the study, 215 were males and 114 were females, thus showing male preponderance as opposed to other studies.[12] The average age of patients in our study was 72.07 years while in the study by Jhaveri et al the average age was 72.69 years.[13]The average hospital stay in our study was 4.72 days while it was 5.07 days in the study by Jhaveri et al.[13]. The most common systems in the study were Cardio-Vascular System (30.29%), Respiratory System (13.98%), Carcinoma (10.33%) compared to Cardiovascular system (80.02%) followed by Central Nervous System (22.18%) and Haematological system (19.23%) found by Jhaveri et al.[13] 28.26% of the patients in our study had 1 co-morbid condition, followed by 27.35% with 2 comorbid conditions and 24.62% greater than 3 comorbid conditions, wherein 66% had 1 comorbid condition and 38% had greater than 3 comorbid conditionsas found in the study by Nayaka SR et al.[13]

The number of drugs prescribed per patient was found to be higher in our study due to the multiple comorbidities present in our geriatric population,[13]with five or more drugs prescribed in 89% cases. Polypharmacy can cause increased Drug Interactions, ADR's and Medication Errors. Total of 21.2% of the patients were prescribed with FDC's in our study, which is higher when compared with study by Jhaveri et al.[13] Salbutamol+ ipratropium bromide, Piperacillin+ Tazobactam and Multivitamins were the commonly prescribed FDC's in our study as opposed to Etofylline + Theophylline (deriphylline) and Multivitamins being the commonly prescribed FDC's in the study by Jhaveri et al.[13]

Pantoprazole, Paracetamol, Atorvastatin and Salbutamol were the most commonly prescribed drugs in our study. Aspirin, Ranitidine, Metoclopramide, Atorvastatin, and Isosorbidedinitrate were commonly utilized drugs by Jhaveri et al., 2014,[13] whereas; Ranitidine, Multivitamins, Amlodipine, Ipratropium and Dinitrosalicylic acid were the commonly observed drugs by Shankar et al., 2010.[14] Pantoprazole were prescribed in 80% of the cases. Pantoprazole was prescribed without any gastrointestinal complication in most of the cases as prophylactic treatment against non-steroidal anti-inflammatory drugs (NSAID) induced gastritis, which is irrational use of the drug. Atorvastatin was prescribed for treatment and prevention of IHD. It's use is justified as the most common system for admission was Cardiovascular system. Paracetamol and Salbutamol use in this study

is justifiable. Ceftriaxone was the most commonly prescribed antimicrobial agent as against Cefotaxim reported by Jhaveri et al.[13] Use of culture sensitivity should be promoted to reduce the incidences of resistance.

ADR's were documented in 1.51% of the patients, which is higher than study conducted by Jhaveri et al.[13] Reported incidences of ADR's in elderly varies from 1.52 to 61.8%.[15, 16,18]Low incidences of ADR's may be due to the lack of awareness among the doctors and other medical professionals, for which an accurate ADR reporting system should be developed in the hospitals.

There were 73 inappropriate medications prescribed accounting for 22.18% inappropriateness of all the prescriptions, which is less when compared to the study conducted by Lima et al.[17] The various inappropriate drugs found in the study using Beers Criteria 2015 are Pheniramine, Hydroxyzine, Prazosin, Clonidine, Amiodarone, Digoxin, Nifedipine, Amitriptyline, Phenobarbital, Alprazolam, Lorazepam, Clonazepam, Ketorolac, and Pentazocine. Drugs to be used with caution are Aspirin, Dabigatran (Increased Bleeding), Diuretics, Carboplatin, Carbamazepine (Exacerbate Hyponatremia), Vasodilators (Exacerbate Episodes of Syncope). Benzodiazepine (32.8%), Alpha blockers (16.43%) and CNS drugs (12.32%) were the most commonly prescribed inappropriate medications. Central nervous system (35.3%), with antipsychotics (26.5%) and analgesics (15.1%) were the PIM's most frequently used in the study by Lima et al.[17] The hospital must develop prescribing guidelines in accordance with the AGS Beer's Criteria to improve the patient quality of life. There is a clear correlation between PIM use and polypharmacy but not with age, sex and hospital admission.

CONCLUSION

Drug Utilization Evaluation was successfully carried out in 329 geriatric patients. From this study, a conclusion can be drawn that more importance needs to be directed towards patient care and also towards improving the quality of life of geriatrics.

Few suggestions for achieving the same:

- Complete and correct data must be collected from the patients so that the correct medication can be prescribed for the correct condition.
- All the medications prescribed must be thoroughly checked for medication errors, drug interactions and for potentially inappropriate medications as per the standard prescribing guidelines for geriatrics.
- The hospital must develop an accurate ADR reporting system, wherein the nurses and doctors can report the ADR immediately.

- The hospital must develop prescribing guidelines in accordance with the international and established guidelines for geriatrics (Example AGS Beers Criteria). These guidelines must be continuously updated. Following these guidelines will help in improving patient care and quality of life.
- The doctors and nurses must work along with the pharmacist to improve patient care.

LIMITATIONS

1. The period of study was six months which was very limited to carryout observations in a wider aspect.
2. Spontaneous ADR reporting system is not effective in the hospital.

ACKNOWLEDGEMENT

We sincerely thank PES College of Pharmacy, Bangalore for their continued support and guidance to make this project a success.

REFERENCE

[1] P D Sachdeva et al., drug utilization studies- scope and future perspectives International Journal on Pharmaceutical and Biological Research. Vol. 1(1), 2010, 11-17

[2] Shalini S, Ravichandran V, Mohanty BK, Dhanaraj SK, Saraswathi R. Drug Utilization Studies – An Overview. International Journal of Pharmaceutical Sciences and Nanotechnology. Volume 3, Issue 1, April – June 2010

[3] Singh H, Dulhani N, Kumar B, Singh P, Tewari P, Nayak K.A pharmacovigilance study in medicine department of tertiary care hospital in Chhattisgarh (Jagdalpur), India. J Young Pharm., 2010; 2(1): 95-100.

[4] Gray CL, Gardner C. Adverse drug events in the elderly: an ongoing problem. J Manag Care Pharm., 2009; 15(7): 568-71

[5] Jose J. Promoting drug safety in elderly – needs a proactive approach. Indian J Med Res 2012; 136(3):362-4.

[6] Shalini S, Ravichandran V, Mohanty BK, Dhanaraj SK, Saraswathi R. Drug Utilization Studies – An Overview. International Journal of Pharmaceutical Sciences and Nanotechnology. Volume 3 • Issue 1 • April – June 2010.

[7] Joseph T. Hanlon, PharmD, MS, Todd P. Semla, MS, PharmD, Kenneth E. Schmader, MD. Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug–Disease Interactions in the Elderly Quality Measures. J Am Geriatr. Soc 2015. DOI: 10.1111/jgs.13807.

[8] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther., 1981; 30: 239-45.

[9] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm., 1992; 49: 2229-32.

[10] Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm., 1992; 27: 538.

[11] Journal of the American Geriatrics Society/ Vol 63, Issue 11.

[12] Swapna R. Nayaka, B. Rajeshwari, T. V. Venkatadri. Drug utilization pattern in geriatric inpatients of medicine department in a Tertiary Care Teaching Hospital. International Journal of Basic & Clinical Pharmacology ;May-June 2015;Vol 4;Issue 3

[13] Binit N. Jhaveri, Tejas K. Patel, Manish J. Barvaliya, C. B. Tripathi. Drug utilization pattern and pharmacoeconomic analysis in geriatric medical in patients of a tertiary care hospital of India. Journal of Pharmacology and Pharmacotherapeutics; January-March 2014; Vol 5; Issue1

[14] Shankar PR, Upadhyay DK, Subish P, Bhandari RB, Das B. Drug utilisation among older inpatients in a teaching hospital in Western Nepal. Singapore Med J 2010; 51: 28-34.

[15] Sikdar KC, Dowden J, Alagheh Bandan R, Macdonald D, Peter P, Gadag V. Adverse drug reactions in elderly hospitalized patients: A 12-year population-based retrospective cohort study. Ann Pharmacother., 2012; 46: 960-71.

[16] Harugeri A, Parthasarathi G, Ramesh M, Guido S, Basavana Gowdappa H. Frequency and nature of adverse drug reactions in elderly in-patients of two Indian medical college hospitals. J Postgrad Med 2011;57:189-95

[17] Lima et al.: Potentially inappropriate medications used by the elderly: prevalence and risk factors in Brazilian care homes.BMC Geriatrics 2013 13:52.

[18] Gorzoni ML, Fabbri RM, Pires SL. Potentially inappropriate medications in elderly. Rev Assoc Med Bras 2012; 58: 442-6.

[19] Joseph T. Hanlon, PharmD, MS, Todd P. Semla, MS, PharmD, and Kenneth E. Schmader, MD, Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug–Disease Interactions in the Elderly Quality Measures. JAGS 2015. The American Geriatrics Society 0002-8614/.

[20] Chitra, N.Senthilvel, R. Sowmya, Sreerekha Sathyan, R.Srisha. A Study on Prescribing Pattern of Drugs in Geriatrics Using Beers Criteria at a Private Corporate Hospital. International Journal of Pharmaceutical Sciences and Research, 2015; Vol 6 (11): 4810-4825.

[21] Shreya M. Shah, Megha Shah. A Study on Safer Alternative to Amiodarone. Indian J Pharmacol. 2012 Nov-Dec; 44(6):805-806.

[22] Jay Cohn, Morton Hawkins, Herbert Levine. Comparative Effects of Therapy with Captopril and Digoxin in Patients with Mild to Moderate Heart Failure. JAMA. 2012; 259(4):539-544.