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Original Research Article

COVID-19 impact on the prevalence of PIMS in elderly patients according to STOPP/START criteria: a record base study

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ABSTRACT

Background: Polypharmacy, contribute to an increased risk of adverse drug reaction morbidity, and mortality, and increases the length of hospital stay, hospital revisits and readmissions. We aimed to evaluate the prevalence and trends of polypharmacy and potentially inappropriate medications in elderly patients with version 2. STOPP/START criteria, and assess the severity of adverse drug events in patients with PIMs.
Methods: This is a retrospective, record-based study of over-the-counter, and potentiallyinappropriate medications in the prescriptions of patients (>60 years). PIMs have been identified and further investigated to determine any adverse effects. If harm occurred, theseverity of an adverse effect was rated using a modified Hartwig and Siegel scale. The causality of the events was assessed by using Naranjo's scale.
Results: Out of 583 patients polypharmacy and excessive polypharmacy were found in 36.0%, and 42.8% of pre-admission medications. The most common over-the-counter (OTC) drugs were hydrocortisone (39.86%), ranitidine (21.62%), bisacodyl (14.86%), and diphenhydramine (12.84%). A statistically significant positive correlation was seenbetween age and the number of drugs prescribed (r2=0.16), while a non-significant positive correlation was found between sex, length of stay (LOS), and the number of drugs prescribed (r2 =0.0002, r2 =0.001). Common PIMs related incidence reported include Insulin (regular) 31.25% (N=20), Trihexyphenidyl (THP) 18.75%, zolpidem 12.5%, acetylsalicylic acid 9.3%, pantoprazole 52 7.81%, furosemide 7.8%, hydrocortisone 6.25%, and glimepiride 6.25%. Total of 130 ADRs 50% were mild, 28.4% were moderate, and 21.5% were severe. Out of 130 incidents, 64.6% were preventable, 22.3% were probably preventable, and 13.0% were not preventable. A total of 50.0% recovered completely from the ADRs, 33.0% had been recovering, 12.3% recovered with a squeal, 2.3% could not recover and 2.3% had been fatal.
Conclusions: The study shows high uses of OTC and PIMs and PGx in elderly patients;which encourage intent need to develop awareness and action plans.

Keywords: STOPP/ START criteria, Potentially inappropriate medicines, Polypharmacy,Geriatrics medicines, Over-the-counter drugs

INTRODUCTION

The COVID-19 outbreak, caused by the severe acute respiratory syndrome coronavirus (SARS- CoV-2) virus was declared a pandemic by World Health Organization (WHO) on 11 March 2020. Its widespread global transmission and unparalleled impact reshaped the world and have strained the medical healthcare services beyond their normal capacity.[1] Global response to the COVID-19 pandemic has exposed inherent weaknesses in our healthcare preparedness and response. The health systems

have been grossly overwhelmed by the pandemic, which resulted in a shift of priorities of the health systems. There was a restricted capacity to provide services and disruption of logistics and supplies of essential drugs. In COVID-19 overburdened hospitals and health facilities, patients were not able to access standard care for their acute or chronic ailments. One of the most critical and vulnerable age groups is elderly with non-communicable diseases and special needs. With better medical facilities life expectancy increased from 66.24 to 69.16 since the year 2010 to 2017.[2] According to population census 2011, there are nearly 104 million elderly persons (Aged 60 years or above) in India; 53 million females and 51 million males. A report released by the United Nations population fund and helpage India suggests that the number of elderly persons is expected to grow to 173 million by 2026.[3] Physiological and cognitive functions tend to change with an age-related change in pharmacokinetics and pharmacodynamics. Subsequently, these patients are often excluded from randomized controlled clinical trials and the pharmacology 89 and recommended dosage regimen of most of the drugs in this population are not well established.[4-6] With advancing in age, there is an excessive occurrence of multiple chronic diseases and comorbidity. Management of these comorbidities is potentially associated with increased prevalence in the use of multiple drugs (polypharmacy and immoderate polypharmacy), which makes them at higher risk of probably beside the point use of PIMS.[7] PIMs are defined as "medications that should be averted because of their risk which outweighs their benefit especially when there equally or more effective but lower risk alternatives are available".[8] PIMs use is normally evaluated using specific scales and the screening tool of older person's prescriptions (STOPP) and screening tool to alert doctors to right treatment (START) criteria.[9] Several types of the research reported the superior use of PIMs in geriatric patients globally; in Canada and the United States, the prevalence was from 14% to 37%, whereas in Europe it was from 23%102 to 43%.[10] A retrospective study from Indonesia in 2014 reported a PIMs prevalence of 52.2%.[11] Moreover, researches with lower rates were reported in South Africa, Korea, and Nigeria, with the prevalence of 13.8%, 27.6%, and 32.1%, respectively.[12,13] Higher rates of 40.39%, 45.2%, and 53.5% were reported in New Zealand, Lebanon, and China, respectively.[14-16] Genetic variability of the different populace can affect the exposure or safety of specific drugs, called pharmacogenomics drugs (PGx) drugs. The Dutch pharmacogenetics working group (DPWG) and the clinical pharmacogenetics implementation consortium (CPIC) have been developing guidelines for more than a decade, and have released public guidelines for implementing PGx, especially for gene-drugs pairs of CYP2C9, CYP2C19, CYP2D6, SLCO1B, and VKORC1.[14,15]

There are studies from the United States, the Netherland and Denmark that reported the use of at least one PGx drug in 20-30% of older patients.[16-18] We are not aware of any study that has reported on the frequency of OTC, PIMs and PGx drugs used in the geriatric population of India. Therefore, we aimed to assess the co-occurrence of three risk factors; OTC, polypharmacy, PIMs and PGx drugs and their potential ADRs amongst Indian elderly patients.

METHODS

This was a retrospective, record-based study conducted involving elderly patients (>60 years) who were admitted to a tertiary care hospital from January 2019 to December 2020). A pharmacologist examined case notes of in-patients in the indoor patient department and ICU over a period of 24 months using version 2. STOPP/START criteria (version 1. modification of STOPP/START criteria on).[8] Classification of diseases was done using the International classification of diseases ICD-10th version, 2019.[8] Data of patients with a length of stay (LOS) greater than 24 hours but less than 70 days was included. Incomplete pre-admission medication history, incomplete case records without discharge summary or discharge coding or stay of the patient more than 70 days were excluded. The patient's case sheet is reviewed using a two-stage process. In initial length patient record was reviewed for polypharmacy, which we defined as an individual's exposure to five or more than five but lesser than 10 drugs, while excessive polypharmacy in an individual was defined as exposure to 10 or more than 10 drugs.[9] PIMs (version 2. STOPP/ START criteria) and Pharmacogenomics drugs for which pharmacogenomic testing is recommended for the following genes: CYP2C9, CYP2C19, CYP2D6, SLCO1B, and VKORC1(based on CPIC and DPWG) have been identified and flagged and then further investigated to determine the presence or absence of any adverse effects.[9,10] Review of the patient notes done in the following order: past medication history, list of over-the-counter drugs, PIMs before admission, PIMs prescribed during the hospitalstay, medical progress notes, shift to ICU, and PIMs at the time of discharge. If harm occurred, the severity of an adverse effect was rated using the criterion developed by the modified Hartwig and Siegel scale.[11] The following factors had been taken into consideration during the review. Any complications resulting from treatment were not considered adverse events. Death was not considered an event unless a PIMs contributed to a death, rather than a part of a normal biologic process. Adverse events with intentional drug overdose were not considered. Adverse event rateper 1000 patient days was calculated using the formula total number of events divided by the total length of stay multiplied by 1000).

Statistical analysis

Collected data had been entered in Microsoft office excel 2016. Categorical variables were presented as frequency, percentages, and mean±SD. Pearson correlation was used for statistical analysis of categorical variables and correlation analysis respectively, $p<0.05$ were considered

statistically significant.

RESULTS

Out of 1245 case records, data of 583 patients meet the inclusion criteria, out of which 61.3% (N=357) males, and 38.6% (N=226) females mainly aged between 65-75 years (37.8%, N=220) and (25.9% N=151) (Figure 1). The demographic clinical characteristics and distribution of patients across the indoor patient department (IPD) of the study population during the study period (Table 1). the comorbid conditions are shown in (Table 2).

Table 1: Demographics and comorbid condition and reason of admission in hospital of studied groups (n=583).

Demographics	Male patients N (%)	Female patients N (%)	Total
Age (years)			
65-75	220 (37.80)	151 (25.95)	371 (63.75)
>75	137 (23.54)	74 (12.71)	211 (36.25)
Mean age	73.47±6.62	72.5±6.35	73.11±6.53
Diagnosis			
Medicine	-	-	475 (81.62)
Cardiology	121 (20.79)	65 (11.17)	186 (31.96)
Neurology	53 (9.11)	39 (6.70)	92 (15.81)
Respiratory	42 (7.22)	40 (6.87)	82 (14.09)
Gastroenterology	37 (15)	15 (2.58)	52 (8.93)
Endocrinology	18 (3.09)	7 (1.20)	25 (4.30)
Endocrine	14 (2.23)	10 (1.72	23 (3.95)
Renal	9 (1.55)	6 (1.03)	15 (2.58)
Surgery			107 (10.81)
Surgery	42 (7.22)	21 (3.61)	63 (3.43)
Orthopedics’	11 (1.89)	9 (1.55)	20 (3.43)
Ophthalmology	8 (1.37)	12 (2.06)	20 (3.43)
Oncology	3 (0.52)	1(0.17)	4 (0.69)
Average length of stay (Mean±SD)	8.6±3.4	Length of stay with PIMS incidence (Mean±SD)	10.9±4.8
Comorbid conditions			
Diabetes type - 2 with dyslipidemia	67 (14.14)	39 (8.23)	106 (22.36)
Hypertension	67 (14.14)	39 (8.23)	106 (22.36)
Hypertension with Dyslipidemia	65 (13.71)	28 (5.91)	93 (19.62)
Hypertension with DM type-2	48 (10.13)	44 (9.28)	92 (19.41)
Hypertension with CKD	31 (6.54)	20 (4.22)	51 (10.76)
Infection	10 (2.11)	11 (2.32)	21 (4.43)
Osteoarthritis	3 (0.63)	2 (0.42)	5 (1.05)

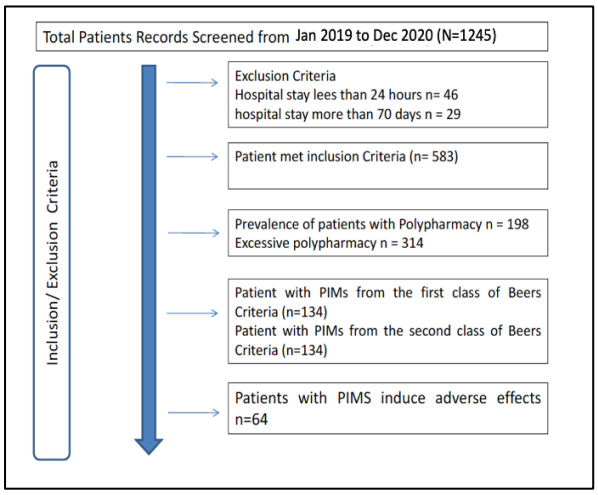

Figure 1: The flow of patients s throughout the study.

The average length of stay (ALOS) was 8.6 (range 1-48 days) while the average length of stay in patients with PIMs was 10.9 (range 1-59 days). Polypharmacy was found in 36.0%, and excessive polypharmacy was found in 42.8% of pre-admission medications. 116 patients were taking 148 Over counter (OTC) drugs, out of which 41.89% (N=52) were PGx drugs. Hydrocortisone (39.86%), ranitidine (21.62%), bisacodyl (14.86%), and diphenhydramine (12.84%) were common (Table 4). The total number of drugs prescribed to 583 patients was 7089, out of which 6% (N=448) were identified to be PIMS (based on version 2 STOPP) (Table 5). Out of these 448 PIMs, 18.2% (N=82) were defined as PGx drugs. About 19.4% (N=87) PIMs and PGx drugs result in serious ADRs (Table 3) in which insulin (regular), PPIs and THP result in more than one ADR in many patients. The most commonly PIMs related incidence reported includes, Insulin (regular) 31.25% (N=20),

Trihexyphenidyl (THP) 18.75% (N=12), zolpidem 12.5% (N=8), acetylsalicylic acid 9.3% (N=6), pantoprazole 5 (7.81%), furosemide 5 (7.8%), hydrocortisone 6.25% (n=4), and glimepiride 6.25% (N=4), (Table 3).

Severity of ADRs were calculated in accordance Hartwig's severity assessment scale and three categories of ADRs had been assessed (mild, moderate and severe). Out of 130 ADRs 50% (N=65) were mild, 28.4% (N=37) were moderate, and 21.5% (N=28) were severe. Out of 130 incidence 64.6% (n=84) were definitely preventable, 180 22.3% (N=29) were probably preventable, and 13.0% (N=17) were not preventable. Total of 50.0% (N=65) recovered completely from the ADRs, 33.0% (N=33) had been recovering), 12.3% (N=16) recovered with squeal, and 2.3% (N=3) could not recovered and 2.3% (V=3) had been fatal (Table 4).

DISCUSSION

The present study was conducted to assess the impact of COVID-19 on the prevalence of OTC, polypharmacy, PIMs and PGx drugs using version 2. STOPP/START criteria, CPIC and DPWG in geriatric patients in an inpatient setting and their clinical outcomes.[10,12] In our populace the most frequently used drug class with ADRs was PPIs (20%) used widely without an evidence-based clinical indication. Most PPIs are actively metabolizedinto active metabolites by hepatic enzyme CYP2C19, genotypes linked to PPIs exposure. Lower exposure results in therapy failure and higher exposure are associated with improved efficacy and adverse effects on long-term use.[13,14] PPIs primarily exert their effect by irreversible inhibiting proton pumps, reducing gastric acid secretion. A resultant hypochlorhydria is associated with an increased risk of colonization of viral and bacterial commensals. It has been proposed that survival of the SARS-CoV-2 in the stomachs of patients taking PPIs may be increased.[15,16] In the present study infection with Clostridium difficile, Hypomagnesemia, bone fractures, deficient absorption of calcium and vitamin B12 and iron deficiency anaemia were the most serious adverse effect related to it. A similar result was found in a study conducted by Cahir et al.[17] STOPP/ START criteria recommended avoiding scheduled use for more than 8 weeks. This recommendation applies to both oral and intravenous PPIs. Histamine-2 receptor antagonists can be another safe alternative but are not recommended in older patients with or at high risk of delirium as they can potentially induce or worsen delirium. The second most common PIMs with incidence was Insulin (regular) at 6.9%. Hypoglycemia, hypokalemia, delirium and loss of consciousness were the most common adverse effect related to it. Together with hypertension, renal, cardiac, lung disease and obesity, diabetes mellitus has been associated with more severe pathology of SARS-CoV-2.

Geriatric age group patients are more susceptible to respiratory tract infections such as influenza, and pneumonia, since chronically raised blood glucose levels result in suppression of the immune system. Moreover, this infection induces a stress response which further can increase serum blood glucose levels and exacerbate the infection. The SARS-CoV-2 virus is believed to cause damage to the insulin-secreting pancreatic beta-cells, so some patients may require insulin for the first time while others may need their insulin doses increased significantly. STOPP/ START s Criteria have revised the use of regular insulin based on a sliding scale. Insulin glargine should be usedfrom evening to morning to reduce the risk of hypoglycemia, and to minimize the confusion about inappropriate insulin regimens.[18,19]

Table 2: Total number of drugs prescribed pre, during and post hospitalization with potentially inappropriate medicines based on updates Beer's criteria 2019.

Parameters	Pre admission N (%)	During hospitalization N (%)	At discharge N (%)
Total number of drugs prescribed			
≤5	123 (21)	69 (11.8)	136 (25.8)
6-10	210 (36)	199 (34.1)	183 (34.7)
11-16	174 (29.8)	218 (37.3)	133 (25.2)
>16	76 (13)	97 (16.6)	75 (14.2)
Total	583	583	527
Medication prescribed per patient			
(Mean±SD)	9.4±2.9	12.65±3.56	10.1±3.1
Prevalence of polypharmacy			
Polypharmacy	36.0	34.1	34.7
Excessive polypharmacy	42.8	54.0	39.4
Total number of PIMs			
1	1 (4)	10 (15.8)	5 (10.4)
2	7 (28)	31 (49.2)	24 (50)
≥3	17 (68)	22 (34.9)	19 (39.5)
PIMS N (%)	128 (28.5)	166 (37.0)	154 (34.3)
Total PIMs	448	PIMs with incidence	87

Table 3: Frequency distribution of adverse drug events with type of adverse drug effects, there evidence and recommendations.

Class of drugs	ATC Classify-cation	Drugs	Metabolizing enzyme	Total number of AEs 130 (%)	Type of AEs	Evidence	Recommendation
Proton pump inhibitors (PPIs)	C05	Pantoprazole	CYP2C19	25 (19.2%)	Hypomagnesemia, bone fractures, deficient absorption of calcium, vitamin B12 and iron deficiency anemia	Weak	**CPIC:** increase the starting dose and to monitor efficacy in normal metabolizers in treatment of H. *Pylori* infection and erosive esophagitis. 50% reduction in daily dose poor metabolizers and chronic therapy **DPWG: -**
Insulin	A10	Insulin (regular)	-	22 (16.9%)	Hypoglycemia, Hypokalemia	Strong	-
Diuretics		Furosemide	-	21 (16.1%)	Hypokalemia, Hyponatremia	Strong	-
NSAIDs	M01	Ibuprofen/ Diclofenac	CYP2C9	20 (15.3%)	Stroke, Cardiovascular disease, Peptic ulcers Gastrointestinal bleeding		**CPIC:** Initiate therapy with 25-50% of the lowest recommended dose. **DPWG: -**
Anticholinergic	N06	THP	CYP2D6 CYP2C19	17 (13.0%)	Tremors, Constipation, xerostomia	Strong	**CPIC:** 50% dose reduction in CYP2D6 poor metabolizers **DPWG:** decreasing dose for CYP2D6 intermediate and poor metabolizers, and increasing a dose or use an alternative in ultra-rapid metabolizers
Second generation sulfonylureas	A10	Glimepiride*	CYP2C9	12 (9.2%)	Delayed recovery from hypoglycemia		-
Non-benzodiazepine's hypnotic	N05	Zolpidem	-	9 (6.9%)		Strong	-
Corticosteroid's	A06	Hydrocortisone	-	4 (3.07%)		Strong	-

CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetic Working Group
*Drug represents that no action is required for this gene-drug interaction; NA indicates not Pharmacogenomic drug Evidence obtained from one or more well-designed and well executed randomized controlled trials (RCTs). Strong -Harms, adverse events and risks clearly outweigh benefits Weak -Harms, adverse events and risks may not outweigh benefits

Table 4: Severity and preventability of adverse drug reactions (ADRs) (n=130).

Category	Number of ADRs	%
Mild (level 1,2)	65	50.0
Moderate (level 3,4)	37	28.46
Severe (level 5, 6, 7)	28	21.54
Definitely preventable	84	64.6
Probably preventable	29	22.3
Not preventable	17	13.0

The third most common PIMs with incidence was Furosemide with a rate of 18.3%. In COVID-19 pulmonary oedema is attributed to a "cytokine storm". SARS-CoV-2 promotes angiotensin-converting enzyme 2 deficit, increases angiotensin II, and triggers volume overload.[20] Furosemide was used as a standard treatment to treat pulmonary oedema and volume overloadguided by the objective: Negative Fluid Balance (NEGBAL approach). Hypokalemia, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion, fatigue and muscle weakness are the most common ADRs seen related to it. This result in increased monitoring of serum electrolytes. STOPP/ START s Criteria recommended its use with caution and change in dose after clinical evaluation from 40 mg to 20mg/day in absence of congestive symptoms.[21]

The fourth most commonly prescribed PIMs and PGx with incidence was NSAIDs with a rate of 16.20%. Early in the COVID-19 pandemic, the use of non-steroidal anti-inflammatory (NSAIDs) particularly ibuprofen, might exacerbate the COVID-19 symptoms. The mechanism through whichNSAIDs could theoretically be of danger in patients with COVID-19 is by upregulation of angiotensin-converting enzyme 2 (ACE2) receptors in the lungs, arteries, heart, kidney, and intestines, which is used by SARS-CoV-2 as an entry point into cells. Additionally, NSAIDs might delay the diagnosis of COVID-19 by masking inflammation and fever [22]. Though none of these outcomes associated with NSAID exposure in the 2 weeks was seen in our study. Stroke cardiovascular events, gastrointestinal hemorrhage, and peptic ulcer disease were most commonly observed ADRs, especially in high-risk patients taking oral or parenteral corticosteroids (3.07%). Topical NSAIDs, lidocaine patches, topical capsaicin cream, acetaminophen, disease-modifying antirheumatic drugs (DMARD) and folic acid are potential alternatives to NSAIDs therapy for chronic pain.[23,24] The fifth most commonly found PIMs and PGx with the incidence of first-generation anticholinergics trihexyphenidyl (THP) at 13.8%. Long-term use (beyond 1 month) in those with Parkinsonism or Lewy body disease is likely to worsen extra-pyramidal symptoms. PHP is associated with a proarrhythmic state, QT prolongation, Torsade de Pointes (TdP) and an increased risk of sudden cardiac death (SCD). They have known drug-to-drug interactions with chloroquine, hydroxychloroquine and azithromycin use frequently for the treatment of COVID-19.Increased tremors, dryness of mouth and constipation were the most commonly observed side effects. STOPP/ START criteria do not recommend its use for the prevention of extrapyramidal symptoms with antipsychotics. Parkinson's disease levodopa with carbidopa can be used as an alternative.[25]

The sixth most commonly used PIMs based on STOPP criteria and PGx with incidence was glimepiride 10.7%. prolonged hypoglycemia was the most commonly observed side effect with it .[26] Repaglinide, dipeptidyl peptidase 4 (DPP-4) inhibitors, or insulin may be used as initial therapy.[27] It's worth recommending, that exercise and diet modifications are important for properly managing diabetes in older patients. The seventh most commonly prescribed PIMS with incidence was non-benzodiazepines (zolpidem) at 7.60%. According to the American Geriatric Society, hypnotics are known to increase the risk of cognitive impairment, delirium and fractures. Serotonin-norepinephrine reuptake inhibitors and buspirone can be used as an alternative, for patients with anxiety, except with a high risk of falls.[28-30]

Lastly acetylsalicylic acid was the eighth most commonly prescribed PIMs. Bleeding and peptic ulcers were the most commonly observed ADRs. STOPP/START criteria recommended using it with caution. Alternatively, nutritional interventions such as the use of fish oils rich in eicosatetraenoic acid should be considered, which has been shown to benefit patients with a high risk of cardiovascular events in a long-term study.[31,32] In our study, the use of PGx drugs was high (18.2%). which was mainly due to the frequent use of PPIs, NSAIDs and anticholinergics in our studied populace. Similar results were reported by the Netherland, Denmark, the United States,and Rhineland where 20-30% of the total drug used was PGx.[33] There will be a potential benefitof pre-emptive pharmacogenetic genotyping especially of CYP2C19 and CYP2D6 as this polymorphism mainly influences the metabolism of over-the-counter painkillers and PPIs used widely without physician consultation. This will reduce potential ADRs and increase beneficial drug outcomes.

Strengths and limitations

To the best of our knowledge, no published research evaluates the prevalence of PIMs and PGx in the Indian population during the COVID-19 pandemic. The key strength of our study is the inclusion of indoor admission-based clinical and health administrative data and examination of medication commonly used medication subjected to quality monitoring. The major limitation of this work was that we could not assess the correlation between the PIMS and COVID-19 infection rate or mortality. Our is a single-centre study so the result cannot be generalized to the entire population. This study exclusively included only the first and second-class drugs of STOPP/START criteria.

CONCLUSION

The results of this study identify high uses of OTC and the prevalence of polypharmacy in elderly patients during the COVID-19 pandemic which make them more prone to exposure to PIMsand PGx drugs. The study identified the most common PIMs and PGx drugs among elderly patients admitted to the hospital with the intent to encourage prescribers to use the v2. STOPP/START criteria and possible alternatives to PIMs and PGx drugs. The findings highlight the need for more efforts to develop awareness and action points in concordance with STOPP/START criteria among healthcare providers.

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