T.R.N.C

NEAR EAST UNIVERSITY INSTITUTE OF HEALTH SCIENCES

Polypharmacy, Drug-Drug Interaction, and Potentially Inappropriate Prescription in Geriatric Hospitalized Patients in Tertiary Hospital in Northern Cyprus

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BY:

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DEDICATION

Dedicated to my great parents, supportive sisters,

Colleagues and friends.

Especially my mother Hafsaha Salaam

Who encouraged me to higher ideas of life,

took pains and sacrificed their comforts for my brilliant future.

And because of their support, help, prayers, and love I got what I'm in.

I dedicate this work and give special thanks to my best Teacher

Assoc. Prof. Dr. Bilgen Basgut

Approval

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Abstract

Advanced age and associated physiological and psychological changes make the geriatric population more susceptible to multi-disease and multi-drug consuming, which may result in high exposure to drug-drug interactions (DDIs), and potentially inappropriate prescriptions (PIPs) or medications (PIMs) use. One of the most corporative explicit tools to detect and minimize PIPs is STOPP/START criteria. This study aims to determine the prevalence of poly-pharmacy, significant DDIs and PIPs in hospitalized geriatric patients.

A non-randomized retrospective medical chart review carried independently by one clinical pharmacist and one researcher pharmacist for patients hospitalized between July to December 2017 was conducted at a tertiary hospital in North Cyprus. STOPP/START version 2/2014 was utilized to identify PIPs. LexiComp interaction checker was used to detect DDIs. Disagreements were resolved through discussion and consent between the two pharmacists at the end of data collection and analysis. Prevalence of poly-pharmacy, incidence of potential drug-drug interactions, potentially inappropriate medications needed to be stopped and medications needed to be started were the main outcomes of the study.

118 patient files were identified to be eligible for the analysis. Patients averagely stayed 6.9 ± 8.9 days and used 8.7 ± 4 mean number of drugs. The patients were found to have a prevalence of 76% of at least one STOPP medication use during hospitalization. 53% of these medications classed as Potentially Inappropriate Medicine (PIM) for geriatric patients and were used by the patients on admission. During hospitalization or on discharge 53% needed at least one medication according to START criteria. Furthermore, 776 Drug-drug interactions (DDIs) were identified during hospitalization, more than 20% being serious interactions. The utilization of STOPP criteria may attenuate 72.5% of both X and D classes of DDIs and decrease 11.7% of the total drugs used.

In conclusion the implementing the 2014 version of STOPP/START criteria would prevent and limit both PIPs in hospitalized elderly patient as well as significant DDIs prevalence and total used medicine. This may result in more compliance and enhance patient safety which is a potential role that clinical pharmacists can introduce to hospitals in North Cyprus.

Key Words: Poly-Pharmacy, Drug-Drug Interaction, Potentially Inappropriate Prescription, Drug Related Problem, Elderly Patient, And STOPP /START Criteria version 2.

Contents Page

GENERAL PAGE	III
APPROVAL	IV
ACKNOWLEDGEMENTS	V
ABSTRACT	VI
TABLE OF CONTENTS	VII
LIST OF ABBREVIATION	IX
LIST OF FIGURES	Х
LIST OF TABLES	XI
Chapter 1	
1. Introduction	1
1.1. Demographic and economic considerations	1
1.1.2. The elderly physiological changes	2
1.2. Age-related pharmacokinetic changes	3
1.2.1. Absorption	3
1.2.2. Distribution	4
1.2.3. Metabolism	6
1.2.4. Elimination	7
1.3. Pharmacodynamic changes that are related with age	8
1.4. Drug related problems in geriatric patient	10
1.4.1. Poly-pharmacy	11
1.4.2. Drug-Drug interactions	12
1.4.3. Potentially inappropriate prescription	16
1.4.4. Non-adherence to medication	19
1.5. Role of clinical pharmacist in DRPs management	20
Chapter 2	
2. PIPs Detection Tools	21
2.1. Explicit Criteria	21
2.1.1. Beers Criteria	21
2.1.2. Screening Tools STOPP/START criteria	23
2.1.3. Others Explicit Tools	25
2.2. Implicit Tools	26

2.2.1. Medication Appropriate Index (MAI)		
2.2.2. Assessment of Underutilization (AOU)		
2.3. Previous studies		
2.4. Aim and objectives	32	
Chapter 3		
3. Methodology	33	
Inclusion Criteria	33	
Exclusion Criteria	33	
Statistical analysis	34	
Ethical consideration	35	
Chapter 4		
4. Result	36	
Demographic	36	
4.1.Medication usage and poly-pharmacy		
4.2. Drug-Drug Interactions (DDIs)		
4.3. Potentially Inappropriate prescriptions (PIPs)		

Chapter 5

Discussion	40
Limitations	42
Conclusion	43
References	44
Appendixes	60
1. Screening tools STOPP/START version 2	60
2. Ethical approval	70
3. Collecting data template	71

LIST OF ABBRREVATIONS

S. #	ABBREVATIONS	EXPLANATION
1	AARP	American association of retired person
2	ADWE	Adverse Drug withdrawal event
3	ACEI	Angiotensin Converting Enzyme Inhibitor
4	ARB	Angiotensin Receptor Blocker
5	AGS	American Geriatrics Society
6	BC	Beers Criteria
7	CME	Continuous Monitoring Emission System
8	Crcl	Creatinine Clearance
9	CYP450	Cytochrome P450 monooxygenase
10	DRP	Drug Related Problems
11	GI	Gastro-intestinal
12	MAI	Medication Appropriateness Index
13	MTM	Medication Therapy Management
14	NP	Nurse Practitioner
15	OTC	Over the counter
16	рН	power of hydrogen
17	PIM	Potential Inappropriate Medication
18	PIP	Potential Inappropriate Prescription
19	START	Screening Tool to Alert to Right Treatment
20	STOPP	Screening Tool of Older Person Prescriptions
21	SPSS	Statistical Package for the Social Science
22	US	United State
23	WHO	World Health organization

List of Figures

Figure 1: Distribution of gender in hospitals

36

List of Tables

Table 1: The Percentage of elderly people throughout the world	1
Table 2: Absorption changes	4
Table.3: Distribution changes	5
Table 4: Metabolic changes	7
Table 5: Elimination changes	8
Table 6: DDIs risk rating	15
Table 7: Drugs that are rarely used in Europe	23
Table 8: The difference between the two STOPP/START versions	24
Table 9: MAI criteria & weighted score	26
Table 10: The variable for analytical processes	34
Table 11: Comparison of Total Drug Used according to gender	36
Table 12: Poly-pharmacy classification	37
Table 13: Percentage of different DDIs	37
Table 14: PIP prevalence	38
Table 15: Patients with at least one STOPP criteria	38
Table 16: Frequency of individual PIPs	38
Table 17: The most frequent pDDIs	39
Table 18: Descriptive statistic	39

Chapter 1: Introduction

1.1 Demographic and economic considerations

According to Turkish Statistical Institute the elderly people who are 65 years and over in 2016 represented 8.3% of the total population(Institute, Turkish Statical Institute, 2017), with expected value of 10.2% by the year 2023, 21% by 2050 and 28% by 2075 (Institute, Turkish Statical Institute, 2013).

According to The World Health Organization (WHO), the percentage of people with 65 years or more in developed countries is 15%, whereas 3-4% for oldest (80 years and older) group the variation in the percentage of elderly population reflects the variation in mortality rate which is an indirect indicator of variations in health care system quality from place to another (Brower HT, 1996).

Region	Years	% of population		
		≥65 years	≥75 years	≥80 years
Europe	1990	13.7 6.1		3.2
	2010	17.5	8.4	4.9
	2025	22.4	10.8	6.4
Asia	1990	4.8 1.5 0.6		0.6
	2010	6.8	2.5	1.2
	2025	10.0	3.6	1.8
USA	1990	12.6	5.3	2.8
	2010	14.0	6.5	4.0
	2025	20.1	8.5	4.6

Table 1: The percentage of elderly people through the world (Brower HT, 1996)

The 85 years or more older patients consume three times as much health care costs per person as those 65–74 years, and twice as much as those 75–84 years old (Fuchs VR, 1998). Nursing home and short-stay hospital use also increases with age, especially for older adults (Liang et al, 1996) (Liang et al. 1996). In US one statistic analysis made in 2011 found that, the median annual health care expenditure for people aged 65 and over was \$4,206 (Mirel 1 & Carper, 2014). On the other hand one study made in Japan found out that the most common cause of death was malignant neoplasm, followed by pneumonia, cardiovascular diseases, cerebravascular accidents, and renal failure (Nakajima et al, 2009). The increase in the elderly population number associated with economical and health challenges made this aged part of the population under focus of many researchers all over the world.

1.1.2 Physiologic Changes in geriatrics

A number of age-related physiologic changes occur which may cause reductions in functional reserve capacity and could affect drug pharmacokinetics and pharmacodynamics, thus increase the rate of medication-related problems. This information's gap can improve with the implementation of Food and Drug Administration guidelines, the Geriatrics associations and studies on older adults (U.S Food and Drug Administration, August 1994).

An important determinant of drug-related problems in the elderly is an increased physiological vulnerability to adverse drug reactions and an impaired ability to recover from drug-induced insults. The progressive decrease in the ability of each organ system to maintain homeostasis in the face of challenge is a definition of physiological aging. Homeostatic mechanisms in the cardiovascular and nervous systems are less efficient, drug metabolism and excretion decrease, body tissue composition and drug volume of distribution change, and drug receptor sensitivity may be altered. Age-associated changes are progressive, occurring gradually over the course of a lifetime, rather than abruptly at any given age (e.g., 65 years of age)(Boss GR & Seegmiller JE, 1981).

There are a reasonable number of age-related physiologic changes that occur and could affect the drug pharmacokinetics and pharmacodynamics (U.S Food and Drug Administration, August 1994).

1.2 Age-related pharmacokinetic changes

With the advancement in age and because of the change in the body weight, several changes in pharmacokinetics may present in many elderly people, especially the changes in the volume of distribution and renal clearance (Hilmer SN, 2007).

Pharmacokinetics is defined as' "how the body processes the drug after administering it". Every drug has its specific pharmacokinetic profile which is based on specific parameters such as age, gender, body weight, body mass index, liver function, and renal function. When a specific drug is studied in specific patient types such as elderly patients rather than one patient group, a better understanding of pharmacology may be achieved. Thus, leading to more proper doses and a clear profile of adverse effects can be determined.

Most of the elderly patients have several different diseases and they take many different medications which cannot be discontinued. Thus, to develop an effective pharmacotherapeutic plan for an elderly patient it is required to get a clear understanding of the pharmacokinetics principles (the absorption, the distribution, the metabolism, and the elimination) and how the pharmacokinetics of a drug may be altered in the geriatric population (Tumheim k, 2004), (Hutchison & O'Brien, 2007), (Miller SW, 2007), (Greenblatt DJ et al, 2002).

1.2.1 Absorption

Although earlier studies reported significant age-related changes in the gastrointestinal tract including increases in gastric ph (Kekki et al, 1982) reduction in gastric emptying (EvansM et al, 1981), reduced intestinal blood flow (Lovat LB, 1996), and intestinal absorptive capacity (Corazza et al, 1986), more recent reports have not confirmed these findings in healthy subjects suggesting perhaps to be due to the effects of disease states (Husebye & Engedal, 1992), (Johnson et al, 1985).

Pharmacokinetic studies relating to the effect of ageing on drug absorption have provided conflicting results. However, some trails have not shown significant age-related differences in absorption rates for different drugs (Gainsborough et al, 1993). The absorption of vitamin B12, iron and calcium through active transport mechanisms is reduced (Blechman & Gelb, 1999), where as an age-related alteration in the activity of peripheral dopa-decarboxylase in

the elderly Parkinsonism patients, result in elevation of Levodopa plasma concentration (Evans et al, 1981). Some of the difference in the results obtained from these studies might be due to different methods of assessing drug absorption.

Hepatic drug metabolism is mainly mediated by the Cytochrome P_{450} system and drug interactions in the elderly are likely related to the progressive decline of this system after the fifth decade of life and another decrease in individuals aged >70 (Anantharaju et al, 2002). As a result, the bioavailability of drugs undergoing extensive first-pass metabolism such as Propranolol and Labetalol can be significantly increased (Castleden & George, 1979). On the other hand, several ACE inhibitors such as Enalapril are pro-drugs and need to be activated in the liver. Therefore, its first-pass activation might be slowed or reduced with advancing age (Davies RO et al, 1984).

Transdermal administration is becoming increasingly common and is used for several medications prescribed to older adults. Alterations in the stratum corneum and lipid composition of the skin, changes in sebaceous gland activity, and changes in the dermis and epidermis may affect drug absorption. For instance, lipophilic drugs (e.g., Estradiol) appear to

be less affected by aging than do hydrophilic compounds (e.g., acetylsalicylic acid [ASA].(Lee et al, 2001),(Kaestli et al, 2008).

The following generalizations can be concluded: the extent of absorption via the oral route is similar in older patients and in young adults, the rate of absorption is reduced or unaltered in older patients, and drugs that undergo firstpass metabolism are absorbed more completely in the older patient. Changes in transdermal absorption of drugs have not been sufficiently studied; thus, close monitoring is warranted.

Table(2):Absorption changes
↓Saliva secretion
↑Gastric PH
↑Gastric emptying time
↓ Gastric surface area
↓Gastrointestinal motility
↓Active transport mechanism

1.2.2 Distribution

Drug distribution is defined as' "where the drug may go after it enters the bloodstream". For the orally drugs, the distribution phase begins after the absorption and the first-pass metabolism. And some drugs are also widely distributed into tissues, body fluids, and to the central nervous system by crossing the blood brain barrier. Some other drugs are never distributed well (Tumheim k, 2004)(Hutchison & O'Brien, 2007), (Miller SW, 2007).

There are various factors that influence the drug volume of distribution, which includes protein binding, pH, the molecular size, and the water or lipid solubility (Mangoni AA, 2004), (Kapadia A, 2010).

With ageing body fat increases and total body water as well as lean body mass decrease (Shi & Klotz, 2011). Consequently, hydrophilic drugs like (Digoxin, Gentamicin, etc.) tend to have a smaller apparent volume of distribution (Vd) resulting in higher serum levels in geriatric. For this reason, the Loading doses of Digoxin need to be reduced to accommodate

these changes (Cusack et al, 1979). In contrast, lipophilic drugs like (Diazepam, Thiopentone, etc.) have an increased Vd with a prolonged half-life, (GreenblattD et al, 1980).

Although plasma protein binding might theoretically contribute to drug interactions or physiological effects for drugs that are highly protein bound, its clinical relevance is probably limited. The reason for this is related to the fact that the initial and transient effect of protein binding on free plasma concentration is rapidly counter balanced by its effects on clearance (Benet LZ & Hoener BA, 2002).

In the Bloodstream, the reduction in the protein binding can result in increased free drug concentration, which causes increase in the pharmacologic effect in an elderly individual.(Greenblatt DJ et al, 2002).

Table(3) : Distribution changes		
↓ Cardiac output		
↓ Hepatic blood flow		
↓Renal blood flow		
↓ Body water content		
↓ Serum albumin		
↓ D for water soluble drug		
↑ PVR		
↑Adipose tissue		
↑D for lipid soluble drugs		

P-glycoprotein can affect the transport of drugs that crosses the blood-brain barrier. Studies have demonstrated that there is a decrease in P-glycoprotein activity in the blood- brain barrier with aging. Thus, the brain of aged individuals may be more exposed to higher levels of drugs and toxins than normal levels of them (Toornvliet R, 2006).

1.2.3 Metabolism

It is known that; the liver is the primary organ responsible for the metabolism of the drug. Also, it can both synthesize various proteins, substrates enzymes and can convert chemicals (Xenobiotic) from one form to another, this cause conversion of substances which are believed to be harmful to a form which can be eliminated more easily from the body. In general, the final by-product of the liver metabolism is water soluble and is readily eliminated via the kidney.

The age-related changes in liver size and hepatic blood flow as the activity of drug metabolizing enzymes is preserved. Nevertheless, reduced liver volume and blood flow in the elderly permit the reconciliation of: (i) the *in vivo* clinical pharmacokinetic data indicative of reduced hepatic drug clearance; and (ii) the absence of significant age-related declines in the amounts or *in vitro* activities of liver microsomal mono-oxygenases (Schmucker DL, 2001). Those changes lead to significant reductions in the clearance of many drugs metabolized by phase-1 pathways (reduction, oxidation, hydroxylation, demethylation) in the liver (O'Malley et al, 1971), whereas compounds metabolized by phase II processes (conjugation, acetylation, sulfonation, glucuronidation) have no change in clearance with age (Hunt et al, 1992),(Wynne et al, 1990).

The liver can use various types of reactions to complete the transformation process. One of them is oxidative reactions (phase 1) which may occur via oxidation, reduction, hydrolysis, or in one of the other types of the chemical conversions. Phase 1 reactions typically involve various types of Cytochrome P450 monooxygenase (CYP450) enzymes, which play roles in drug metabolism. The Phase 2 reactions involve conjugation and the products of conjugation reactions may have an increased molecular weight and they are usually inactive, unlike phase 1 reactions, which seldom produce active metabolites (Hutchison & O'Brien, 2007), (Miller SW, 2007).

Alteration of the normal metabolic process can affect the pharmacokinetics of drugs significantly. We note that one of the most remarkable characteristic factors of hepatic function in elderly adults is the increase in inter-individual variability compared with other age groups (Herrlinger C, 2001).

Recently, it has been observed that a reduction in renal function may significantly affect not only the drugs which are excreted by the kidney, but also those drugs suspected to extensive metabolism in the liver (Rostami-Hodjegan et al, 1999). A decrease in liver cytochrome P450 activity, secondary to reduced gene expression, has been observed in renal failure (Pichette, 2003).

 Table(4): Metabolic changes

 ↓Microsomal hepatic oxidation

 ↓Clearance

 ↓1st pass metabolism

 ↑Steady state levels

 ↑Half life

 ↑Active metabolites level

1.2.4 Elimination

Age-related changes in renal function result in more adverse drug events than any other agerelated physiological alteration. Alteration in renal function in elderly people, particularly glomerular filtration rate, affects the excretion of many drugs such as in lithium, the 50% dosage reduction seemed necessary to compensate for an age-related decrease in lithium excretion and to reduce lithium side effects to a level comparable to that acceptable in younger patients (Hewick et al, 1977). Other examples of drugs which are suspected for alteration in excretion rate include potassium sparing diuretic Amiloride (Somogyi et al, 1990), Digoxin (Portnoi VA, 1979), beta blockers (e.g. Atenolol, Metoprolol, Oxprenolol and Propranolol) (Rigby et al, 1985), and Non-steroidal Anti-inflammatory Drugs (e.g. indomethacin), (Oberbauer et al, 1993).

The clinical importance of such reductions of renal excretion is dependent on the likelihood toxicity of the drug. Drugs with a narrow therapeutic index like Aminoglycoside antibiotics, digoxin, and lithium are likely to have serious adverse effects if they accumulate only marginally more than intended. However, a recent study has questioned the importance of age-related reduction in renal function in affecting pharmacokinetics. Although creatinine clearance was slightly reduced in healthy elderly subjects, excretion of Atenolol, Hydrochlorothiazide and Triamterene was similar to young subjects (Fliser et al, 1999).

The calculations of renal function based on laboratory measurements (as serum creatinine) or other data can estimate a patient's renal function. In older adults, a low level of serum creatinine is not always indicative of normal renal function. Because older adults have a lower muscle mass than younger people, so low serum creatinine may not always indicate normal renal function but can be indicative of a reduction in muscle mass. For some patients in whom the serum creatinine may not be an exact indicator of renal function, collecting an actual 24-hour creatinine may be accurate (Hutchison & O'Brien, 2007), (Miller SW, 2007).

The reduction in glomerular filtration rate is a noted consequence of aging and the renal elimination impact of medications cannot be overstated. Knowing which drugs are excreted via renal and knowing the way of adjusting the doses of those drugs is imperative to ensuring the safety and effectively of drug dosing in all patients (Tumheim k, 2004)

Table (5):Eliminition
changes
↓Renal perfusion
↓Renal size
↓GFR
↓Tubular secretion
↓Tubular reabsorption
excretion

1.3 Age-related pharmacodynamic changes

Pharmacodynamic changes can be characterized as modifications in concentration– reaction connections or receptor affectability. There is proof of changed medication reaction or affectability in the elderly. Four components have been recommended: (a)the changes in the quantities of the receptor, (b) changes in the fondness for receptor, (c)the adjustments of post-receptor, and (d)the disability of the homeostatic instruments that are age-related (Swift CG, 1990), (Trifiro & Spina, 2011).

In blood changes the more established patient touchier to comparative measurements of warfarin when contrasted and youthful patient (Shepherd et al, 1977), the exact mechanism of such increase in sensitivity unknown. By contrast, the relationship between plasma heparin concentration and anticoagulant effect does not change with increasing age (Whitfield & Levy, 1980).

The variation in geriatric sensitivity was observed in CVS drugs, for instance, the effect of Verapamil on blood pressure and heart rate tends to be greater in older than in younger patients, however geriatrics are less sensitive to the effects of Verapamil on cardiac conduction (Schwartz JB, 1996). Such variation might be explained by an increased sensitivity to the negative inotropic and vasodilator effect of Verapamil in addition to diminished baroreceptor sensitivity. The dromotropic effect of Diltiazem causes greater prolongation of the PR interval (in young than in elderly subjects, also Diltiazem was found to

has a greater hypotensive effect, and increased Reflex heart rate in the younger patients and decreases in the elderly (Schwartz & Abernethy, 1987).

The diminished responsiveness of the β -adrenoceptor to both agonist and antagonist drugs were associated with advancing years. Elderly patients are less sensitive to the chronotropic effect of Isoprenaline (Vestal et al, 1979). However, the age-associated reduction in cardiac chronotropic responses to bolus Isoprenaline is primarily due to an age-related reduction in the influence of reflex cardiovascular responses on heart rate and not to an age-related reduction in cardiac β -adrenergic sensitivity (Ford GA & James OF, 1994).

On the other hand, the pharmacodynamics age-related changes were found to be in respiratory system too. Both Salbutamol (b2-adrenoceptor agonist) and Propranolol (beta-adrenoceptor antagonist) show reduced responses with age. This is secondary to impaired b-receptor function due to reduced synthesis of cyclic AMP following receptor stimulation. The total number of receptors seems to be maintained but the post receptor events are changed because of alterations of the intracellular environment (Pan et al, 1986), (Vestal et al, 1979). The responsiveness of a-adrenoceptors, on the other hand, is preserved with advancing age (Elliott HL, 1988).

In other section, CNS of elderly patient has shown high sensitivity to the central nervous system effects of benzodiazepines (Kruse WH, 1990). Sedation is induced by diazepam at lower doses and lower plasma concentrations in elderly subjects (Reidenberg et al, 1978), (Swift CG et al, 1985). Advancing age is also associated with increased sensitivity to the effects of (Nitrazepam, Flurazepam, and Loprazolam) associated with greater elimination half time and plasma concentration-time curve too (Castleden et al, 1977), (GreenblattDJ et al, 1981), (SwiftCG et al, 1985). The exact mechanisms responsible for the increased sensitivity to benzodiazepines with ageing are unknown. A particularly vulnerable to advancing age is also associated with adverse effects of neuroleptics, including delirium, extrapyramidal symptoms, arrhythmias, and postural hypotension (Gregory C & McKenna P, 1994), (Maixner et al, 1999).

To foresee the degree of the medication related pharmacodynamic changes will be troublesome in light of the fact that the more established grown-ups might be touchy to the medications' pharmacological activities. At whatever point new pharmaceuticals are started, care ought to be taken and by beginning the lower tranquilize dosages and by titrating the measurement as endured perhaps, anticipates and diminish the undesirable impacts of medication related pharmacodynamic. By comprehension about checking patients for a particular restorative reaction and understanding numerous medications related antagonistic impacts can assist human services experts with determining the coveted pharmacodynamic impact. Additionally, by the best possible titration of measurements and observing of patient will guarantee that the right treatment is recommended (Toornvliet R, 2006).

1.4 Drug-related issues in geriatric patient

Maturing is known be related with high commonness of various chronic diseases and that prompt utilization of complex therapeutic regimes, changes in pharmacokinetics and pharmacodynamics that are identified with the age, in addition to the co-morbidity, and multidrug utilization that all make the elderly an extraordinary gathering of patients who ought to be treated with more consideration (Wan He, March 2016).

Alternate causes are the absence of progression in doctor contacts, the absence of a predictable medication list; deficient medicine and observing of medication treatment are additionally a portion of the purposes behind medication related issues.

Drug-related problems (DRPs) are prevalent in elderly patients, either in the community (Gosney M & Tallis R, 1984), (Mulroy R, 1973), or hospital (Becker PM et al, 1987), and are responsible for hospital admission (Black AJ & Somers K, 1984), (Roughead et al, 1998).

Especially for the treatment of chronic diseases, elderly patients were found to use around three times a higher number of medications than more youthful patients (Vinks et al, 2006). They are along these lines at a higher danger of encountering drug-related problems (DRP) (LeendertseA et al, 2008), (Runciman et al, 2003).

DRPs depicted in the writing incorporate contraindications, DDIs, ADRs, prescription errors, and rebelliousness with drug use (Vinks et al, 2006), (PassarelliCG et al, 2005), (Strand et al, 1990).Regarding elderly patients with comorbidities and using multiple drugs, DRPs related with an expanded danger of hospital readmissions, morbidity, and mortality(Roughead & Semple, 2009), (Stewart et al, 1998).

In Sweden, deaths associated with drug-related problems (DRPs) are estimated to 3000 annually and 6-16 % of the hospital admissions can be derived to drugs (Peterson &

Gustafsson, 2017). DRPs and associated factors to these are important to identify, since this knowledge can be used to improve patient safety.

A DRP can be defined as an occasion or situation including drug treatment that really or possibly meddles with wanted wellbeing results (Chua et al, 2012).

Several factors can affect a patient's risk of having a DRP. Female gender has in previous research been suggested to increase the risk of having ADRs (Fattinger et al, 2000). The exposure of drugs per kilogram is usually higher in females and there are immunological and hormonal physiological differences between the genders, which may affect drug response (Soldin et al, 2011). Due to the age relating changes (pharmacokinetic & pharmacodynamics) to gather with multi comorbidity in elderly patient, the advancing age considered an essential risk factor for the prevalence of DRPs (LeendertseA et al, 2008), (Shi et al, 2008). A literature study investigated risk factors for DRPs and determined Poly-morbidity, dementia, renal impairment and cardiovascular diseases important for the risk of having DRPs (Kaufmann et al, 2015).

1.4.1 Poly-pharmacy

The elevation in prevalence of multi-morbidity and presence of more than one chronic disease in older people (Marengoni et al, 2008) is generally required to treat each chronic condition in agreement with disease-specific guidelines, because there is no clinical practice guideline dealing with multiple diseases instead of each disease separately. That's result in multiple drug regimens (Poly-pharmacy).

Poly-pharmacy is associated with an increased risk for medication errors (Boyd et al, 2005) and adverse drug events (ADE) (Hajjar et al, 2007), which in turn are frequent causes of hospitalization (LeendertseAJ et al, 2008) also Poly-pharmacy and inappropriate medication have been shown to contribute substantially to the burden of morbidity, hospitalization and death (Lau et al, 2005). A recent study found that while the use of 10 or more concomitant medications was associated with poorer nutritional and functional status, and limitations in cognitive performance, the use of six to nine medications was only associated with poorer functional status in older people (Jyrkkä et al, 2011).

Poly-pharmacy could affect mortality risk through several pathways, including inappropriate drug prescribing, (Hudhra et al, 2016), adverse drug events (Alhawassi, 2014), drug-drug interactions (Sharifi, 2014), and reduced medication adherence (McKillop & Joy, 2013).

There are various meanings of poly-pharmacy a few creators have characterized Poly-drug store in regards to the quantity of medicine as the associative utilization of at least three meds (Jensen et al, 2001), and others as the long haul concurrent utilization of at least two pharmaceuticals (Veehof, 1999).What's more, assist qualifiers have been investigated to characterize kinds of Poly-pharmacy including Hyper Poly-pharmacy (utilization of at least 10 drugs) (Gnjidic et al, 2012). Excessive Poly-pharmacy (use of 10 or more medications) (Jyrkkä J et al, 2006), Non Poly-pharmacy (use of less than five medications), and Oligo-pharmacy (use of five or less medications) (O'mahonyD & O'connor, 2011).The most normally detailed classification (around by 46.4% of studies) of definitions for Poly-pharmacy and related terms was numerical as it were. Which characterize the Poly-pharmacy as simultaneous utilizing of at least five medicines (Masnoon et al, 2017).

1.4.2 Drug-Drug Interactions

Drug-drug interactions (DDIs) describe the ability of a drug to modify the action or effects of another drug administered successively or simultaneously (Hansten & Horn, 2009).

Adverse drug events (ADEs) are an essential cause of mortality, hospital admission, and visits to the emergency department (Juntti-Patinen & Neuvonen, 2002), (Pirmohamed et al, 2004), (Zed et al, 2008). The drug–drug interaction is one of important factors in ADEs. In which it is representing between the 4.4 and 4.4% and 25% of all ADEs (Guédon-Moreau et al, 2004), in addition the studies from Latin America have reported that 54.4–80.0% of elderly outpatients presented with one or more potential drug-drug interactions (DDIs) (Obreli Neto et al, 2011), (Doubova et al, 2007).

Although prescription of more drugs for one patient is common and a necessary practice, it was shown that the incidence of potential DDIs (pDDIs) is close to 40% in patients taking 5 drugs, and exceeds 80% in patients taking 7 or more medications (Grattagliano et al, 2010), in addition to the geriatric patients more susceptible to multiple drug regimen, they are also at higher risk for DDIs (Sitar, 2007).

The estimated proportion of patients receiving interacting drugs with potential for an ADR or changes in therapeutic effect varies between 0.63 and 56% (Janchawee et al, 2005) (Vonbach et al, 2008), (ZhanC et al, 2005) depending on the study, Becker et al. found that 0.054% of emergency department visits, 0.57% of hospital admissions and 0.12% of re-hospitalizations are caused by DDIs. Although the percentages are modest the number of ADRs due to DDIs is substantial because of the large numbers of emergency department visits and re-hospitalizations (BeckerML et al, 2007). In a geriatric outpatient cohort the percentage is higher, and 21.31% of patients are experiencing at least one ADR as a consequence of a DDI (Tulner LR et al, 2008), in addition a recent prospective study conducted in an internal medicine department in Cluj-Napoca, Romania showed that 25.9% of all validated ADRs were consequences of drug interactions (Farcas, 2010).

Different research groups have studied drug interactions in terms of potential DDIs (Aparasu et al, 2007), (ZhanC et al, 2005), whereas other authors studied the prevalence and the outcome of the association of certain drugs in clinical practice (Aparasu et al, 2007). The prevalence of potential DDIs is elevated among elderly outpatients (range from 42.5% to 54.4%), and they present some characteristics (e.g., physiologic modifications attributable to the ageing processes, frailty, several comorbidities, and Poly-pharmacy) that could augment the risk of DDI-related ADRs (Aparasu et al, 2007), (Grattagliano et al, 2010), (Sitar, 2007).

Drug interactions that decrease the effectiveness of a drug are often overlooked and explained as worsening disease or poor medication adherence (Tulner LR et al, 2008). In a nursing home setting, 70% of the potential drug interactions involved some loss of action of one or more drugs (Armstrong et al, 1980). In particular, the focus is on the aging population, as they use a disproportionate amount of medications and have the highest risks for severe adverse outcomes from their drug therapy (Hanlon et al, 1997), (Bero et al, 1991).

Lexi-Interact is a drug and herbal interaction analysis tool that designed to identify potential drug-drug interactions, drug-allergy interactions, and duplicate therapy interactions. The interactions tool allows users to enter medications (both prescription and over-the-counter), natural products, foods and/or alcohol.

The seriousness of interaction relies upon the different variables that may impact the event or seriousness of the association. The elements may include tolerant particular factors, for example, organ brokenness (e.g., renal/hepatic), smoking status, genotype (e.g., VKORC1

haplotype), or phenotype (e.g., CYP2D6 poor metabolizer). Extra factors may identify with particular pharmaceutical dose shapes, courses of organization and additionally particular dosing regimens. The nearness of at least one element may bring about an expanded hazard or potentially seriousness of connection, or then again, exclude a communication. Featuring this data at the highest point of the monograph enables the clinician to assess the cooperation importance for a particular patient.

The hazard rating of lexi-comp collaborate gives a marker to help a clinician rapidly choose how to react to the communication information. Each medication tranquilize cooperation is doled out a hazard rating of A, B, C, D, or X. The movement from A to X appears, as a general issue, an expanding earnestness related with the information. A and B monographs are of more scholastic than clinical concern. Monographs appraised C, D, or X show circumstances that will probably request a clinician's consideration (Wolter SK, 2018). Table (6) shows the different risk ratings and the action required for each.

— 11 (0) — 1			
Table (6) $Drug-drug$	interactions r	stings in L	exi-comp database
Tuble (0). Drug urug	interactions i	annes in L	CAI comp database

Risk	Action	Description	
rating			
Α	Unknown	Data have not demonstrated either pharmacodynamic or	
	interaction	pharmacokinetic interactions between the specified agents	
В	No action	Data demonstrate that the specified agents may interact with each	
	needed	other, but there is little to no evidence of clinical concern resulting	
		from their concomitant use	
С	Monitor	Data demonstrate that the specified agents may interact with each other	
	Therapy	in a clinically significant manner. The benefits of concomitant use of	
		these two medications usually outweigh the risks. An appropriate	
		monitoring plan should be implemented to identify potential negative	
		effects. Dosage adjustments of one or both agents may be needed in a	
		minority of patients.	
D	Consider	Data demonstrate that the two medications may interact with each	
	Therapy	other in a clinically significant manner. A patient-specific assessment	
	Modification	must be conducted to determine whether the benefits of concomitant	
		therapy outweigh the risks. Specific actions must be taken in order to	
		realize the benefits and/or minimize the toxicity resulting from	
		concomitant use of the agents. These actions may include aggressive	
		monitoring, empiric dosage changes, or choosing alternative agents.	
X	Avoid	Data demonstrate that the specified agents may interact with each other	
	Combination	in a clinically significant manner. The risks associated with	
		concomitant use of these agents usually outweigh the benefits. These	
		agents are generally considered contraindicated.	

1.4.3 Potentially inappropriate prescription

Potentially inappropriate prescription (PIP) is a term used to characterize an assortment of problematic recommending hones and is for the most part pervasive among the elderly populace. Basically, it incorporates;

• The prescribing of potentially inappropriate medications (PIMs) that carries an unacceptable risk of ADR when a safer alternative is available.

• The prescribing of medications at a dose or duration unsuitable for older patients and the under-prescribing of medications which may benefit the elderly patient.

These latter cases are commonly referred to as potential prescribing omissions (PPOs) (O'mahony & Gallagher, 2008), (Gallagher PF, 2011).

PIP prevalence rates of 21%, 51% and 70% in primary, secondary and long-term care respectively have been reported in Ireland alone (Gallagher et al, 2011), (Ryan et al C. O., 2009), (O'Sullivan DP et al, 2013). Further afield, PIP prevalence studies have shown rates amongst older patients to be high also e.g. USA (42%) (Davidoff et al, 2015), Japan (40.4%) (Hamano J & Tokuda Y, 2014), Australia (32.3%) (Doody et al, 2015), Europe (30.4%) (Gallagher et al, 2011), Brazil (28%) (Cassoni et al, 2014) and Canada (16.3%) (Howard et al, 2004).

The PIP was the major contributory factor to hospitalization, ADEs and expanding of wellbeing costs (Gallagher et al, 2011), (Hamilton et al, 2011), (Jano & Aparasu, 2007), in 2013, 37% of more seasoned Canadian individuals filled at least 1 remedy meeting the Beers Criteria, and it was assessed that \$75 per more seasoned Canadian, or \$419 million altogether, was spent on conceivably improper prescriptions for outpatients setting (Morgan et al, 2016). In 2010, Cahir *et al.* performed a cost analysis of PIP in Ireland. They reported that the total PIP expenditure was estimated to be €45 631 319, 9% of the overall expenditure on pharmaceuticals in those \geq 70 years in 2007 without regarding to other costs associated with PIP such as increased length of hospital stays or hospitalization due to adverse drug events (Cahir et al, 2010).

A standout amongst the most genuine outcomes of PIP is the event of ADRs. An ADR is defined as "any response to a medicine that is noxious or unintended attributable to a medicine, which occurs at a dose which is normally for use in human beings, for the purpose of prophylaxis, diagnosis, therapy or modification of a physiological function" (Edwards IR & Aronson JK, 2000), (Organization., 1972). An adverse drug event (ADE) refers to "any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury" (Edwards IR & Aronson JK, 2000). An ADR is an extraordinary kind of ADE in which a causative relationship can be promptly appeared. ADRs have been accounted for to be between the fourth and sixth driving reason for death in hospitalized patients in the US (Lazarou et al, 1998). For elderly individuals the chances of being hospitalized by ADR

related issues are 4 times higher than for more youthful ones (16.6% versus 4.1%), (Beijer et al, 2002).

As of late, there are clear investigations appeared in certainly the connection amongst PIP and ADR as predominantly reason of event (Hanlon JT & Schmader KE, 2010). It has been accounted for that ADR rates in patients seen at confirmation are as high as (12.8%) (Alexopoulou et al, 2008).

ADRs are a noteworthy reason for expanded human services usage (Spinewine et al, 2007), moreover ADRs have been demonstrated longer length of remain than those without ADRs, and furthermore brought about an additional 2000 bed days for each annum, which likened to a cost of £171 million (DaviesEC et al, 2009). This cost ascends to £1 billion when all ADRs are represented (DaviesE et al, 2007). Ahern et al assessed that for 8.8% of ADR-related admissions to an Irish clinic, 57.3% of these could be anticipated (Ahern et al, 2014).

As mentioned before, geriatric patients are especially helpless to PIP and related results, for example, ADRs. With an expanding weight of co-morbidities as patients' age, prescribers end up under expanding strain to recommend various pharmaceuticals. Best practice manages that any choice a prescriber makes concerning initiating a medicine for a patient, ought to be confirm based and the sign for which the medication is being recommended is entrenched through confirmation in light of randomized controlled trials (RCTs). The trouble while endorsing for more seasoned patients however is that they are regularly barred from such trials because of their frequently complex wellbeing status and different morbidities (O'connorM et al, 2012).

Along these lines the circumstance emerges where a clinician must endorse without the confirmation base he/she may have for somebody in the more youthful grown-up populace. Likewise, with maturing comes declining renal capacity and liver capacity, volume of appropriation of lipid-solvent medications increment, and affectability to a few classes of medications is frequently changed. These age-related pharmacokinetic and pharmacodynamics changes imply that more seasoned patients encounter expanded inter-individual fluctuation with respect to how they utilize medications and how sedates influence them physiologically (Mangoni AA, 2004).

Underuse of medicines is a vital and progressively perceived issue in older patients, its characterized as the oversight of medication treatment that is demonstrated for the treatment or anticipation of a malady condition. An examination identified with the group staying seniors found that half of 372 powerless grown-ups were not endorsed a demonstrated prescription. A standout amongst the most well-known issues were that the absence of a gastro defensive operator for high-chance Nonsteroidal Anti-Inflammatory medication clients, no calcium as well as vitamin D for those with osteoporosis and no angiotensin-converting enzyme inhibitor for patients with diabetes and proteinuria.

Underuse has an important relationship with an older adults' negative health outcomes, which includes functional disability, health services use and death (Kaufman DW, 2002).

1.4.4 Non-adherence to Medication

Medication adherence as defined by (W.H.O) is "the extent of the person's behavior—taking from a healthcare provider the medication corresponds with agreed recommendations. The range of 40% to 80% was the prevalence rate of medication non-adherence in older adults (Kapadia A, 2010).

As per the AARP (formerly the American Association of Retired Persons) and furthermore, an investigation in the Medicare populace, the cost is one regular reason that causes the more established grown-ups not to fill their remedies. Despite the fact that, in light of some conceivable unfriendly impacts, the more established patients additionally may not hold fast to their regimens, a powerlessness to peruse the marks of the item or an absence of full comprehension of data about the recommended drugs (Korrapati MR, 1997).

Some limited retrospective data suggest that non-adherence may associate with increased health service use and ADRs. A study that was done in 2001, found that non-adherence was one of the possible factors that may cause more than 10% of older adult hospital admissions (Brenner et al, 2003). As well as the study of Col et al. which evaluated 315 of older patients admitted to a hospital and concluded that 11.4% of admissions resulted from non-adherence. Because of the errors in patient adherence, Gurwitz et al. found that 21% of ADRs in elderly outpatients were preventable. On the positive side, a study found that the fewer

hospitalizations were associated with increased medication adherence and decreased cost in patients with chronic medical conditions (Krupka et al, 2006), (Ujhelyi MR, 1997).

1.5 Role of Clinical pharmacy in DRPs management

The conventional role of pharmacists dispensing medications has shifted to a role where pharmacists' work is more patient-oriented (Chisholm-Burns et al, 2010)]. Several studies have showed clinical pharmacists' cost savings (GallagherJ et al, 2014), (Loh et al, 2016).

Clinical pharmacy is a patient-oriented practice including for example medication reviews or medication reconciliation (Ahmed et al, 2010). A medication review can be defined as "a structured evaluation of patient's medicines with the aim of optimizing medicine use and improving health outcomes. This entails detecting drug related problems and recommending interventions". A medication reconciliation is a comparison between the medications the patient is actually taking, and the medications prescribed, with the aim to maintain complete information about the patient's medications and thereby achieve appropriate drug usage (Peterson & Gustafsson, 2017).

Several studies showed well implementation of the clinical pharmacist service and positive effects on medication use, health service use and costs which result in patient outcomes improve (Graabæk T & Kjeldsen LJ, 2013), (Nkansah et al, 2010).

In a meta-analysis, 25/38 included studies showed positive effects on at least one primary outcome. Pharmacist interventions improved outcomes in management of chronic conditions, for example cardiovascular disease and diabetes (Tan et al, 2014). Previous studies also suggest that interventions to improve appropriate use of Poly-pharmacy, for example medication reviews can reduce inappropriate prescribing (Cooper et al, 2015),(Patterson et al, 2012). However, Pharmacist-led medication review interventions do not have any effect on reducing mortality or hospital admission in older people (Holland et al, 2008).

Chapter 2: PIP Detection Tools

Adults 65 years old or older are at high risk of complications of drug therapy and the vulnerability to poor quality medication prescribing patterns and potentially inappropriate medications (PIM) due to the age-related changes, the comorbidities, poly-pharmacy, and medication interactions. These complications include also mortality and morbidity, ADE, dementia, and falls (Roth, 2009).

Accordingly the high morbidity as well as complex poly-pharmacy which result in PIP and ADR occurrence in elderly population around the world, it was needed to focus more on interventional studies to detect and minimize those consequences (O'SullivanD et al, 2014), (Gallagher PF, 2011). Unfortunately, till now, little advancement has been made in accomplishing noteworthy upgrades in propriety of endorsing in more seasoned patients on a worldwide scale. The fundamental systems utilized to address PIP and its results are effective much in the accompanying area.

Keeping in mind the end goal to fundamentally lessen PIP and PIP related results, solid techniques for PIP recognition must be connected. Verifiably, there have been a few endeavors to create approved criteria to distinguish PIP. In any case, absence of transferability and approval by randomized controlled trials (RCTs) implies that the result of these endeavors has not had the coveted validity (O'connorM et al, 2012). Criteria's' generally fall into two types explicit and implicit.

2.1 Explicit (Express) Criteria:

Explicit criteria usually consist of rundown of medications, sedate classes and measurements which have been accounted for in the writing or settled upon by agreement strategies to be conceivably improper in geriatric patient.

2.1.1 Beers criteria:

The first explicit tool for identifying PIP was Beers' criteria, which initially published in 1991 by Dr. Mark Beers through a consensus panel of experts by using a Delphi method with focusing on medication use in nursing home residents (Beers et al, 1991). The criteria consisted of a list of 30 drugs which were either to be completely avoided or avoided at certain doses/durations.

The Beers list was expanded to include all geriatric care settings, such as inpatient or outpatient and primary care (Davidoff AJ, 2015). It was also updated and expanded to include all geriatric care settings in 1997 and in 2003 (Beers MH, 1997). In 2012, an expert panel arranged in collaboration with the American Geriatrics Society to update the Beers criteria and released updates in 2012 and 2015 (Lau DT, 2009).

The updated 2012 Beers Criteria consist of 53 classes of medications divided into three categories:

(i) Potentially Inappropriate Medications to be avoided in older patients-independent of diagnoses or conditions

(ii) Potentially Inappropriate Medications to be avoided in older patients due to drug-disease interactions

(iii) Drugs to be used with caution in older patients.

The slightly modifications in the 2015 update were limited compared to the previous updates, the two major components which have been added were drugs which required the dose adjustment based on kidney function and drug–drug interactions. Because such lists would be too widespread, the new additions are intended to be comprehensive (American Geriatric Society 2015 Beers Criteria Update Expert Panel, 2015).

They are extensively used in the US and have also been applied in several European studies. In Ireland, a study using the Beers' criteria reported PIP prevalence of 25% in secondary care (Gallagher P & O'Mahony D, 2008) while rates of 20% in a home care (Fialová et al, 2005), and 16-20% in primary (Van Der Hooft et al, 2005) have been reported in other European sites. However, Beers' criteria have several important limitations. They are very much focused on US prescribers. Many of the drugs (>50%) included are not available in Europe. Several are not commonly prescribed for older patients and there is much disagreement surrounding the identification of some of the medications as drugs which should be avoided in all situations (O'connor et al, 2012). Drug-drug interactions (previous updates), drug duplication (prescribing of two drugs from the same pharmacological class) and PPOs are not accounted for. Considering that there have not been any RCTs assessing Beer's criteria's capacity to improve outcomes such as ADRs and hospitalizations, consequently, they have not found their way into common clinical usage.

Table (7): Drugs that are rarely used in European						
Amphetamines	Cyproheptadine	Hyoscyamine	Pemolin			
Carisoprolol	Discyclomine	Isoxsurpine	Phenylpropanolamine			
Chlorpropamide	Ethacrynic acid	Meprobamate	Reserpine			
Clidinium	Guanedrel	Mesoridazine	Thioridazine			
Clonidine	Guanethidine	Metaxalone	Trimethobenzamide			
Cyclandelate	Halazepam	Methocarbamol	Tripelenamine			
Cyclobenzaprine	Hydroxyzine	Oxaprozin				

The Table (7) was extracted from 2003 updated version (Waller & Maclean, 2003)

2.1.2 Screening Tools STOPP/START criteria

As a result of Beers criteria limitation's, O'Mahony*et al.* developed new PIP criteria to accomplish the need to widespread criteria with good inter-rater reliability, detection sensitivity and applicability, as well as covers the drug duplication, drug-drug, drug disease interaction, and under prescription. The Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) were published initially in 2008 using a Delphi consensus methodology by a panel of 18 experts in geriatric pharmacotherapy in Ireland and the UK (Gallagher P et al, 2008),and updated the version 2 in 2014 (O'mahony et al, 2015). The differences between version 1 and 2 are shown in the Table 8.

The latest update of Screening Tool of Older Persons' Prescriptions (STOPP) consists of 87 prescribing situations, which was classified by disease area, and contain the potentially inappropriate prescription in older patients.

Criteria	Version 1 (2008)		Version 2 (2014)	
Items	STOPP	START	STOPP	START
Numbers	65	22	81	34
Classification	Ву	Ву	By disease area	By physiological
	physiological	physiological		system
	system	system		
New added			1-Indication classes	1-Vaccines
classes			2-Antiplatelate	2-Analgesic
			/Anticoagulant	
			3- Renal system	
			drug	
			4-Antimuscarinic	
			/Anticholinergic	
			drug burden	

 Table (8): The difference between the two versions

The advantage of latest update in that it overcomes some defects of the first edition regarding the indication of medication, however this addition made the criteria time consuming and tedious to use in that manner required to deal with every drug to identify the evidence-based indication, and duration to each medication separately. An example for STOPP criteria is inappropriate usage of Phosphodiesterase type-5 inhibitors (e.g. Sildenafil, Tadalafil, Vardenafil) in severe heart failure characterized by hypotension i.e. systolic BP < 90 mmHg (drug disease interaction), or concurrent nitrate (drug-drug interaction) therapy for angina due to the risk of cardiovascular collapse.

The Screening Tool to Alert doctors to Right Treatment (**START**) consists of 34 prescribing situations, classified by physiological systems, where certain medications should be considered for an older patient. An example of START criteria is the using of High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective. The complete list of STOPP/START criteria version 2 is found elsewhere of this thesis.

The studies relying on STOPP/START criteria have shown good inter-rater reliability between physicians and pharmacists (Ryan C et al, 2009), (LiuCL et al, 2012), as well as explored the use of the criteria in all levels of care (RyanC et al, 2009), (O'SullivanDP et al, 2013), (Gallagher P& O'Mahony D, 2008), in addition have shown implementation of the guidelines to result in sustained improvement in medication appropriateness and superior performance in terms of PIP detection and ADR prevention when compared to Beers' criteria (GallagherP et al, 2011), (SpinewineA et al, 2007). STOPP/START has recognized itself as the principle tool in PIP detection, certainly outside of the US; however, to uphold its clinical significance, the criteria will require regular up-dating and validation.

2.1.3 Other Explicit Tools

Other explicit tools have been developed around the world including: the Improved Prescribing in the Elderly Tool (IPET), which is a Canadian guideline, derived by Naugler et al from the criteria developed by McLeod et al., and based on the most prevalent instances of PIP found in a geriatric unit using the McLeod criteria. (Naugler et al, 2000), the other tool is Prescribing Appropriateness Index (PAI)which was developed by Cantrill et al, consisted of 9 indicators of prescribing appropriateness, and was considered suitable for application to the medical record of any patient on long term medication in United Kingdom general practice(Cantrill et al, 1998), Zhan's Criteria to detect the Potentially inappropriate medication use in the community-dwelling elderly in USA (Zhan C et al, 2001), also the French Consensus Panel List (Laroche et al, 2007), the Australian Prescribing Indicators Tool (Basger et al, 2008), the Norwegian General Practice Criteria (NORGEP) (Rognstad et al, 2009), the PRISCUS List (Holt et al, 2010), the Thailand criteria,(Winit-Watjana et al, 2008), and the Rancourt criteria (Rancourt et al, 2004). A recent review has highlighted the

pros and cons of these various tools (O'connor et al, 2012). Lack of under-prescribing criteria, lack of availability of drugs outside the country of origin, lack of studies outside the country of origin, lack of drug-drug interaction data and lack of transferability are common drawbacks for most of these explicit criteria sets.

2.2 Implicit criteria

Implicit criteria are judgment based and rely on the prescriber's knowledge. They consist of quality indicators of prescribing that a prescriber or pharmacist must use their own judgment to apply to a person's prescription. However, they do not focus on particular drugs or disease areas, time-consuming and rather boring to use, implicit criteria focus more on the patient and address their drug therapy at a more individual level (O'connor et al, 2012).

2.2.1 Medication Appropriateness Index (MAI)

The MAI was initially published in 1992by Dr. Joseph Hanlon and colleagues as one of the most commonly used and cited of implicit criteria is the Medication Appropriateness Index (MAI)(HanlonJT et al, 1992).

Table (9): MAI criteria & whieghted socore				
Criterion	Socore			
Is there an indication for the drug?	3			
Is the medication effective for the condition?	3			
Is the dosage correct?	2			
Are the directions correct?	2			
Are the directions practical?	1			
Are there clinically significant drug-drug interactions?	2			
Are there clinically significant drug-disease interactions?	2			
Is there unnecessary duplication with other drugs?	1			
Is the duration of therapy acceptable?	1			
Is this drug the least expensive alternative compared to others of	1			
equal utility?				
Total	18			
However, these criteria require Wide-going clinical subtle elements, therapeutic information and clinical judgment to be relevant. This instrument evaluates recommending suitability by methods for ten criteria: indication, effectiveness, dose, correct direction, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and cost (Table 9). The degree of appropriateness arranged according to the total score of ten criteria from zero (indicating a completely appropriate prescription) to a maximum score of 18 (indicating a completely inappropriate prescription).

The changed MAI is a solid instrument for assessment of pharmaceutical suitability in a non-Veterans Affairs, walking, elderly populace and may furnish drug specialists with a functional and standard strategy to assess patients' medication regimens and recognize some potential medication related issues that's make gain it a good intra-rater and inter-rater reliability among hospital pharmacists and hospital physicians (Fitzgerald et al, 1997).

An advantage of the MAI is that it encompasses elements of drug prescribing that are applicable to any medication and to any clinical condition in any clinical setting. However, the MAI does not address under prescribing and is time consuming to use (approximately 10 minutes per medication) thus limiting its applicability to everyday clinical practice.

The MAI has been widely utilized as a part of research to survey recommending suitability as a result and demonstrated that the MAI apparatus has great between rater unwavering quality among drug specialists and doctors and performs superior to Beers' criteria with respect to anticipating adverse drug events (Lund et al, 2010), (Fitzgerald et al, 1997).

2.2.2 Assessment of Underutilization (AOU)

The AOU device depends on an instrument announced by Lipton et al. (Lipton et al, 1992), it requires that the client have a definite rundown of medicinal conditions and current prescriptions for the patient with a specific end goal to decide recommending exclusions in view of existing proof in the therapeutic writing. Evaluations for singular things are dichotomized into "no recommending oversight" or "exclusion of a showed tranquilize". The AOU apparatus has been appeared to have great between rater dependability (Jeffrey et al, 1999).

One investigation of 196 more established patients demonstrated that 64% (125 patients) had proof of under prescribing as indicated by the AOU instrument (Steinman et al, 2006).

The Assessment of underutilization of pharmaceutical (AOU) apparatus notwithstanding exclusively recognizes recommending oversights. Once more, the AOU device has indicated great between rater unwavering quality however with more vigorous devices accessible now, especially those which can recognize both wrong recommending and under-endorsing, the AOU isn't ordinarily detailed in the writing (Steinman et al, 2006).

2.3 Previous studies

The STOPP/START criteria were the second commonly explicit tool in PIP detection studies after beers criteria. Mainly in Europe country the studies for detection of PIP prevalence was depending on stop start criteria.

One study made by O'Sullivan et al in 2013 who study the prevalence of PIP in long term care facilities for 732 elderly patients in Ireland found that the prevalence depending on STOPP criteria version1 was 70% of patients whom experienced at least one PIP compared with 53.4% by using beers criteria 2003, there is no STARRT criteria in this study. The median age of participants was 85 years, whereas the median of total number of prescribed drug (poly pharmacy) was 11, they concluded that the STOPP criteria version 1 more sensitive than Beers criteria 2003 in detection of PIP (O'SullivanDP et al, 2013).

Not far away from Ireland, Ryan et al prospectively studied the PIP prevalence in 313 nursing home elderly patients depending on STOPP/START criteria version 1. The median age was 84.4 years and the median of total prescribed medication was 8 for each patient, they found that the PIP prevalence was 59.8% for STOPP and 42.2% for START, in addition they found that the number of medicines prescribed was positively associated with PIP identified by STOPP (rs = 0.303, P < 0.01). Age, sex and the number of medicines prescribed were not associated with prescribing omissions using START (Ryan et al C. O., 2012).

In Spain, García-Gollarte et al, in one prospective, randomized, multicenter study assessed the effect of an educational intervention directed to nursing home physicians in reducing inappropriate prescription and improving health outcomes and resource utilization, they found

that a sum of 716 occupants completed the investigation (344 intercession bunch and 372 control physicians), with the Mean age was 84.4 ± 12.7 years; 73% were female .The he mean number of improper medications (STOPP criteria) was higher toward the finish of the examination in the control than in intervention gathering (1.29 ± 1.56 versus 0.81 ± 1.13), similar to the quantity of inhabitants on at least 6 drugs (76.5% vs.67.0%), utilizing antipsychotics (9.1% versus 3.2%) or copy prescriptions (32.5% versus 9.2%). The quantity of fallers expanded in the control gathering (from 19.3% to 28%) and did not fundamentally change in the mediation gathering (from 25.3% to 23.9%) (García-GollarteF et al, 2014).

Extra examination in Spain by the García-Gollarte et al influenced a Cross-sectional to investigation of 100 back to back patients (mean age 84.7 ± 7.5 years, 80% ladies) admitted to 6 helped living nursing homes, with methodical survey of medicines utilized at the season of nursing home confirmation utilizing the STOPP-START and the Australian criteria searching for possibly improper medication medicines. They found that 79% of the subjects appeared no less than one possibly wrong solution by utilizing STOPP. Oversights of conceivably suitable medications were found by the START criteria in 74% of them. The Australian criteria identified no less than one potential issue in 95% of the example. The quantity of subjects with at least 2 issues identified was most noteworthy utilizing the Australian criteria (72%) (García-Gollarte F et al, 2012).

In contrast one study made in Malaysia for 212 residents in long term facilities with the median age of 77 years and 4 as median number of prescription medicines. It was found out there was a significant difference in the number of residents with PIMs detected by STOPP (23.7 %) version 1 compared with (32.7 %) detected by beers criteria 2003, p < 0.001. it was the only study which mentioned that the STOPP criteria less sensitive than Beers criteria in detection PIM, may be the regional factors play role in such result (Chen et al, 2012).

In China, one study made by Lao et al for 114 elderly residents with median age 86.6 years and consumed an average of 6.9 ± 3.1 different medications were found out that about 46.5 % of them regularly used one or more PIMs. The prevalence of DDIs was 37.8 % among the 111 elderly residents who consumed at least two different medications. An increased number of drugs used were identified as the independent factor associated with PIM use and DDIs (p < 0.05). However, the use of STOPP-related PIMs did not appear to raise the likelihood of DDIs among the study population (LaoCK et al, 2013).

A parallel-group randomized trial was carried in a geriatric chronic care facility to assess the effect of STOPP/START criteria found out that, in intervention group (n = 183). There was a significant reduction in PIPs and PPOs (P <0.001 for each) in the intervention group but noting the control group (n = 176) (P = 0.10 for each). In addition, there is no significant difference in the total number of prescribed medication (poly-pharmacy) in both groups. The PIP prevalence after 6 months flow up in intervention group was (37.4, 9.2) % for STOPP and START, respectively compared with (56, 26.2) % for STOPP and START, respectively in control group. The mean of total medication prescribed number was (8.1, 9) for both intervention and control group respectively (Frankenthal et al, 2014).

In UK England, a retrospective, non-randomized study for 195 patients with median age of 85.5 years conducted in the Specialist Health and Ageing Unit (HAU) of a 950-bed acute hospital to assess the prevalence of PIP according to STOPP criteria version 1. It was found out that an admission PIM prevalence was 26.7 % (95 % CI 20.5–32.9; 52 patients, 74 PIMs) with 9 as a median of total number of prescribed medicine, whereas the discharge PIM prevalence was 22.6 % (95 % CI 16.7–28.5; 44 patients, 51 PIMs) with 10 as median of total number of prescribed medicine (Onatade et al, 2013).

Also, one prospective interventional study in 150 acutely ill elderly patients was carried to evaluate the effect of interdisciplinary geriatric and psychiatric care on the appropriateness of prescribing. Assessed using STOPP/START criteria version 1, the study found out that the intervention reduced the total number of medications prescribed at discharge from 1347 to 790 (P < 0.0001) and incidence rates for potentially inappropriate medications and PO reduced from 77% to 19% (P < 0.0001) and from 65% to 11% (P < 0.0001), respectively (LangPO et al, 2012).

Away from Europe in Taiwan, the IP was evaluated by the STOPP /START version 1 criteria for 520 elderly medicinal ward inpatients (mean age = 79.2 ± 6.7 years, 73.8% guys). Altogether, 3455 things of drug were recommended for these 520 patients (mean = 6.6 ± 3.2 things). As indicated by STOPP criteria, 36.2% of the examination subjects had no less than one conceivably improper pharmaceutical (PIM). The most common PIMs were medicine that may unfavorably influence the individuals who are inclined to falls, flowed by Ca-channel blockers with chronic constipation, neuroleptic utilization (5.6%), long-term, long-acting benzodiazepines, and 1stantihistamine classes, respectively. Also, 218 patients (41.9%) had no less than one START criteria. The most frequented START PIMs were: statin prophylaxis in DM in CVS risky patients flowed by antiplatelet therapy in diabetes mellitus with co-existing major cardiovascular risk factors, Metformin with type 2 diabetes with or without metabolic syndrome (in the absence of renal impairment), ACEIs or ARBs with chronic heart failure, and Aspirin or Clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm. Strategic relapse demonstrated that more seasoned age and number of pharmaceuticals were huge hazard factors for PIPs (LiuCL et al, 2012).

In addition, one study aimed to determine the prevalence of and risk factors for inappropriate prescribing (IP) and prescribing omission (PO) by mean of STOPP/START criteria version 1 in 115 elderlies (mean age 80 ± 9 , 70% of women) with mental co-morbidities found out that over 95% were taking ≥ 1 medication (median = 7) which amounted to 1,137 prescriptions. The prevalence of IP was 77% and PO was 65% (Lang PO et al, 2010).

In the hospital too, Ordonez G, studied the prevalence of PIM in 179 poly-pharmacy elderly patients admitted to an Internal Medicine Department. It was found out that the prevalence of patients with PIM on admission and discharge were 71% and 48%, respectively. Out of the 50 selected PIM, 27 and 26 were detected on admission and discharge, respectively (55.5% and 57.69% included on STOPP criteria). The difference in the 50 created criteria, language of full article and unclearly explaining in the abstract may affect the result and understanding of this study in addition, the dependence on the poly-pharmacy as inclusion criteria may mask the actual result (Ordóñez G, 2014).

In India an observational cross-sectional study for 236 cardiacaged \geq 65yearspatients were conducted in tertiary hospital to study the prevalence of PIM depending on Beers criteria 2012. It was found out that 29.3% patients received at least one PIM (Shah et al, 2016).

Also, a study carried out in Cork, Ireland to compare Beers (2003, 2012) and STOP/START (2008 & 2014 versions) according to the effect on the incidence of potentially inappropriate prescribing medication, poly-pharmacy and clinical relevance of medication changes. They found out that the number of medications was most reduced by STOP/START v2. In addition, STOP/START v2 identified more instance of potential major clinical relevance (Boland et al, 2016).

In conclusion, the difference in the design, participant number, health care setting, using tools, and regional sitting of study may create the variation in the results from one to another study, there are no or limited studies dealing with STOPP/START criteria version 2 in addition, it was rarely to find all of our three components in one study, we will try to determine the prevalence of total number of medication with drug-drug and drug disease interactions by means of evidence based tools.

2.4 Aim and Objectives:

AIM: To describe the frequency of medication related problems in geriatric patients and to identify the associated factors using evidence-based tools.

Objectives:

- To identify the prevalence of Poly-pharmacy, DDIs and PIPs before and after STOPP/START criteria application and showing how these criteria will affect both of Poly-pharmacy and DDIs.
- 2- To determine the time-variance in the DDIs and PIPs occurrence.

Chapter 3. Methodology

A non-randomized retrospective medical chart review carried independently by one clinical pharmacist and one researcher pharmacist for all inpatients ≥ 65 years hospitalized between July to December 2017 was conducted at a tertiary hospital in North Cyprus. The latest medicines chart, hospital staying periods, and lap results which were available in the patient files were scanned for the evaluation in addition to the physician report for each case.

All patients with 5 or more medications (except electrolytes and nutrition supplements) were considered to have a poly-pharmacy, whereas those patients taking more than 10 medications were classified as hyper poly-pharmacy. The number of medications after criteria application was calculated using this equation:

NO. Med. AFTER = NO. med. Before + added drug(s) - deleted drug(s)

Potentially inappropriate prescription as defined by STOPP/START criteria version-2(2014), which are explicit criteria consisting of 115 scenarios aimed to limit the drug-drug and drugdisease interaction in older patients and divided in two parts; the first part is the STOPP criteria contains 81 scenarios and classified by diseases area which is potentially inappropriate medications in older patients, the second part is the START criteria with 34 scenarios classified according to physiologic system that should be applied to improve the certain situations of elderly patients. The indication part of criteria was done by using lexi-drug to determine if there is any indication for every drug in every case. The final judgment made after negotiation between the two pharmacists and reviewed by the third one.

Drug-drug interactions were checked by using Lexi-comp which classifies the drug-drug interaction into five categories which are A category "no interaction", B category "no action needed", C category "monitor therapy", D category "therapy modification" and X category "avoid combination", the X and D classes were to be accounted for evaluation due to their clinical significances, every patient who take two or more medication for one day or more will be involved in the evaluation.

The inclusion criteria for this study was all patients aged 65 or more who stayed at least one day in hospital units, whereas the excluding patient's files which do not contain the complete documented required data.

We identified the time and date of every drug which is responsible for any of DDIs or PIPs events and classified them into four groups according to the time they occurred, time started use in Weekend (holiday) or Working-day and morning (9.00-16:59 o'clock) or evening (17.00-08:59 o'clock) according to the calendar of 2017 (Turkey) and the working hours of the hospital.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows 11.0 program. Continuous variables were presented as mean ± standard deviation; ordinal and nominal values were presented as n (%). Whether there is any correlation between the numerical data was examined using Pearson correlation test and Spearman correlation test for nominal or ordinal data. Chi-square test was used for analysis of categorical variables, Fischer exact test was applied where chi-square test conditions were not met.

The total variables are 28	attached in the Table 10.
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	Table (10): The variable for analytical processes						
No	Name	Defenition					
1	PatientID	Patient identical number					
2	Age	Years					
3	Gender	Male or Female					
4	Hospitalization	Hospital staying periods" days"					
5	HU	Hospital Unit					
6	At least 1	Patient has at least one STOPP, START, or both PIP					
7	Classification	Poly pharm numerical classification					
8	No.medB	Total number of medication before criteria application					
9	STOPPT	Total STOPP PIP					
10	START	Total START PIP					
11	UnnecessaryD	Number of unnecessary (without indication) drugs					
12	Deleted.drug	Number of drug"s" deleted by STOPP criteria					
13	Added.drug	Number of drug"s" added by START criteria					
14	NO.MED.AFTER	Number of medication's after Criteria application					
15	X.DDIs	Number of DDIs class X					
16	D.DDIs	Number of DDIs class D					

17	C.DDIs	Number of DDIs class C
18	B.DDIs	Number of DDIs class B
19	A.DDIs	Number of DDIs class A
20	Clash.point	Shared point's" between DDIs and STOPP PIP
21	No.DDI.HAM	Number of DDIs happened in weekend morning
22	NO.DDIs.HOL.AM	Number of DDIs start happening in weekend morning
23	NO.DDIs.HOL.PM	Number of DDIs start happening in weekend evening
24	NO.DDIs.NHOL.AM	Number of DDIs start happening in working-day
		morning
25	NO.DDIs.NHOL.PM	Number of DDIs start happening in working-day
		evening
26	NO.PIPs.HOL.AM	Number of PIPs start happening in weekend morning
27	NO.PIPs.HOL.PM	Number of PIPs start happening in weekend evening
28	NO.PIPs.NHOL.AM	Number of PIPs start happening in working-day morning
29	NO.PIPs.NHOL.PM	Number of PIPs start happening in working-day evening
30	Semester	Summer or winter
31	START.time	When the STAR happened

3.1 Ethical approval

This study was approved by "Institutional Review Board of Near East University Hospital" with YDU/2017/53-500 number and dated 21.12.2017 (Appendix 2).

Chapter4. Results

Out of (428) patients aged ≥ 65 , 118 with a mean age (75 \pm 6.7) years patients were eligible for including and excluding criteria. The participants (60.2%, and 39.8% male and female respectively) had mean of (6.9 \pm 8.9) days as staying periods in the hospital units.



Figure (1): Distribution of gender in hospital units

4.1 Medication usage and polypharmacy

The total number of medications used was 1029 medicines with an average of 8.72 ± 4 (1-17) for each patient the Table (11) shows the variance of means between genders. Around 44.1% of the patients were consuming 5 to 10 medicines, whereas 34.7% were taking more than 10 medicines as shown in the Table (12).

Table (1	1): Comparison of Total	I Drug Used according to	
Gender			
Gender	Before Mean (±SD)	After Mean (±SD)	P value
Male	8.71 (±4.6)	7.54 (±3.3)	< 0.01
Female	8.72 (±4.6)	7.4 (±4.0)	< 0.01

SD: Standard deviation

Table(12): Poly-pharmacy	Frequency		Percent%	
Classification	Before After		Before	After
No Poly-Pharmacy	25	26	21.2	22
Poly-Pharmacy	52	65	44.1	55.1
Hyper Poly-Pharmacy	41	27	34.7	22.9

There is a significant difference between the total number of medications that used before form and used after STOPP/START criteria application (Wilcoxon test, P value=.000), in which the criteria were able to reduce 11.7% of the total medications used. In another direction, according to the definition of poly-pharmacy as the unnecessary (no clear evidence for indication) medications around 63.6% of patients were taking at least one unnecessary medication, in which the total of unnecessary medications was 142 (13.7% of the total medications).

4.2 Drug-Drug Interactions (DDIs)

64 (54.2%) of patients have at least one X, D, or both DDIs; every patient (of the 118 patients) has a mean of 1.38 ± 2.29 significant DDIs (X, D, or both DDIs). The Table 13 shows the percent of each class from the total number of interactions, out of 164 (the sum X and D) 15(9.1%) happened in the weekend morning, where 41 (25%) happened in the evening, whereas in working-day (normal days) the percent of 58 (35.36%), and 51 (31%) happened in the morning, and evening respectively.

Table (13):Percent of different DDIs							
DDIs classes	No Percent%						
Х	51	6.57					
D	113	14.56					
С	531	68.42					
В	77	9.92					
А	4	0.51					

There is a significant difference in the sum of the total number (X and D) between before and after STOPP criteria application (Wilcoxon test, p-value < 0.001), in which these criteria were able to reduce 72.5% of the total X and D DDIs. Although there is no significant difference in the sum of X and D between the gender and the age groups (Mann-Whitney test, P-value= 0.681, and Kruskal-Wallis Test, P-value= 0.454, respectively), there is a significant difference between the poly-pharmacy numerical classification and the total sum of X and D (Kruskal-Wallis Test, P-value < 0.001).

4.3 Potentially Inappropriate Prescriptions (PIPs)

76.3% of the patients were with at least one STOPP PIPs, 41.5 % (49 patients) with one STOPP, 23.7 % (28 patients), and 10.2% (12 patients) with two, and three STOPP respectively and one patient 0.8% with more than three. In the overall the total number of the STOPP was 145 PIPs (mean= 1.5 ± 0.78). 11 (7.58%) of these PIPs were started during weekend morning, while 17 (11.7%) were prescribed first during evenings, whereas in the normal days (working days), 38 (26.2%) and 77 (53.1%) of STOPP PIPs were prescribed during morning, and evening respectively.

On the other hand, 53.4% of the patient had at least one START, 20% was discharged during weekend whereas 80% discharged in a working-day.

Table(14): the prevalence of PIPs						
PIP type	Frequency	Percent%				
STOPP	42	35.6				
START	15	12.7				
BOTH	48	40.7				

There is no significant difference in the PIPs sum between the genders (Mann-Whitney test, P-value=0.946), also no significant difference between the age groups (Kruskal-Wallis Test, P-value=0.936), in contrast there is a significant difference between the poly-pharmacy numerical classification and PIP sum (Mann-Whitney test, P-value=0.02).

Table (15): Patients with at least one STOPP criteria					
Place	Frequency	% of (118)			
On admission	56	47.5%			
On discharge	65	55.1%			
Hospitalization	90	76.3%			

Table (16): Frequency of each PIPs					
STOPP item"S"	F*	START item "S"	F		
A1*	75	A5	36		
A3	21	A3	33		
K1	12	E5	12		
N	10	F1	7		
C5	4	B1	4		
B5	4	A1	3		
C6	4	A6	3		
B9 & A2	4	D1, A4,& E1	3		
F1, B3, K3,	10	G1,& B3	2		
C4,J1,C3,					
B6,B1, B2,& D6					
*The letter indicates the section while the number					
indicates the item in, F*= frequency					

Table (17): The most frequent pDDIs*					
X class DDIs	F*	D class DDIs	F		
Triprolidine +Ipratropium	8	Pantoprazole + Clopidogrel	12		
Cefuroxime + Pantoprazole	5	Ticagrelor + Aspirin	6		
Haloperidol + Ipratropium	4	Diltiazem + Atorvastatin	4		
Pheniramine + Ipratropium	3	Cefuroxime + Gaviscon	3		
* pDDIs= potential drug –drug interactions, F= frequency					

Table (18): Descriptive statistics							
	Ν	Min	Max	Sum	Mean	SD	Variance
Number of STOPP PIPs on	93	0.00	3.0	94	1.0	0.81	0.663
Number of STOPP PIPs on	93	0.00	3.0	77	0.82	0.80	0.644
admission							
Total STOPP PIP	118	0.00	4.0	145	1.2	0.95	0.913
Total START PIP	118	0.00	3.0	103	0.87	0.93	0.881
Number of drug"s" deleted by	118	0.00	7.0	219	1.8	1.6	2.637
STOPP criteria	110	0.00	1.0		1.0	1.0	21007
Number of drug added by	118	0.00	3.0	99	0.83	0.91	0.837
START criteria	110	0.00	210		0.00	0171	01007
Shared points between DDIs	118	0.00	13.0	119	1.0	19	3 820
and STOPP PIP	110	0.00	15.0	117	1.0	1.9	5.020
Sum of STOPPSTART	118	0.00	6.0	248	2.1	1.3	1.853
Sum X&DDDIs Before	118	0.00	13.0	164	1.3	2.2	5.266
Sum X&D,DDIs After	118	-1.00	4.0	45	0.38	0.90	0.819

Chapter 5. Discussion

To our knowledge, this is the first study to determine the prevalence of three major drug related problems (poly-pharmacy, DDIs, PIPs) in Northern Cyprus hospitalized geriatric patients, with the time variance in DDIs and PIPs, and to show how the STOPP/STAR version2 application will affect the incidence of poly-pharmacy, and how STOPP criteria will effect on DDIs prevalence.

The new STOPP/START criteria (2014 edition) contains more PIP items than the old one, which results in high ability in detect and prevent drug–drug and drug disease interactions, although these updates are tedious to use and time consuming, especially the indication section of the criteria which is responsible for most PIPs as mentioned before and as we will discuss below.

Polypharmacy is more prevalent in elderly patients because of the nature of this group and (their) its susceptibility to more diseases (Proulx & Hunt, 2015). In comparing to the study made by Vetrano et al the prevalence of patients (taking 5-10 drugs) is slightly higher, whereas those patients (more than 10) are highly smaller (Vetrano et al, 2014).

The significant effect of STOPP/START version-2 criteria on the total used medicine is due to the interpretation between the drugs which added by START items and the those drugs which deleted by the STOPP criteria, in which the indication section (unnecessary drugs) plays the main role in this effect due to that it was able to reduce around 13.7% of the total consumed, by the way reduce the incidence of potential DDIs, medicine although we account all skin medication as indicated for unclear situation and we didn't account the vaccines section of START too (see limitations part).

It was approved that the increased numbers of drugs taken by patients usually accompanied by increase in the DDIs prevalence (Grattagliano et al, 2010), there are no comparable studies to compare our findings, the percentage of patient who has at least one X, D, or both and the percentage of each X and D are much reduced in our cohort than those percentage found by Greene et al, although the difference in the population groups should be taken in consideration, due to the fact that this study deals with the elderly HIV-infected patients (Greene et al, 2014).

As we mentioned in the result part the STOPP version2 criteria has high ability to reduce the incidence of the potential drug-drug interactions, it is important to know that, some potential interaction will still be present without treatment, for example the interaction between the oral Cefuroxime and PIPs (e.g Pantoprazole) which is classified as X category (Lexi-interact), the STOPP criteria fails to prevent this interaction especially when there is a clear indication for PPIs, additionally the interaction that occurs between Clopidogrel and Pantoprazole (D category, Lexi-interact), especially when the dual therapy (Aspirin plus Clopidogrel) was indicated which result in GIT bleeding prophylaxis necessity, the most common way for such prophylaxis is using Pantoprazole which gives rise to antiplatelet effect reduction, which will result in increased in the clots formation susceptibility.

Finally, it is beneficial to point out that the high ability of STOPP criteria version2 to reduce the prevalence of potential drug-drug interaction in contrast to the previous study which failed to find any relationship between the first version of STOPP criteria and potential DDIs (LaoCK et al, 2013).

The PIPs prevalence depending on the version2of STOPP/START criteria used in our study is higher than that depending on version 1 (Hill-Taylor et al, 2016), this is because that the version 2 is more sensitive in detection and prevention the PIMs in elderly patient due to the new added items (Boland et al, 2016).

Most of the previous cohorts (which studied the prevalence of PIM in hospitalized geriatric patients depending on the version1) were dealing with admission and discharge but they ignored the period in between, the new update has taken the acute care in account to be more applicable, for example utilizing of benzodiazepines found in two different places: one in Section D number 5 when used for long duration of time (more than 4 weeks), and the later presents in Section K number 1 without duration consideration (see appendix), although there is no clear written term for the classification of the items in the tool itself.

The new additions of the criteria are responsible for its characteristic (sensitivity and prevention ability) especially the indication part which is a part of implicit tool Medication Appropriate Index (MAI) that result in more individualization and specification, at the same time makes the criteria more tedious to be used and time consuming tools, in addition there are no alternative solutions for most of STOPP items, may be the addition of the Assessment Of Underutilization (AOU) to START will solve this matter in the future edition.

The aging and age-related problems is the most widespread issue throughout the world, the different tools have been designed to reduce such matters, one of most important tools and its updated version, that shows high ability in detection and prevention the PIPs and also has positive effect in reduction of medication used and incidence of potential DDIs.

Actually, there is a need for more studies to show the relation between the time and drugrelated occurrence, the variation in the knowledge and experiences between the different staff members during different shifts may be one of the risk factors, the research on this part is not available, although our cohort shows the variation in the periods when prevalence of DDIs and PIPs occur it is important to recommend more specific investigation in the future.

Limitations

Due to the retrospective design (which was made to overcome the language difficulties, and the small number of study sample) of these studies there are some limitations; firstly we considered all dermatologic medications as indicated thus, they were accounted for polypharmacy tests and avoided in the DDIs tests. This is because patients were not met personally to check the situation also most of the medical reports didn't mention about specific skin diseases. one of the most the indication part for dermatologic drug, because we couldn't meet the patient to check the situation by eyes contact, and most of the medical reports didn't mention about the specific skin diseases so we considered all dermatologic medications as indicated they were accounted for polypharmacy tests and avoid in the DDIs tests.

Also, few drugs which prescribed as needed we counted them as indicated (no PIPs) except when this indication interfere or be responsible with or for other STOPP items, for instance Pheniramine when prescribed as needed this is considered as indicated prescription, but when there were other drugs with anticholinergic effect this will account as Section N STOPP PIPs.

The second limitation was the evaluation the utilization of suitable vaccines (as indicated by START items section I 1&2) or not, because of the periodic nature of this vaccine and there is no information relating to, we didn't account those categories for any evaluation tests.

Conclusion

In conclusion the implementing the 2014 version of STOPP/START criteria would prevent and limit both PIPs in hospitalized elderly patient as well as significant DDIs prevalence and total used medicine. Although criteria application was tedious to be used, and time consuming, yet it has significant role in detection and prevention of an inappropriate prescription in elderly patients, in addition it had positive impact on reduction of the total number of medications used and minimize the incidence of potential drug-drug interactions, which are reported to be prevalent in elderly patients sampled in the current study. Applying the criteria in such settings may result in more compliance and enhance patient safety which is a potential role that clinical pharmacists can introduce to hospitals in North Cyprus

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Appendixes

1. Screening tools STOOP/START criteria

Appendix 3: Screening Tool of Older Persons' Prescriptions (STOPP) version 2.

The following prescriptions are potentially inappropriate to use in patients aged 65 years and older.

Section A: Indication of medication

- 1. Any drug prescribed without an evidence-based clinical indication.
- Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
- Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).

Section B: Cardiovascular System

- Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).
- 2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
- 3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
- Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
- Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).
- Loop diaretic as first-line treatment for hypertension (safer, more effective alternatives available).
- Loop diuretic for dependent arkle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
- Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).
- Loop diaretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
- 10. Centrally acting antihypertensives (e.g. methyldopa, clonidine, moxoridine, rilmeridine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of

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antihypertensive: (centrally active antihypertensives are generally less well, tolerated by olderpeople than younger people).

- 11. ACF inhibitors or Angioters in Receptor Blockers in patients with hyperkalaemia.
- 12. Alkosterone isntagonists (e.g. sprovolaciona, epieranone) with concurrent potassiumconserving drug: (e.g. ACEI'S, ARK'S, amiloride, triamierene) without monitoring of serum obtassium (ritk of dameerous hyperkalaemia Le. > 6.0 mmobil - serum K should be monitored regularly, i.e. at least every 6 mentas).
- 18 Phosphodiesterase type-5 inhibitors (e.g. silienafi, tadalafi, vandenafi) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular callapse)

Section C: Antiplatelet/Anticoagulant Drugs

- Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
- Aspirin with a past history of peptic uber disease without concomitant PPI (risk of recurrent peptic ulcer).
- Aspirin, clopicogrel, clipylidamole, vitamin i antegenists, direct thrombin inhibitors on factor Xe inhibitors with concurrent significant: bleeding risk, i.e. uncontrolled severe: hypertension, bleeding clathesis, recent non-trivial spontaneous: bleeding) (high risk of bleeding).
- Aspirin plus clopidogrel as secondary strole prevention, unless the patient has a coronary stents) inserted in the previous 12 months or concurrent acute cursoary syndrome or has a high grade symptomatic carotid arterial stenosis (no exidence of added benefit over clopicogrelmonotherapy).
- Aspirin in combination with vitamin K smagpnist, direct thrombin inhibitor or factor Ka inhibitors in patients with chronic strial fibrillation (no added benefit from aspirin)
- Antipatelet agents with vitamin K antagerist, direct thrombin inhibitor or factor Ka inhibitors in gatients with stable coronary, carebrovascular or peripheral asterial disease (No added benefit from dwal therapy).
- Ticlopidine in any discumstances (clobidogrelland pracugal have similar efficacy, stronger evidence and tever side-effects).
- Vitamin K antigonist, kirect thrombin inhibitor or factor Xa inhibitors for first deep venous, thrombosis without continuing provoking fisk factors (e.g. thromoophilia) for > 6 months, (no proven added kensfit).
- Vitamin K antigonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmenary embdus without continuing provoking risk factors (e.g. thrombophilia) for > 12 marths (no proven added barrefit).
- NSMD and whamin K autagonist, cirect thrombin inhibitor or factor Xa inhibitors in combination (itsk of major gastrointestinal bleeding).
NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease).

Section D: Central Nervous System and Psychotropic Drugs

- TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
- Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).
- Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
- Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).
- Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).
- Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms).
- Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),
- Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
- Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
- Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
- Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).
- 12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).

13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)

14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)

- Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).
- 2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2 (risk of bleeding).
- Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2 (risk of bleeding).
- NSAID's if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function).
- Colchicine if eGFR < 10 ml/min/1.73m2 (risk of colchicine toxicity).
- Metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis).

Section F: Gastrointestinal System

- Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).
- PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).
- Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where nonconstipating alternatives are available (risk of exacerbation of constipation).
- Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).

Section G: Respiratory System

- Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).
- Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).
- Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).

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- Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).
- Benzodiazepines with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

- Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).
- NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).
- Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).
- Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis (risk of systemic corticosteroid side-effects).
- Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).
- Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthineoxidase inhibitors are first choice prophylactic drugs in gout).
- COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).
- NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).
- Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).

Section I: Urogenital System

- Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).
- Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

Section J. Endocrine System

- Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
- Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure).
- Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
- Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).
- Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
- Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

Section K: Drugs that predictably increase the risk of falls in older people

- 1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
- 2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
- Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls).
- Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Section L: Analgesic Drugs

- Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).
- Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
- Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain).

Section N: Antimuscarinic/Anticholinergic Drug Burden

Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).

Appendix: 4: Screening Tool to Alert to Right Treatment (START), version 2.

Unless an elderly patient's clinical status is end-of-life and therefore requiring a more palliative focus of pharmacotherapy, the following drug therapies should be considered where omitted for no valid clinical reason(s). It is assumed that the prescriber observes all the specific contraindications to these drug therapies prior to recommending them to older patients.

Section A: Cardiovascular System

- Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
- Aspirin (75 mg 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
- Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
- Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.
- Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.
- Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.
- 7. Beta-blocker with ischaemic heart disease.
- Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.

Section B: Respiratory System

- Regular inhaled β2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.
- Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
- Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%).

Section C: Central Nervous System& Eyes

- L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.
- 2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.
- Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mildmoderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
- 4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.
- Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
- Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.

Section D: Gastrointestinal System

- Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.
- Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.

Section E: Musculoskeletal System

- 1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.
- Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.
- Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).
- Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).
- Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).
- Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.
- 7. Folic acid supplement in patients taking methotexate.

Section F: Endocrine System

 ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.

Section G: Urogenital System

- Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
- 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.
- 3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.

Section H: Analgesics

- High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency
 opioids are not appropriate to the pain severity or have been ineffective.
- 2. Laxatives in patients receiving opioids regularly.

Section I: Vaccines

- 1. Seasonal trivalent influenza vaccine annually
- 2. Pneumococcal vaccine at least once after age 65 according to national guidelines

2. Ethical approval

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