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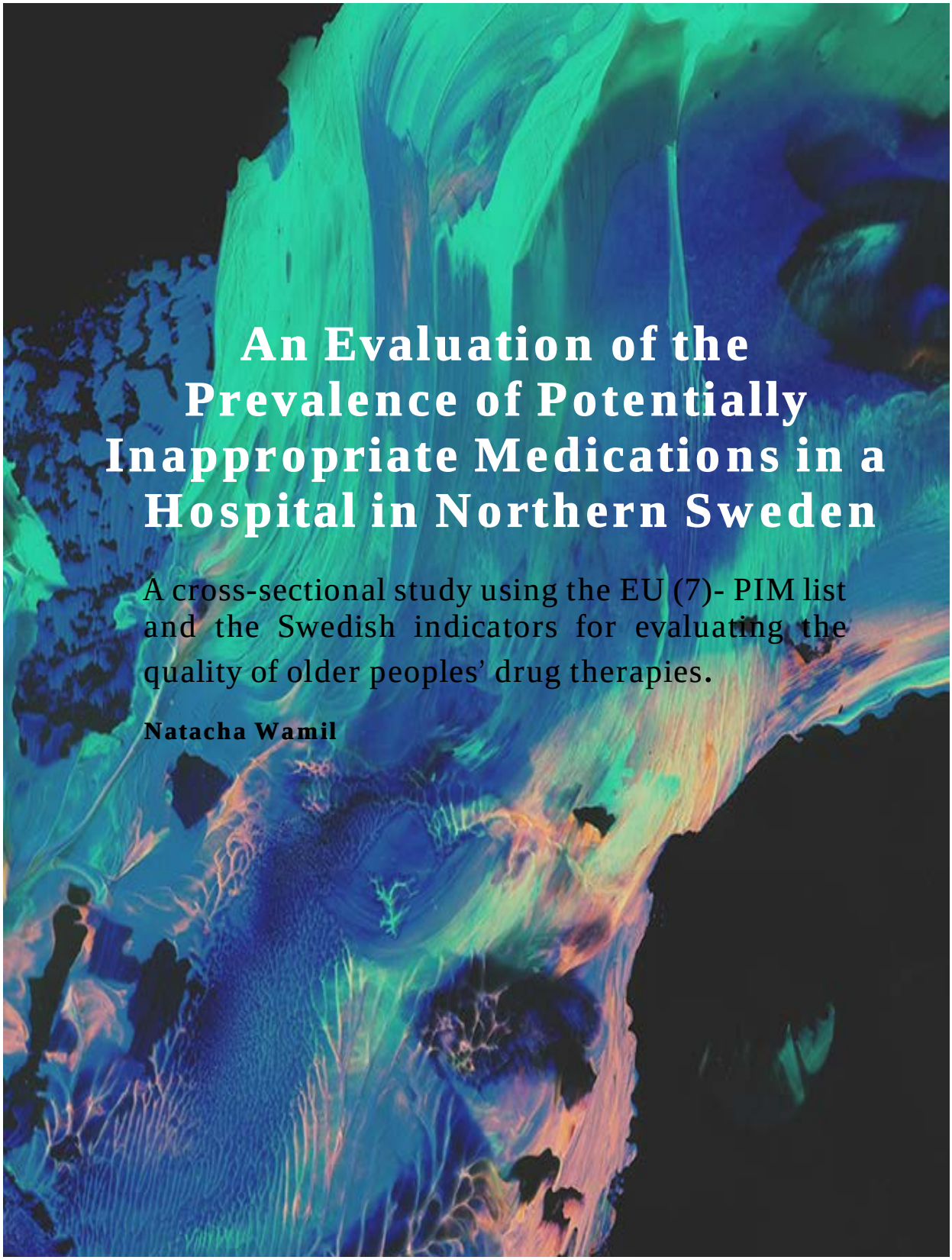

An Evaluation of the Prevalence of Potentially Inappropriate Medications in a Hospital in Northern Sweden

A cross-sectional study using the EU (7)- PIM list and the Swedish indicators for evaluating the quality of older peoples' drug therapies.

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Abstract

Introduction: As people get older their sensitivity to drugs increases due to pharmacodynamic and pharmacokinetic changes. Multiple morbidity in the elderly contributes to the need of increased use of medication and the use of potentially inappropriate medication (PIMs) among older people is a worldwide problem. Many studies show a high prevalence of PIMs prescribed to the elderly. To be able to describe drug use in terms of quality, and to be able to assess the elderly patients' medication, tools to evaluate the appropriateness of prescriptions are required. The explicit European Union (EU) (7)- PIM list was established to identify PIM and compare prescribing patterns of PIMs for elderly, who live in European countries. Sweden has its own guidelines, known as the Swedish indicators for evaluating the quality of older peoples' drug therapies.

Aims: The aim of this study was to investigate the prevalence of PIMs among elderly admitted to a medical ward using the EU (7)- PIM list and the Swedish quality indicators. Secondary objectives were to investigate factors associated with the use of PIM and to compare the identification tools.

Method: Medical records for patients admitted to Lycksele hospital in Northern Sweden were reviewed by clinical pharmacists during September – November 2015 and February – April 2016. Patients aged ≥ 65 were selected for the present analysis. PIMs were identified using the Swedish quality indicators and the EU (7)- PIM list as identification tools.

Result: A total of 93 patients participated, with a mean age of 79.5 ± 8.2 and 51 of them were women. Mean number of medications at admission was 8.2 ±3.6. Of 93 patients, 16% had one or two PIMs according to the Swedish quality indicators. No significant associations between PIMs and different factors were found. The most commonly PIM class according to this identification tool was analgesics (4.3%) and tramadol was the most commonly prescribed PIM (3.2%). According to the EU (7)- PIM list, 45% of the study population was prescribed one or more PIMs. No significant associations between PIMs and different factors were found. The most commonly PIM class found in the present study according to the EU (7)- PIM list was hypnotic and sedative (11.8%) and the highest prescribed PIM was apixaban (9.7%)

Discussion: The prevalence of PIM according to the Swedish quality indicator was relatively low compared to previous studies. The prevalence of PIM according to the EU (7)-PIM list was somewhat higher, and the result is in line with previous studies. The most common PIM class and the highest prescribed PIM in the present study have some similarity with the previous studies using the same identification tools. The prevalence of PIMs according to the two used identification tools in the present study differs a lot. The EU (7)-PIM list is deemed to be a sensitive identification tool, which may explain the higher prevalence of PIMs found in the present study. The present study is the first study that investigates the association between a certain disease and the risk to have a PIM. No significant associations between PIM and different factors were found when the Swedish indicators or the EU (7)- PIM list were used as identification tools. Associated factors with PIM varies from study to study in previous research and may depend on the location that the study was performed in and the study sample used, even though the same identification tool was used.

Conclusion: The prevalence of PIMs was relatively low in the study sample according to the Swedish guidelines (16%), but high according to the PIM EU (7) list (45%). No significant associations between PIM and different factors were found when using the Swedish indicator or the EU (7)- PIM as identification tools. Since there were different tools used the results were inconclusive. However, it is still important to continuously evaluate the need of PIMs in elderly patients in order to decrease the risk of adverse drug reactions.

Key words: potentially inappropriate medication, elderly, EU (7)- PIM list, the Swedish quality indicators.

List of the abbreviations and acronyms

CI	Confidence interval
CNS	Central nervous system
EU (7) PIM list	European Union (7) potentially inappropriate medication
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odd ratio
PIM	Potentially inappropriate medication
SPSS	Statistical Package for the Social Sciences.
The Swedish quality indicators	The Swedish indicators for evaluating the quality of older people's drug therapies
STOPP/START	STOPP (screening tool of older persons' prescriptions) and START (screening tool to alert doctors to right treatment)

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Introduction

Ageing is characterised by a loss of functional capacities of most organs and processes that provide functional incorporation between cell and organ (1). The term “older people” or “elderly” describes people aged 65 years or older, due to that usually, individuals must be 65 years old to be eligible to live in a nursing home in Sweden (2). In 2016, the population in Sweden was 9,995,153, of whom 1,976,857 (19.8%) were 65 years or older, of whom 55,298 (0.5 %) lived in the county of Västerbotten (3). Multiple morbidity in the elderly contributes to the need of increased use of medication and the number of drugs prescribed per elderly person is two- three time higher compared to younger people per year (4). Today people living in nursing homes are prescribed an average of 8-10 different medications due to multiple morbidity, and this makes the treatment of these people more complicated (2). Symptoms may be signs of both new and impaired diseases, but also it may be a result of ageing or signs of adverse drug reactions. However, with polypharmacy, the effects of drug treatments are more difficult to predict and evaluate. Adverse drug reactions can also be misinterpreted as symptoms that may lead to further treatment, known as cascading prescription (5).

The use of potentially inappropriate medication (PIM) among elderly is a worldwide problem and many studies show a high prevalence of PIMs using different tools (6; 7; 8). PIMs have been associated with increased risk of adverse drug reactions and for example one study demonstrated an elevated risk of unplanned hospitalisation with increasing number of different PIM using Beers criteria as a tool (9; 10). To be able to describe drug use in terms of quality, and to be able to assess and correct the elderly patients’ medication, tools to evaluate the appropriateness of prescriptions is required. Many criteria have been developed to measure the quality of drugs used in the elderly (5). Criteria can be classified as implicit or explicit criteria. Implicit criteria (or patient specific criteria) rely on expert professional judgement and focus on the patients, addressing the entire medication regime. Explicit criteria on the other hand can be applied with little or no clinical judgement and the criteria is not person-specific (5). However, previously only evaluation tools following country-specific guidelines have been available in order to identify PIM use (11), for example, Beers criteria, the first criteria that was developed in the USA which is the most commonly used instrument for the evaluation of potentially inappropriate medications among the elderly (12). However, the use of medication differs significantly between USA and Europe and from country to country. The explicit European Union (EU) (7)- PIM list was established to identify PIM and to compare prescribing patterns of PIMs for elderly, who live in European countries (13). Sweden also has its own guidelines, the Swedish indicators for evaluating the quality of older peoples’ drug therapies (5).

Pharmacokinetic changes in elderly

Pharmacokinetic is a study of how the organism affects the drugs and as people get older, the pharmacokinetics of drugs is affected. Pharmacokinetic changes affect the drugs’ concentration in the blood and therefore consequently the effect of the drugs (14). Pharmacokinetics can be divided into different phases; absorption, distribution, metabolism, and elimination, in which the most important is the decrease in elimination rate due to decline of renal function in the elderly. The ageing of the kidney begins already at the age of 40, and at the age of 80 the renal function can be decreased by 50% (14). As the elimination rate decreases the risk of drug accumulation increases. This is especially important for water-soluble drugs with a narrow therapeutic index such as digoxin and lithium, and drugs with

active metabolism such as morphine and glibenclamide in which dose reduction might be necessary (2).

Even though there is a delay in gastric emptying and reduction in gastric acid, this does not significantly affect the absorption of most drugs (15). Other physiological changes that can affect pharmacokinetics are; reduction of lean body mass, reduction of total body water, and increase of total body fat that might lead to increased distribution of lipid-soluble drugs which result in longer half-life of these drugs (16). An important group of fat-soluble drugs are psychotropic drugs such as flunitrazepam and diazepam. Hepatic extraction is dependent on hepatic blood flow, enzymatic capacity and liver size that all decrease with ageing. Drugs that are metabolised by the liver, for example theophylline, nitrates, barbiturates, and propranolol may have reduced hepatic metabolism in elderly people (2; 14). Hepatic clearance of some drugs can be reduced in elderly by up to 30% and cytochrome P450 in phase I metabolism is more likely to be impaired than phase II, which is relatively preserved in elderly (17).

Pharmacodynamic changes in elderly

Besides the altered pharmacokinetics in the elderly, another important mechanism is the changes in pharmacodynamics that occur due to ageing (18). Pharmacodynamic studies how drugs affect the organism. Age-related pharmacodynamic changes may be divided in two categories; those due to a reduction in homeostatic reserve and those that are secondary to changes in specific receptor and target sites (15). Homeostatic regulation mechanisms decline, which mean that the sensitivity of cardiovascular system to beta-adrenergic agonists and antagonists decreases and the incidence of orthostatic episodes in response to drugs that lower blood pressure is increased (19). The central nervous system (CNS) is particularly sensitive in the elderly, especially when it comes to drugs that are acting on the central nervous system, such as antipsychotics, antidepressant, benzodiazepines, and lithium resulting in a higher potential for adverse drug reactions (20). Age-related reduction in activity of choline acetyltransferase in some areas of the cortex and limbic system, and the reduction in dopamine (D2) receptors predisposes individuals for increased risk of adverse drug reactions when exposed to anticholinergic and antidopaminergic drugs (2; 15).

Clinical Pharmacy

Clinical pharmacy can be defined as “a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices” (21). The clinical pharmacists work directly with physicians, other health professionals and patients to ensure that patients’ medical treatment is optimised (22). In 1980, clinical pharmacy grew in UK due to promoting cost-effective use of medicines in hospitals, resulting in governmental endorsement of clinical pharmacy implementation in 1988 (15). However, in Sweden, clinical pharmacy services are not routinely implemented in the hospital and community settings as in the UK, nonetheless the number of clinical pharmacists working as part of health care teams has increased during the recent years. Clinical pharmacy services in Västerbotten County Council started in 2002 as a collaboration project between the hospital pharmacy and the County Council in Västerbotten. Today there are six clinical pharmacists working in outpatient and inpatient care in Västerbotten.

Potentially inappropriate medication – evaluation tools

PIM has many definitions; one is "those drugs which should not be prescribed for this population because the risk of adverse events outweighs the clinical benefit, particularly when there is evidence in favour of a safer effective alternative therapy for the same condition" (13). Many evaluation tools have been developed in order to identify PIM and the most commonly used are Beers criteria. These criteria are widely used in geriatric care, education, research and in development of quality indicators (12). Another well-known criterion is STOPP (screening tool of older persons' prescriptions) and START (screening tool to alert doctors to right treatment) which were developed by a European panel of experts. The STOPP/START criteria require the patients' clinical information to make a correct evaluation of the PIM use (23).

The EU (7) potentially inappropriate medications list

In May 2015, an explicit European PIM list (EU (7)- PIM list) was established to identify and compare prescribing patterns of PIMs across European countries. This list was developed based on the German PRISCUS list of potentially inappropriate medications and another PIM list from France, Canada, and USA. The EU (7) PIM list is deemed to be a sensitive tool that can be used even if the clinical information available is minimal and is therefore suitable for pharmacoepidemiologic investigations using administrative databases without any clinical information about the individuals (13).

The Swedish indicators for evaluating the quality of older people's drug therapies.

The Swedish indicators for evaluating the quality of older peoples' drug therapies were published for the first time in 2004. The aim of the indicators was to support and improve the quality of older peoples' drug therapies. The working group compiled data from previously published international explicit criteria and the Swedish recommendations from the National Board of Health and Welfare, Medical Product Agency and Swedish Agency for Health Technology Assessment and Assessment of Social Services. The indicators are divided into two categories; drug specific and diagnosis specific indicators. In 2008 the National Board of Health and Welfare decided to revise the indicators. The revised version includes three new drugs specific indicators; drug and its function, drugs and certain symptoms, and psychotropics. The newest version used in the present study was published in 2017 and contains many changes compared to the previous version. Many of the drug-specific indicators have been extended, while some have been removed (5).

Potentially inappropriate medications in elderly

Potentially inappropriate medication in elderly include, for example, drugs from the following drug groups:

Antipsychotic drugs

Antipsychotic drugs can be divided into two different groups; first generation or typical antipsychotic drugs (e.g. chlorpromazine, haloperidol, flupentixol), and second generation or atypical antipsychotic drugs (e.g. clozapine, risperidone, quetiapine, aripiprazole). Antipsychotic drugs are D_2 dopamine receptors antagonist, but most of them also block a variety of other receptors resulting in unwanted effects such as the activity at muscarinic, H1 and α receptors, giving different side effect profiles among antipsychotics (table 1) (24).

According to the Swedish National Board of Health and Welfare the antipsychotic drug used should only be limited to patients with psychotic conditions or extreme aggressiveness (5).

Table 1. Characteristics of antipsychotics drugs **(2; 24)**

Drug	Receptor affinity						Main side effects		
	D_1	D_2	α_1	H_1	mACh	5-HT_{2A}	EPS	Sed	HT
Chlorpromazine	+	+++	+++	++	+	++	+++	++++	+++ +
Haloperidol	+	+++	++	-	-	+	++++ +	+	+
Flupentixol	++	+++		+++	-	+	++	+	+
Clozapine	+	+	++	++	++	++	+	++++	+++ +
Olanzapine		++	++	++	+++	+++	+	+++	++
Risperidone	+	++	++	++	-	+++	+	+++	+++
Quetiapine	-	+	++	+	+	+	-	++	++
Aripiprazole	-	+++	+	+	-	++	+	++	++

D1, D2, dopamine types 1 and 2 respectively; α1, α_1- adrenoreceptor; H1, histamine type1; mACh, muscarinic acetylcholine receptor; 5-HT2A, 5- hydroxytryptamine type 2A; EPS, extrapyramidal side effects; Sed, sedation; HT, hypotension
+++++, very high effect; ++++ high effect
+++, high affinity; moderate effect
++, moderate affinity; low effect
+, minimal affinity; very low effect
-, none affinity

Anticholinergic drugs

Anticholinergic drugs are a group of drugs that affect the function of many organs by preventing acetylcholine from binding to its receptors. When it comes to anticholinergic drugs, muscarine receptors are involved (so called muscarinic receptor antagonists) both centrally and peripherally (25; 26). Anticholinergic drugs are used in elderly for the treatment of disorders such as Parkinson's disease and overactive bladder (27). However, many drug classes have anticholinergic effects even though the effect is not important for their therapeutic effect, such as antihistamines, antipsychotic drugs or antidepressants (28). Typical side effects of the anticholinergic drugs include dry eyes, vision changes, dry mouth, urinary retention, constipation, sedation, and confusion (25). Further, side effects such as sedation and confusion might lead to fall risk, therefore the Swedish quality indicators and the Beer's criteria classified anticholinergic drugs as inappropriate drugs that should be avoided for elderly patients (5; 12)

Anxiolytic, hypnotic, and sedative drugs

The difference between hypnotic and sedative drugs is usually the dose (29; 30). Drugs in this class include benzodiazepines, barbiturates, alcohol, and benzodiazepine-like drugs such as zolpidem and zopiclone. Most anxiolytic and hypnotic drugs increase the effects of GABA through GABA transmission, facilitating the opening of GABA-facilitated chlorine channels. The term benzodiazepine refers to a distinct structure, which is composed of a benzene ring fused to a seven-membered diazepine rings (24). Drugs such as zopiclone and zolpidem have a different chemical structure and are therefore not classified as benzodiazepines, yet they have the same site of action and therefore they are discussed along with the benzodiazepines. Benzodiazepines are classified as short to intermediate-acting and long-

acting based on their elimination half-life (table 2). Long-acting benzodiazepines metabolise via the lever to active metabolites and cause accumulation and prolonged clinical effects among the elderly. Adverse effects associated with benzodiazepines are increased confusion, agitation, sedation, and impaired cognition (15). Benzodiazepines have been associated with the risk of falling and increased risk of fractures. The mechanism behind the increasing risk is probably psychomotor effect such as problem with coordination, muscle relaxation and sedation induced by the drugs (31).

Table 2. Characteristics of benzodiazepines in humans *(24; 32; 33)*

Drug(s)	Half- life of parent compound (h)	Active metabolite	Half- life of metabolite (h)	Overall duration of action
Short to intermediated half- life				
Oxazepam, Lormetazepam	8-12 h	no	-	~ 12-18 h
Alprazolam	6-12h	Hydroxylated derivative	6 h	
Long half- life				
Flunitrazepam	No data	desmetylflunitrazepam and 7-aminoflu-nitrazepam	No data	16-35 h
Nitrazepam	16-40h	No	-	24 h
Diazepam	20-40h	nordazepam	60 h	24-48 h
Z – hypnotics				
Zolpidem	2 h	No	-	~4 h
Zopiclone	3,5-6,5 h	No	-	

NSAID

Nonsteroidal anti-inflammatory drugs (NSAID) is a group of drugs that have analgesic and anti-inflammatory effects. The drugs inhibit the enzyme cyclooxygenase, which in turn inhibit the production of prostaglandins and thromboxanes. The decrease of prostaglandins causes reduced vasodilation and less sensitization of nociceptive nerve ending to inflammatory mediators such as bradykinin and 5- hydroxytryptamine. However, the decrease in prostaglandins leads also to gastrointestinal disturbances, adverse renal effects, and cardiovascular side effects. Evidence shows high frequency of adverse drug reactions when NSAID is used in elderly patients (34; 35; 36) and these drugs should therefore be prescribed cautiously to the elderly (5).

Objective

The overall aim of this study was to investigate the prevalence of PIMs among elderly patients admitted to a medical ward using the EU (7)- PIM list and the Swedish quality indicators. Secondary objectives were to investigate factors associated with the use of PIM and to compare the identification tools.

Specific aims of this study are to answer the following questions:

- What is the prevalence of PIMs at admission to the medical ward according to the EU (7)- PIM list and the Swedish quality indicators?
- Which drugs were most commonly prescribed according to the two used tools?
- Which factors were associated with the increased risk of having PIM(s) according to the EU (7) PIM list and the Swedish quality indicators?

- Are there any differences between the two used identification tools when comparing the prevalence of PIM, risk factors associated with the increases risk of having PIM and most commonly prescribed drugs?

Method

Population

This is a cross-sectional study and a part of another study that investigated the impact of medication reviews performed by clinical pharmacists at a medical ward at a hospital in Lycksele, a small, sparsely populated area of Northern Sweden, with no previous experience of clinical pharmacy (37). Data was collected between September – November 2015 and February – April 2016. Patients 18 years or older and admitted to the medical ward at the same time the clinical pharmacists were working at the ward were invited to participate in the study. Exclusion criteria included patients with dementia, palliative patients, patients who did not speak Swedish and patients with impaired cognitive function due to alcohol or drug intake (37). In this specific study, patients younger than 65 years were excluded due to the definition of older people.

Definitions and data extraction

Data from the previous study regarding background data was used (37). In that study, the patients' data was collected from the medical records when the patients were admitted to the hospital. Data regarding the patients' background such as age, diagnosis, gender, drug history, if they had multidose drug dispensing, if they were living at home or in nursing home was collected. The collected data was listed in the Microsoft Excel program with the identification number of the respective patients for analysis. In the present study the medication and doses that the patients used at admission to the hospital ward were collected from the patients' medical records. *Pro re nata* drug administration were not included in the analysis due to lack of information about the patients' use. Drugs with local administration such as creams and ointments were also excluded from the analysis. In the present study, the drug list for each patient was assessed to identify PIMs, using the Swedish indicators for evaluating the quality of older peoples' drug therapies and the EU (7)- PIM list as described below.

The Swedish indicators for evaluating the quality of older peoples' drug therapies (2017)

The Swedish indicators for evaluating the quality of older peoples' drug therapies item number 1,1 involved the drug with considerable risk for adverse events in older people. Those preparations should be avoided unless there is a special reason (5). Item number 1.1 includes long-acting benzodiazepines (nitrazepam, flunitrazepam and diazepam), drugs with significant anticholinergic effects, tramadol, propiomazine, codeine, glibenclamide and doxazosin.

This study also included NSAIDs (M01A excl. M01AX05, M01B) and antipsychotic drugs (N05A excl. N05AN) as PIMs (see appendix A). These drugs are according to the indicators classified as preparations for which correct and current indication is of particular importance. Due to the risk of adverse drug reactions among old people, these drugs are classified in this study in the same way as the others, i.e. these drugs should be avoided unless there is a special reason.

The EU (7) - PIM list

The complete EU (7)- PIM list comprises 282 drugs substances classified as PIMs. Drugs that were defined as treatment duration-dependent PIMs according to the EU (7) – PIM list (PPI (pantoprazole, lansoprazole, omeprazole, esomeprazole, rabeprazole), loperamide, nitrofurantoin, naproxen, ibuprofen, naproxen, codeine, and risperidone) and regimen- dependent PIMs according to the same list (insulin, sliding scale) were excluded due to lack of information in medical records. Drugs not approved for the Swedish market were also excluded. In this study total 127 substances were selected for the analysis (see appendix B).

Data analysis

The drug lists (both the EU (7)-PIM list and the Swedish quality indicators) were listed in the Microsoft Excel program. Each patient's drug list was assessed to identify PIMs according to these lists, and this was recorded for each patient. The number of PIMs for each patient was recorded, and this was further dichotomised to having or not having a PIM, making it possible to investigate associations with patients having a PIM and different factors (in the regression model described below).

Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) Statistics 23 software program. Prevalence was presented for dichotomous variables such as gender, if the patients had PIM or not, if the patients have the certain diagnoses or not. These certain diagnoses were; arrhythmias, cancer, chronic respiratory disease, depression, diabetes mellitus, hypertension, heart failure, ischaemic heart disease and stroke or TIA. The continuous variables such as age and number of medications at admission were presented as mean values with standard deviation (SD) (38; 39).

A logistic regression analysis was conducted to investigate the association between patients with PIM(s) and risk factors. The risk factors investigated were age, gender, number of medications at admission and certain diagnoses. The dependent variable was having a PIM/not having a PIM as a dichotomous variable. This variable was coded in SPSS as 1 if the patients had PIM(s) and 0 if patients had no PIM. The independent variables were the risk factors as described above. First, a simple regression was conducted; this is an analysis conducted separately for the dependent variable and for each of the independent variables. All significant associations (i.e. results with confidence intervals (CI:s) not including the number 1) were analysed in a multiple model, including age and gender. Results were presented as odd ratios (ORs) with 95% confidence intervals. An OR higher than 1 means that there is an increased risk for having a PIM if the specific variable is higher (for example increased age) or if a specific variable exists (for example being female). Corresponding, an OR lower than 1 means a lower risk. An odd is the probability that something will happen, divided by the probability that it will not occur. The program used (SPSS statistics 23) in the present study presented the odds as B-coefficient. The B-coefficient is the value for logistic regression equation for predicting the dependent variable from the independent variable and presents in log- odds units. The odds ratio in the present study showed as Exp (B) and present as the exponentiation of the coefficients (e^B). A p-value of <0.05 was considered statistically significant. A confidence interval is an estimate of uncertainty associated with estimates of population parameters that have been developed using a set of sample data. Sample size, and the variability in the sample are reasons that may affect the width.

Ethic approval

The study was approved by Regional Ethical review board in Umeå, Sweden with registration number: 2014/322-31Ö. All patients had been informed about the study and gave their informed consent.

Results

Between September – November 2015 and February – April 2016, 103 patients were included in the main study. In this specific study, 10 patients <65 years were excluded, leaving 93 patients' data to be analysed (table 3). Of 93 patients 71% were 75 years old or older. The average number of medications at admission was 8.2. A total 810 prescriptions were found among the study sample, of theses the most prescribed drugs were the cardiac therapy (36%), vitamin supplements (10%) and anticoagulant (9.6%). The most commonly disease found in the study sample was hypertension with almost the half of the study sample had this diagnosis follow by the arrhythmias and heart failure.

Table 3. Patients characteristics

Characteristics	Total (N=93)
Age, mean ± SD, years	79.5 ± 8.2
Women, no (%)	51 (54.8%)
Number of medications at admission	8.2±3.6
Anamnesis	
Arrhythmias	26 (28.0%)
Cancer, n (%)	21 (22.6%)
Chronic respiratory disease, n (%)	15 (16.1%)
Depression, n (%)	1 (1.1%)
Diabetes Mellitus, n (%)	17 (18.3%)
Hypertension, n (%)	46 (49.5%)
Heart failure, n (%)	22 (23.7%)
Ischaemic heart disease, n (%)	16 (17.2%)
Stroke/ TIA, (%)	10 (10.8%)

The Swedish quality indicators

According to the Swedish quality indicators, 15 people in the study sample (16.1%) had one or two PIMs; 14 (15.1%) had one PIM; 1 (1.1%) had two PIMs. A significant association (in the simple regression analysis) was observed between having a higher number of medications prescribed at admission and having one or more PIMs [OR=1.19, CI=1.01-1.40]. Since the CI does not include number 1, the association was significant. When the multiple analysis was applied (including significant factors from the simple analysis, gender and age), all CI:s included number 1, i.e. no significant associations were seen (number of medications at admission [OR=1.18, CI= 1.00-1.38,], age [OR=0.98, CI=0.92-1.05], gender [OR=1.45, CI=0.43-4.87]) (table 4). A large width of CIs was seen in many cases in the analyses regarding for example hypertension, diabetes mellitus, and chronic respiratory disease. The small sample size, and the variability in the sample are probably reasons for the large width.

Table 4 Characteristic of study population and comparison between patients with and without PIMs using the Swedish indicators for evaluating the quality of older peoples' drug therapies

Characteristic of study sample	PIM (s)	No PIM	Simple analysis (95% CI)	Multiple analysis (95% CI)
Cases, n	15	78		
Gender, n (%)				
Female	10	41	1.8 (0.57-5.77)	1.45 (0.43-4.87)
Age (years), Mean ± SD	78.6±8.72	79.64±8.17	0.98 (0.92-1.05)	0.98 (0.92-1.05)
Number of medications at admission, mean ± SD	10±2.53	7.50±3.65	1.19 (1.01-1.4)	1.18 (1.00-1.38)
Anamnesis				
Arrhythmias, n (%)	2 (2.2)	24 (25.8)	0.35 (0.07-1.66)	
Cancer, n (%)	3 (3.2)	18 (19.4)	0.83 (0.21-3.28)	
Chronic respiratory disease, n (%)	4 (4.3)	11 (11.8)	2.22 (0.60-8.21)	
Depression	0	1 (1.1)	0	
Diabetes Mellitus, n (%)	4 (4.3)	13 (14.)	1.82 (0.50-6.61)	
Hypertension, n (%)	11 (11.8)	35 (37.6)	3.38 (0.99-11.54)	
Heart failure, n (%)	4 (4.3)	18 (19.4)	1.21 (0.34-4.27)	
Ischaemic heart disease, n (%)	0	16 (17.2)	0	
Stroke/ TIA, (%)	1 (1.1)	9 (9.7)	0.548 (0.06-4.68)	

Total 16 drugs defined as PIM according to the Swedish quality indicators were found. The three most commonly represented PIM classes among the identified prescriptions were analgesics- opioids, anxiolytic and other urological, including antispasmodics together with anti- inflammatory and antirheumatics. The most commonly involved PIMs were, tramadol, hydroxyzine and diclofenac (table 5).

Table 5 Prescribing frequency for each identified PIM according to the Swedish quality indicators.

ATC code	Drug class/name	Patients, n (col%) 93
A 10	Blood glucose lowering drugs	1 (1.08)
	Glibenclamide (A10BB01)	1 (1.08%)
C02	Antihypertensive	1 (1.08%)
	Doxazosin (C02CA04)	1 (1.08%)
G04	Other urological, incl. antispasmodics	2 (2.15%)
	Tolterodine (G04BD07)	1 (1.08%)
	Solifenacin (G04BD08)	1 (1.08%)
M01	Anti- inflammatory and antirheumatic products- NSAID (oral)	2 (2.15%)
	Diclofenac (M01AB05)	2 (2.15%)
N02	Analgesics- opioids	4 (4.30%)
	Codeine (N02AJ06)	1 (1.08%)
	Tramadol (N02AX02)	3 (3.23%)
N05A	Antipsychotics	1 (1.08%)
	Flupentixol (N05AF01)	1 (1.08%)
N05B	Anxiolytic	3 (3.23%)
	Hydroxyzine (N05BB01)	2 (2.15%)
	Diazepam (N05BA01)	1 (1.08%)

TABLE 5 (continued)

ATC code	Drug class/name	Patients, n (col %) 103
N05C	Hypnotics and sedatives	1 (1.08%)
	Propiomazine (N05CM06)	1 (1.08%)
N06A	Antidepressants	1 (1.08%)
	Amitriptyline	1 (1.08%)

The EU (7) – PIM list

According to the EU (7) PIMs list the occurrence of PIMs was higher. Of 93 study samples 42 (45.2%) had one or more PIMs; 26(28.0%) had one PIM; 13 (14.0%) had two PIMs; 2 (3.2%) had three PIMs and 1 (1.1%) had four PIMs. No significant associations between age, gender, various diseases, number of medications at admission or having one or two PIMs were found in the simple analysis since all CI:s include number 1 (table 6). Because there were no significant associations in the simple analysis, no multiple analysis was performed.

Table 6 Characteristic of study population with and without PIMs using EU (7) PIMs List as an identified tool.

Characteristic of study sample	PIM (s)	No PIM	Simple analysis (95% CI)	Multiple analysis (95% CI)
Cases, n	42	51		
Gender, n (%)				
Female, n (%)	21 (22.60)	30 (32.30)	0.7 (0.31- 1.60)	
Age (years), Mean ± SD	79.93±8.00	79.10±8.46	1.01 (0.96- 1.06)	
Number of medication at admission, mean ± SD	8.05±3.15	8.28±3.88	0.98 (0.88- 1.10)	
Anamnesis				
Arrhythmias, n (%)	13 (14.00)	13 (14.00)	1.31 (0.53- 3.25)	
Cancer, n (%)	9 (9.70)	12 (12.90)	0.87 (0.33- 2.36)	
Chronic respiratory disease, n (%)	8 (8.60)	7 (7.50)	1.48 (0.49- 4.48)	
Depression	0	1 (1.10)	0	
Diabetes Mellitus, n (%)	6 (6.50)	11 (11.80)	0.61 (0.20- 1.81)	
Hypertension, n (%)	22 (23.70)	24 (25.80)	1.24 (0.55- 2.80)	
Heart failure, n (%)	9 (9.70)	13 (14.00)	0.80 (0.30- 2.10)	
Ischaemic heart disease, n (%)	4 (4.30)	12 (12.90)	0.34 (0.10- 1.16)	
Stroke/ TIA, (%)	3 (3.20)	7 (7.50)	0.48 (0.12- 2.00)	

Total 68 drugs defined as PIM according to the EU (7)- PIM list was found. The three most commonly represented PIM classes among the identified prescriptions were hypnotic and sedatives, antithrombotic and cardiac therapy. The most commonly involved PIMs were apixaban, zopiclone and digoxin (table 7).

Table 7 Prescribing frequency for each identified PIM according to the EU (7)- PIM list.

ATC code	Drug class/name	Patients, n (col %) 93
A03F	Drugs for functional gastrointestinal disorder- propulsive	1 (1.08%)
	Metoclopramide (A03FA01)	1 (1.08%)
	Sodium picosulfate (A06AB08)	5 (5.38%)

TABLE 7 (continued)

ATC code	Drug class/name	Patients, n (col %) 103
N06A	Antidepressants	2 (2.15%)
A06A	Laxatives	5 (5.38%)
A 10	Blood glucose lowering drugs	2 (2.15%)
	Glibenclamide (A10BB01)	1 (1.08%)
	Glipizide (A10BB07)	1 (1.08%)
B01A	Antithrombotic agents	10 (10.75%)
	Rivaroxaban (B01AF01)	1 (1.08%)
	Apixaban (B01AF02)	9 (9.68%)
C01	Cardiac therapy	9 (9.68%)
	Digoxin (C01AA05)	6 (6.45%)
	Amiodarone (C01BD01)	3 (3.23%)
C02	Antihypertensive therapy	1 (1.08%)
	Doxazosin (C02CA04)	1 (1.08%)
C03D	Diuretics- potassium- sparing agents	5 (5.38%)
	Spironolactone (>25mg/d)	5 (5.38%)
C08	Calcium channel blockers	1 (1.08%)
	Cardizem (C08DB01)	1 (1.08%)
G03C	Oestrogens (oral)	1 (1.08%)
	Estradiol (G03CA03)	1 (1.08%)
G04	Other urological, incl. antispasmodics drugs	2 (2.15%)
	Tolterodine (G04BD07)	1 (1.08%)
	Solifenacin (G04BD08)	1 (1.08%)
M01	Anti- inflammatory and antirheumatic drugs- NSAID (oral)	2 (2.15%)
	Diclofenac (M01AB05)	2 (2.15%)
N02	Analgesics- opioids	3 (3.23%)
	Tramadol (N02AX02)	3 (3.23%)
N03A	Antiepileptics	1 (1.08%)
	Carbamazepine (N03AF01)	1 (1.08%)
N04	Antiparkinsonian drugs	2 (2.15%)
	Pramipexole (N04BC05)	2 (2.15%)
N05A	Antipsychotics	1 (1.08%)
	Flupentixol (N05AF01)	1 (1.08%)
N05B	Anxiolytic drugs	3 (3.23%)
	Hydroxyzine (N05BB01)	2 (2.15%)
	Diazepam (N05BA01)	1 (1.08%)
N05C	Hypnotics and sedatives	11 (11.83%)
	Zopiclone (N05CF01) >3,75 mg/d	8 (8.60%)
	Zolpidem (N05CF02) >5 mg/d	1 (1.08%)
	Clomethiazole (N05CM02)	1 (1.08%)
	Propiomazine (N05CM06)	1 (1.08%)
	Amitriptyline	1 (1.08%)
	Venlafaxine (N06AX16)	1 (1.08%)

Discussion

Method discussion

The present study used the EU (7) PIM list and Swedish quality indicators as identification tools due to the minimal requirement of patients' information and the non-obligatory inclusion of clinical information about the individual. The EU (7) – PIM list is a European guideline and enables this study's result to be compared with studies performed in different European countries. However, the STOPP/START criteria were also developed by a European panel of experts, but the application of the STOPP/START criteria required clinical information, which makes these criteria more suitable in a clinical situation for a complete drug review of individual patients (23). Since the study took place in Sweden, the Swedish quality indicators were selected to be used as identification tool (5). It is important to bear in mind that the present study used explicit criterion as identification tools, which could be applied with little or no clinical judgement but did not address individual differences between patients. The present study therefore did not consider the patients' diseases and treatment and that sometimes prescribed medication might be necessary even though it is a PIM.

The patients' information used in the regression analysis were age, sex, number of medications at admission and certain diagnoses since many previous studies had analysed if these risk factors were associated with PIM (6; 7; 40; 41). Another risk factor that somehow might be interesting to include is the patients' type of housing, if patients lived in nursing homes or at home. Since there were only four patients that lived in nursing homes, this factor was excluded from the analysis. The information about patients' use of over the counter (OTC) drugs could have been interesting but was not included due to the lack of information. The present study identified PIMs from medicines that the patients had at admission at the hospital ward due to the lack of information about the patients' medication after admission, otherwise the comparison of before and after the admission would have also been interesting to include in this study. The level of education might be an interesting risk factor but since the patients' medical records did not include this type of question this was not possible to include in the analysis.

The SPSS program can be used to analyse data collected from surveys, tests and observations; therefore, the program was deemed to be suitable for analysis of the data in the present study. The program itself can perform a variety of data analyses and presentation function including graphical presentation of data and the statistical data analysis (38). Since the dependent variables in the present study is a Yes or NO question (PIM or not) the logistic analysis was chosen over the linear regression analysis in order to analyse the association between the risk factors and the odd of having PIM (42). The confidence interval had a huge range in many cases when associations between PIM and the risk factors according to the Swedish quality indicators were investigated. The large width of the confident intervals might depend on the low prevalence of patients with PIM, and the huge standard deviation which resulted in the huge standard error which in turn lead to the huge confident intervals (43). The conclusion draws from this small sample with the huge standard error which may give false conclusions and the results therefore need to be interpreted with caution.

Result discussion

The Swedish quality indicators

Of the 93 patients in the study sample, 15 (16.1%) of them had one or more PIMs. Of the 15 persons with PIM, 10 were women, but there was no significant association between gender and having PIM. This is in contrast with the findings of a nationwide, cross-sectional, register based study that took place in Sweden using the criteria from the Swedish quality indicators (2010), where a prevalence of 19% was found and with a significant association between women and having PIM (40). In the simple analysis conducted in the present study, it was found that patients with a higher number of medications at admission were more likely to have PIM in the present study, but this was not found in the multiple analysis. This is also inconsistent with the result of the nationwide study mentioned above (40). Further, no associations between age and having PIMs were found in this study even if the result from the nationwide study showed that age independently correlated with an increased prevalence of PIM even if the same age span used in both studies. These differences in results between the present study and the nationwide study may be due to the size of the study sample, the different tools and different methods used to detect the prevalence of PIM and the gender distribution in the study.

From a total 16 PIMs identified in the present study, three of them were new drugs defined as PIM according to the 2017 version (5; 44) these are codeine, glibenclamide and doxazosin which at the time of data collection were not on the PIM list (44). According to the report from the Swedish National Board of Health and Welfare, the use of codeine in combination with paracetamol, which is a normal combination in clinical practice, increases the risk for over dosage of paracetamol. Glibenclamide is also a new drug defined as PIM according to the Swedish quality indicator due to its long half-life and active metabolite, which results in an increased risk for hyperglycaemia, especially for people with an impaired renal function. Doxazosin on the other hand is associated with high risk for orthostatic hypotension (5). According to another study that summarises and evaluates medication reviews in Västerbotten County Council in 2012, the use of PIM with regards to the use of antipsychotic drugs (20.0% of 895 people), was higher than the prevalence of PIM of all drug classes in this present study that is 16.1% (45). The most commonly PIM class in this study was analgesics, and tramadol was the most commonly prescribed drug (3.2%). However, the 2012 study (45) found a prevalence of 1,9% of tramadol. Tramadol use in elderly increases risk for nausea, fatigue, dizziness and confusion and therefore should be prescribed carefully to this patient group (5). These results indicate that the use of PIMs has decreased despite the fact that the tramadol is still used regardless of the side effects as mentioned above.

Since 2005, older peoples' drug therapies have been improved. The Swedish National Board of Health and Welfare reported that the use of PIMs, NSAID, and antipsychotic had been reduced with 53%, 51% receptive 43% in older people ≥ 75 years old between 2005 and 2017 according the Swedish quality indicators (5). The low prevalence of PIM according to Swedish guidelines in this study's population may indicate that the physicians prescribe medicines carefully and are following the updated recommendations derived from the national guidelines.

The EU (7) PIM list

The prevalence of PIMs according to the EU (7) PIM list (45.2%) in the study population is in the line with previous studies among older people. Prevalence between 40,9 % and 66,7% have been reported (11; 41; 46; 47), according to the same list. A previous study using the same study population as in the present study found drug-related problems in 66% of the

study population also, 39 inappropriate medications were found (37.9%) (37). However, the prevalence of PIMs and the drugs that were involved in the previous study could not be directly related to the present study due to the different in inclusion and exclusion criteria and method to identified of the inappropriate drugs used, even if the same study sample used was investigated (37).

No significant association was found between various diseases and the risk to have PIM. As far as we know, there have been four other studies performed in different locations in the world that have investigated the prevalence of PIM using EU (7)- PIM list as an identification tool (11; 41; 46; 47) . Of these, the present study is the first study that investigates the association between a certain disease and the risk to have a PIM. There was no association between higher number of medications prescribed and PIMs in the present study. Previous studies show inconsistent results (11; 41). Further there was no association between age and gender found in the present study, which also is inconsistent with previous research with the same age span as the present study (41). Associated factors varies from study to study and may depend on the location that the study was performed in and the study sample used, even though the same identification tool was used (11; 41; 46; 47). Also, the EU (7)- PIM list is relatively new and little research has been conducted that has used the list to identify prevalence of PIM. The result in this study therefore must be confirmed with further research.

According to the EU (7)- PIM list hypnotics and sedatives were the most common type of PIM class prescribed in the present study (11.8%) and the most common drug was zopiclone (8.6%). The prevalence of zopiclone was higher in previous study (11). The reasons for why zopiclone was common in the present study, is probably that this drug is the first-line sedative recommendation among older people in Sweden, with maximum daily dose of 7.5 mg, which is higher than the recommendation in the EU (7)- PIM list with maximum daily dose of 3.5 mg. However, this recommendation is only for short term use, ≤ 30 days (5; 33), which we did not account for in the present study.

The second highest PIM class in the present study was antithrombotic drugs (10.8%) with apixaban as the most commonly prescribed drug (9.7%) in this class and the highest prescribed drug in total. Apixaban presented the highest prescribing frequency among PIMs for cardiac therapy, with nearly 10% of all patients being prescribed this drug. There is limited experience regarding the use of apixaban in elderly patients and the drug presents an increased risk of bleeding events and there is also no reversal agent available in case of overdose. It is therefore important to continuously evaluate the drug used and adjust the dosage. However, the current recommendation published in Sweden 2017, states that apixaban is recommended for the first-line treatment of arrhythmias and complicated venous thromboembolic disease. The recommendation states that the apixaban causes fewer haemorrhagic strokes, severe bleeding and a lower mortality compared to warfarin. Apixaban is also least renal function dependent for its elimination among current novel oral anticoagulants (NOACs) (48). This probably explains the high prevalence of apixaban in the present study. The third highest PIM class in the present study was cardiac therapy (9.7%), with digoxin (6.5%) as the most commonly prescribed in this class and the third highest prescribed drug. Digoxin concentrations might increase with increased risk of intoxication due to the pharmacodynamic and pharmacokinetic changes in elderly. It is therefore important to continuously evaluate the serum concentration to ensure the right dose of the drug (13).

The fourth highest prescribed drug in the present study was sodium picosulfate (5.4%). The drug is often used in combination with treatment of opioids in order to treat constipation caused by these drugs. Due to the risk of adverse events including abdominal pain, fluid,

electrolyte imbalance, hypoalbuminemia and exacerbate bowel dysfunction, it is only recommended to be used periodically (13). The present study excluded pro re nata, which means the prevalence of sodium picosulfate probably is underestimated. It is important to periodically evaluate drug use and if needed to change to other preparations in accordance to first-line treatment recommendations.

There are differences in prevalence of describe PIM classes and PIMs when comparing studies using the same identification tool (11; 41; 46). However, these studies have some similarity with the present study when it comes to the PIM class and PIM such as the high prevalence of digoxin and laxatives (11; 41; 46). The reasons for different prevalence and different PIM may depend on the country specific recommendations, the study samples and the cost of medicines, even if the same identification tools had been used.

Comparison between the EU (7) PIM list and the Swedish indicators

The prevalence of PIMs according to the Swedish quality indicators (16.1%) is much lower than the EU (7) PIM list (45.2%) in the present study. There are total 68 substances classified as PIMs according to the Swedish quality indicator (including NSAID group and antipsychotic) and 127 substances according to the EU (7)-PIM list (see appendix A and B). Of total 16 PIMs found according to the Swedish quality indicators, the most commonly prescribed PIMs was tramadol, hydroxyzine and diclofenac (total 7 prescribed found), in which also defined as PIM according to the EU (7)- PIM list. Of total 68 PIMs according to the EU (7)- PIM list, the most commonly prescribed PIMs was apixaban, zopiclone and digoxin (total 23 prescriptions) which do not define as PIM according to the Swedish quality indicators. The most prescribed PIMs varies from study to study, due to the different identification tools were used, the study sample and the location the study performed in (11; 41; 46; 47). In the present study even though the same study sample were used, the use of different identification tools gave an inconclusive result.

Some drugs defined as PIMs according to the EU (7)- PIM list, are recommended as first-line treatments according to the Swedish guidelines such as zopiclone (maximum daily dose 7.5 mg) and apixaban (33; 48). These drugs increase the prevalence of PIM according to the EU (7)- PIM list (18.3%). If these two drugs were excluded, the prevalence of PIM would decrease to 26.9%, which is lower than prevalence in previous research (11; 41; 46; 47). The difference in prevalence between using the two using tools may depend on how the EU (7)-PIM list was evaluated. The EU (7)- PIM list is deemed to be a sensitive tool, which may explain the high prevalence of PIM (13). On the other hand, the Swedish quality indicators is a country specific guideline and more adapted to other guidelines in Sweden. High prevalence of PIMs according to the EU (7)- PIM list may therefore be misleading to some degree due to the high prevalence of apixaban and zopiclone that are recommended as first-line treatments according to the Swedish guidelines. However, the use of EU (7)- PIM list as identification tool allows this study to compare the PIM prescribing patterns for elderly across European countries.

The simple analysis showed a significant association between a high number of medications and PIM according to the Swedish quality indicators. No associations with PIM in the multiple analysis were however found, and this accounted for both the Swedish quality indicators and the EU (7)- PIM list. Perhaps an association between EU (7) PIM and arrhythmias would have been expected due to the high prevalence of apixaban, but such an association was not found.

Limitations

There are some limitations with this present study. This study used the new version of the Swedish quality indicator that was published 07 June 2017. Since the data used in this study was collected between September – November 2015 and February – April 2016, an error might occur due to the overlap of the previous version (published 29 June 2010) of the Swedish quality indicator and the new version used in this study (44). Of a total of 282 substances identified as PIM according to the EU (7)- PIM list, only 127 substances were evaluated in this present study because many drugs are not approved in the Swedish market. The duration and regimen-dependent PIM and Pro re nata were also excluded as well, which may lower the prevalence of PIMs among the study population. Another limitation in the present study is the small study sample, which makes it difficult to generalise the results across other populations in previous studies.

Since the present study is a cross-sectional design, it is impossible to draw conclusion about the prescribing quality, negative outcomes of PIM such as adverse drug events and the use of explicit criterion. Strengths with the present study are the fact that the medication records applied are a reliable source and the identification tools used in the present study are well evaluated. As far as we know, the present study is also the first study that compares the prevalence of PIMs using EU (7)- PIM list and the Swedish quality indicators, which reflect the PIMs prescribing patterns in Sweden.

Conclusion

The prevalence of PIMs according the Swedish quality indicators is relative low (16.1%). According to the EU (7) PIM list the prevalence of potentially inappropriate medicines is much higher (45.2%). No associated factors with PIM were found in the present study, this accounts for both the Swedish quality indicators and the EU (7)- PIM list. The most prescribed PIM according to the Swedish quality indicators was tramadol, which was also defined as PIM according to the EU (7)- PIM list. The most prescribed PIM according to the EU (7)- PIM list was Apixaban, which recommended as first-line treatment in Sweden. Since there were different tools used in the present study the results were inconclusive. However, it is still important to continuously evaluate the need of PIMs in elderly in order to decrease risk of adverse drug events.

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Appendix A. Drugs' list according to the Swedish quality indicators.

Substances	*Drugs' name*	*ATC code*
Anticholinergic drugs		
Atropine	Atropin/ Isopto- Atropin	A03BA01
Glycopyrrolate	Robinul/Seebri Breezhaler/ Trimbow/ Ultibro	A03AB02
Hyoscyamine	Egazil	A03BA03
Butyl scopolamine	Buscopan	A03BB01
Scopolamine	Scopoderm	A04AD01
Disopyramide	Durbis Retard	C01BA03
Oxybutynin	Ditropan/Kentera/Oxybutin	G04BD04
Tolterodine	Detrusitol/ Tolterodin	G04BD07
Solifenacin	Versicare	G04BD08
Darifenacin	Emselex	G04BD10
Fesoterodine	Toviaz	G04BD11
Scopolamine + Morphine	Morfin-Skopolamin, Spasmofen	N02AG01
Trihexyphenidyl	Partigan	N04AA01
Biperiden	Akineton	N04AA02
Levomepromazine	Nozinan/ Levomepromazine	N05AA02
Chlorprothixene	Truxal	N05AF03
Clozapine	Leponex/ Clozapin F	N05H02
Hydroxyzine	Atarax/ Hydroxizin F	N05BB01
Clomipramine	Anafranil/Klomipramin F	N06AA04
Amitriptyline	Saroten/ Amitriptylin F	N06AA09
Nortriptyline	Sensaval	N06AA10
Maprotiline	Ludiomil	N06AA21
Dimenhydrinate	Dimenhydrinat	R06AA02
Alimemazine	Theralen	R06AD01
Promethazine	Lergigan / Prometazin	R06AD02
Clematis	Tavegyl	R06AA04
Meclizine	Postafen	R06AE05
Long-acting benzodiazepines		
Diazepam	Diazepam	N05BA01
Nitrazepam	Apodorm/ Mogandon/ Nitrazepam	N05CD02
Flunitrazepam	Flunitrazapam	N05CD03
Antipsychotic drugs		
Levomepromazine	Nozinan/ Levomepromazine	N05AA02
Fluphenazine	Siqualone decanoat	N05AB02
Perphenazine	Trilafon dekanoat	N05AB03
Haloperidol	Haldol	N05AD01
Melperone	Buronil	N05AD03
Sertindol	Serdolect	N05AE03
Ziprasidone	Zeldox/ Ziprasidon	N05AE04
Flupentixol	Fluanxol	N05AF01
Lurasidone	Latuda	N05AE05

Substances	**Drugs' name**	**ATC code**
Chlorprothixene	Truxal	N05AF03
Zuclopenthixol	Cisordinol	N05AF05
Clozapine	Clozapine / Leponex	N05AH02
Olanzapine	Arkolamyl/ Zalasta/ ZY-PADHERA/ Zyprexa/ Olanzapin	N05AH03
Quetiapine	Biquetan/ Ketipinor/ Seroquel/ Quetiapine	N05AH04
Risperidone	Medorisper/ Risperdal/ Risperdon	N05AX08
Aripiprazole	Abilify/ Lemilvo/ Aripiprazole	N05AX12
Paliperidone	INVEGA	N05AX13
NSAID		
Diclofenac	Eeze/ Eezeneo/ Ignorin/ Voltaren/ Diclofenac / Dicuno	M01AB05
Ketorolac	Toradol	M01AB15
Piroxicam	Brexidol	M01AC01
Tenoxicam	Alganex	M01AC02
Meloxicam	Meloxicam	M01AC06
Ibuprofen	Brufen/ Ibumaz/ Ibumetin/ Ibuprofen F/ Ibuzin/ Ifenin/ Ipren/ Iprenza/ Nurofen apelsin	M01AE01
Naproxen	Alpoxen/ Naprocur/ Naprosyn/ Pronaxen	M01AE02
Ketoprofen	Orudis	M01AE03
Dexibuprofen	Tradil	M01AE14
Dexketoprofen	Enantyum	M01AE17
Celecoxib	Celebra/ Celecoxib	M01AH01
Parecoxib	Dynastat	M01AH04
Etoricoxib	Arcoxia/ Etoricoxib	M01AH05
Nabumetone	Relifex	M01AX01
Other PIMs		
Propiomazine	Propavan	N05CM06
Tramadol	Gemadol/ Nobligan/ Tiparol/ Tradolan/ Dolatramyl	N05AX02
Glibenclamide	Daonil/ Glibenklamid Recip	A10BB01
Doxazosin	Alfadil/ Doxazosin	C02CA04
Propiomazine	Propavan	N05CM06
Codeine	Kodein + Paracetamol/ Citodon	N02AJO6, N02AJ09, R05DA04

Appendix B. Drugs list according to the EU (7)- PIM list

Substances	*Drug available in Sweden*	*ATC- cod*
Alimentary tract and metabolism		
Aluminium-containing antacids	Novaluzid	A02AD01
Ranitidine	Zantac/ Stomacid/ Inside Brus	A02BA02
Famotidine	Pepcid	A02BA03
Atropine	Atropin	A03BA01
Hyoscyamine	Egazil	A03BA03
Metoclopramide	Primperan/ Metoclopramide	A03FA01
Hyoscine (scopolamine)	Scopoderm	A04AD01
Senna glycosides	Pursennid Ex- Lax	A06AB06
Sodium picosulfate	Cilaxoral/ Laxoberal	A06AB08
Prucalopride	Resolor	A06AX05
Racecadotril	Hidrasec	A07XA04
Glibenclamide	Daonil/ Glibenklamid Recip	A10BB01
Glipizide	Mindiab	A10BB07
Glimepiride	Amaryl/ Glimepirid F	A10BB12
Acarbose	Glucobay	A10BF01
Pioglitazone	Actos/ Piolitazone F	A10BG03
Sitagliptin	Januvia	A10BH01
Vildagliptin	Galvus	A10BH02
Blood and blood forming organs		
Dipyridamole	Dipyridamol/ Persantin Depot	B01AC07
Prasugrel	Efient	B01AC22
Dabigatran	Pradaxa	B01AE07
Rivaroxaban	Xarelto	B01AF01
Apixaban	Eliquis	B01AF02
Ferrous sulfate	Niferex/ Duroferon	B03AA01/07
Cardiovascular system		
Digoxin	Lanoxin/ Digoxin BioPhausia	C01AA05
Disopyramide	Durbis Retard	C01BA03
Propafenone	Rytmonorm	C01BC03
Flecainide	Tambocor	C01BC04
Amiodarone	Amiodaron Hameln/ Cordarone	C01BD01
Dronedarone	MULTAQ	C01BD07
Ivabradine	Procoralan	C01EB17
Clonidine	Catapresan	C02AC01
Moxonidine	Moxonidin F/ Physiotens	C02AC05
Doxazosin	Alfadil/ Doxazosin F	C02CA04
Hydralazine	Apresolin	C02DB02

Substances	***Drug available in Sweden***	***ATC- cod***
Spironolactone	Spironolactone F	C03DA01
Pindolol	Pindolol F	C07AA03
Propranolol	HEMANGIOL/ Inderal/ Propranolol F	C07AA05
Sotalol	Sotacor	C07AA07
Labetalol	Labetalol SALF/ Trandate	C07AG01
Nifedipine	Adalat	C08CA05
Verapamil	Isoptin/ Verapamin F	C08DA01
Diltiazem	Cardizem	C08DB01
Genito-urinary system and sex hormones		
Estradiol	Divigel/ Estradot/ Femanest/Lenzetto/ Oestring/ Progynon/ Vagifem	G03CA03
Estriol	Blisel/ Estrokad/ Oestriol Aspen/ Ovesterin	G03CA04
Tibolone	Livial/ Tibocina/ Tobolon F	G03CX01
Oxybutynin	Ditropan/ Kentera/ Oxybutynin F	G04BD04
Tolterodine	Destrusitol/ Tolterodin F	G04BD07
Solifenacin	Vesicare	G04BD08
Darifenacin	Emselex	G04BD10
Fesoterodine	TOVIAZ	G04BD11
Terazosin	Hytrinex/ Sinalfa	G04CA03
Musculo-skeletal system		
Diclofenac (oral)	Eeze/ Eezeneo/ Ignorin/ Voltaren/ Diclofenac F/ Dicuno	M01AB05
Ketorolac	Toradol	M01AB15
Piroxicam	Brexidol	M01AC01
Meloxicam	Meloxicam	M01AC06
Ketoprofen	Orudis	M01AE03
Dexketoprofen	Enantyum	M01AE17
Celecoxib	Celebra/ Celecoxib F	M01AH01
Etoricoxib	Arcoxia/ Etoricoxib	M01AH05
Nabumetone	Relifex	M01AX01
Orphenadrine	Norflex	M03BC01
Baclofen	Baklofen F/ Lionova	M03BX01
Strontium ranelate	Protelos	M05BX03
Nervous system		
Pethidine	Petidin Meda	N02AB02
Tramadol	Gemadol/ Nobligan/ Tiparol/ Tradolan/ Dolatramyl	N02AX02
Acetylsalicylic acid	Acetylsalicylsyra F/ Albyl/ Aspirin/ Bamyl	N02BA01
Sumatriptan	Imigran/ Priptan/ Sumatriptan F	N02CC01
Naratriptan	Naramig	N02CC02
Zolmitriptan	Zomig/ Zolmitriptan	N02CC03
Rizatriptan	Maxalt/ Rizasmelt/ Rizatriptan F	N02CC04
Almotriptan	Almogran	N02CC05

Substances	***Drug available in Sweden***	***ATC- cod***
Eletriptan	Relpax	N02CC06
Frovatriptan	Unregistered medicines	N02CC07
Phenobarbital	Fenemal Meda	N03AA02
Phenytoin	Epanutin/ Fenantoin Meda/ Lehydan	N03AB02
Clonazepam	Iktorivil	N03AE01
Carbamazepine	Carbamazapine F/ Hermolepsin/ Tegretol/ Trimonil	N03AF01
Topiramate	Topimax/ Topiramat	N03AX11
Trihexyphenidyl	Pargitan	N04AA01
Biperiden	Akineton	N04AA02
Bromocriptine	Unregistered medicines	N04BC01
Ropinirole	ADARTREL/ Requip/ Ropinirole F	N04BC04
Pramipexole	Derinik/ Mirapexin/ Oprymea/ Pramipexol/ Sifrol	N04BC05
Cabergoline	Cabaser/ Cabergoline F	N04BC06
Rotigotine	Neupro	N04BC09
Selegiline	Eldepryl/ Selegilin Mylan	N04BD01
Levomepromazine	Nozinan/ Levomepromazine F	N05AA02
Fluphenazine	Siqualone decanoat	N05AB02
Perphenazine	Trilafon dekanoat	N05AB03
Haloperidol	Haldol	N05AD01
Droperidol	Dridol/ Droperidol Carino	N05AD08
Sertindole	Serdolect	N05AE03
Ziprasidone	Zeldox/ Ziprasidon F	N05AE04
Flupentixol	Fluanxol	N05AF01
Chlorprothixene	Truxal	N05AF03
Zuclopenthixol	Cisordinol	N05AF05
Clozapine	Clozapine F/ Leponex	N05AH02
Olanzapine	Arkolamyl/ Zalasta/ ZYPADHERA/ Zyprexa/ Olanzapin F	N05AH03
Lithium	Lithionit	N05AN01
Aripiprazole	Abilify/ Lemilvo/ Aripiprazole F	N05AX12
Diazepam	Diazepam F	N05BA01
Oxazepam	Oxascand/ Sobril	N05BA04
Lorazepam	Larazapan F/ Temesta	N05BA06
Alprazolam	Xanor/ Alprazolam	N05BA12
Hydroxyzine	Atarax/ Hydroxizin	N05BB01
Nitrazepam	Apodorm/ Mogadon/ Nitrazapam Recip	N05CD02
Flunitrazepam	Flunitrazapam F	N05CD03
Triazolam	Unregistered medicines	N05CD05
Midazolam	BUCCOLAM	N05CD08
Zopiclone	Imovane/ Zopiclon	N05CF01

Substances	Drug available in Sweden	ATC- cod
Zolpidem	Edluar/ Stilnoct/ Zolpidem	N05CF02
Clomethiazole	Heminevrin	N05CM02
Propiomazine	Propavan	N05CM06
Clomipramine	Anafranil/ Klomipramin F	N06AA04
Amitriptyline	Saroten/ Amitriptylin F	N06AA09
Maprotiline	Ludiomil	N06AA21
Nortriptyline	Sensaval	N06AA10
Fluoxetine	Fluoxetin F/ Fontex	N06AB03
Paroxetine	Paroxetin F/ Seroxat/ Paroxiflex	N06AB05
Fluvoxamine	Fevarin	N06AB08
Amfebutamone (Bupropion)	Voxra/ Zyban/ Bupropion F	N06AX12
Venlafaxine	Efexor/ Venlafaxin	N06AX16
Reboxetine	Edronax	N06AX18
Methylphenidate	Concerta/ Equasym/ Medanef/ Medikinet/ Metylphenidate/ Ritalin	N06BA04
Piracetam	Nootropil	N06BX03
Methadone	Metadon F	N07BC02

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