



UMEÅ UNIVERSITY

PREVALENCE OF DRUG RELATED PROBLEMS

STOPP/START in elderly people with dementia

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Abstract

Introduction

Drug related problems (DRPs) are common among elderly people with dementia. Different tools to detect DRPs can be used, either implicit or explicit criteria. An explicit tool to detect DRPs among elderly people is Screening Tool of Older People's Prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START). STOPP/START is developed by a group of experts in Europe and has been shown to decrease DRPs among elderly people without dementia.

Objectives

The objective of this study was to investigate the prevalence of DRPs among elderly people with dementia, by using STOPP/START. The objective was also to compare number and type of DRPs identified by STOPP/START with DRPs identified by clinical pharmacists among the same population.

Method

Extract from the medical journal was used to identify DRPs of 212 peoples' drug list by using STOPP/START. The people were ≥ 65 years with dementia or cognitive impairment. An earlier study was performed in the same study population in 2012-2014, where DRPs were identified by clinical pharmacists in order to decrease number of rehospitalizations.

Results

STOPP/START identified DRPs in 72.2 % of the people, compared with 66.0 % identified by the clinical pharmacists. The number of DRPs identified by the different methods was 326 and 310 respectively. Different types of DRPs were identified with the different tools. STOPP/START did mainly identify DRPs in the categories "ineffective/inappropriate drug" and "needs additional drug therapy", whereas the clinical pharmacists identified DRPs in several categories.

Discussion

Even though STOPP/START was able to identify quite equal number of DRPs compared with DRPs identified by clinical pharmacists, STOPP/START failed to identify DRPs in several important categories. STOPP/START may be used as a complement to medication reviews by clinical pharmacists, alternatively be developed more specifically to elderly people with dementia.

Conclusion

The prevalence of at least one DRP in elderly people with dementia according to STOPP/START was found to be 72.2 %. The number of DRPs identified by STOPP/START was quite equal to the number identified by clinical pharmacists. However, different types of DRPs was identified with the different methods.

Key words: STOPP/START, elderly people, dementia, drug related problems (DRPs).

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1. Introduction

1.1 Drug related problems among elderly people

Drug related problems (DRPs) are very common among elderly people (≥ 65 years) (1). Elderly people often have several diagnoses and thereby indications for many drugs. Polypharmacy is a common problem among elderly people and is often defined as ≥ 5 or ≥ 10 drugs. Polypharmacy increases the risk for drug-drug interactions, side effects and prescribing cascades. Prescribing cascades indicate prescribing of drugs to cure side effects of other drugs (1). Polypharmacy does also increase the risk for inappropriate prescribing of drugs. Inappropriate prescribing can be defined as “medication for which the potential risk outweighs the potential benefit” (2).

Several diagnoses also entail a risk for under-prescribing of drugs. For a person with a history of stroke and heart failure for example, an angiotensin converting enzyme (ACE)-inhibitor, a betablocker, an aldosterone antagonist, thrombocyte aggregation inhibitors and a statin are indicated (unless the person has contraindications) (3). Under-prescribing of drugs refers to untreated diseases or poor prevention which as well as inappropriate prescribing can be a risk for the person (2).

In general, elderly people have less marginal to the effect and adverse effects of drugs due to increased pharmacodynamic sensitivity. In addition to pharmacodynamic changes in elderly people, the pharmacokinetics of drugs can also be affected by age. Elderly people do often have impairment in renal- and hepatic function, which is the eliminating and metabolizing organ for drugs. Impairment in metabolizing or eliminating organs extends the clearance of drugs and the risk for higher plasma concentrations and accumulation of drugs and thereby risk of side effects or toxicity increases. Due to renal- or hepatic impairment dose adjustment of drugs can be necessary, and some drugs can in some cases become inappropriate. Decreased hepatic function can particularly cause side effects in cases of polypharmacy because of induction or inhibition of drug metabolizing enzymes (4). Elderly people do also have an increased proportion of body fat where fat soluble drugs can accumulate due to increased distribution of these drugs. Decreased function in cholinergic system is another common reduction among elderly people and makes these people more sensitive to anticholinergic drugs. Anticholinergic drugs are included in several categories of drugs; for example, antipsychotic drugs, tricyclic antidepressant and urinary tract spasmolytic (5). Another example of DRPs among elderly people is non-adherence to prescribed drugs that obviously reduce the efficacy of drugs (6).

In addition to inappropriate prescribing of drugs by the doctor, people can also use drugs over-the-counter (OTC). The use of herbal or dietary supplements occurs in more than 60 % of elderly people. These supplements often interact with other drugs. The main problem is that the doctors rarely take these in to account when prescribing other drugs to the people (7). DRPs have been found to increase if different doctors are involved in drug treatment of a person. With different doctors involved, it is hard for someone to have complete control over the persons' drugs. This makes drug-drug interactions and other inappropriate prescribing more likely to occur. Other risk factors to DRPs are generic drugs, which can cause confusion and mix up of drugs, health care organizational deficiencies and lack of complete medication lists, both for doctors and pharmacists (5).

1.2 Elderly people with dementia

Elderly people with dementia are even more vulnerable to several drugs. These people have a greater reduction in cholinergic function and are even more sensitive to anticholinergic drugs (8). Anticholinergic drugs among elderly people is common, and one study found that 23.3 % of elderly people with dementia are prescribed anticholinergic drugs despite opposing recommendations. Use of anticholinergic drugs in

elderly people with dementia can for example cause adverse effects such as dry mouth, confusion, impairment in memory and urinary retention (9). Dementia is also associated with bad adherence to drugs (10). In people with dementia, one study found that 41 % of hospitalizations were due to drugs related problems, compared with up to 30 % in elderly people without dementia (11-15). A study on elderly people with dementia found that the most common inappropriate drugs prescribed are benzodiazepines, antipsychotic drugs and opiates. The same study showed that statins, calcium- and vitamin D supplements were the most under-prescribed drugs in this group of people (16). Another study in elderly people with dementia showed that 60 % of these people were prescribed at least one potentially inappropriate drug (17), compared with 31.6 % in a healthy population (18). However, the different frequencies were measured in different countries and with different tools (17, 18). The study on elderly people with dementia showed that the number of potentially inappropriate drugs increased with increasing age. The most common group of inappropriate drugs was antipsychotic drugs which were associated with higher risk of falls (17).

1.3 Prevention of DRPs

One way of preventing DRPs is by using clinical pharmacists in the ward team (19). In several countries, clinical pharmacists have been a part of the ward team for years (20-22). The clinical pharmacists aim is to improve the peoples' use of drugs, for example by medication reviews. These medication reviews include an analysis of a peoples' drug list where suggestions of changes of drugs are proposed to the prescribing doctor. A definition of a medication review is: "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions." according to the Pharmaceutical Care Network Europe (PCNE) (23). By optimizing a persons' drug therapy, DRPs could be prevented. In a medication review, the identification of inappropriate drugs is included (6).

There have been many tools developed in order to identify inappropriate drugs. One of these is Beer's criteria, which is an example of explicit criteria. Explicit criteria are rigid guidelines developed from an expert panel, unlike implicit criteria where an overall individual assessment is made by professional judgement. Both implicit and explicit criteria is usually used in medication reviews by clinical pharmacists (24). Beer's criteria consist of 50 explicit criteria and refers to reduce ineffective drugs or drugs with high risk for adverse effects in elderly people. These guidelines are divided in three categories; "drugs that always should be avoided", "drugs that are potentially inappropriate", and "drugs that should be used by caution". Beer's criteria have shown to decrease the number of inappropriate drugs with 34.2 % (25). The criteria were developed in 1991 and have been updated three times since then (26).

1.4 STOPP/START

Another explicit criteria is Screening Tool of Older People's Prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START) of explicit criteria which was developed in 2008 by a group of experts in UK and Ireland (27). In 2015, STOPP/START version 1 was revised to version 2, since new recommendations and new drugs have been developed. STOPP/START version 2 is an updated version from STOPP/START version 1 by a panel of group of 19 experts from 13 countries in Europe. STOPP/START includes two lists for elderly people (≥ 65 years). One of the lists, STOPP, includes drugs which should be withdrawn in some groups of people or in certain diseases. The other list, START, includes drugs which should be prescribed for certain indications. STOPP/START has shown to decline adverse effects of drugs and the length for hospitalization (28).

A systematic review published 2016 investigated four studies where STOPP/START has been evaluated in different populations. None of these populations included specifically people with dementia, but in all populations, the people were ≥ 65 years. All studies

showed that potential DRPs identified by STOPP/START in the population is 32.4-66.8 % (29).

Previous studies have been performed where medication reviews are compared with explicit tools, such as STOPP/START. One study compared medication reviews performed by communal pharmacists with medical reviews using STOPP/START version 1. The communal pharmacist could identify 1654 DRPs among the 457 people in the study. Correspondingly, the percentage of DRPs identified according to STOPP/START was only 19 % of the DRPs the pharmacists identified (2). STOPP/START has also been used in combination with Beers criteria, where the combination identified 41 % of DRPs identified by pharmacists (30). STOPP/START has also been compared with other tools, for example Beers criteria, in a systematic literature review. STOPP/START was shown to be the only tool that had evidence to reduce DRPs compared with Beers criteria and three other explicit criteria; Mimica, Assessing Care Of Vulnerable Elderly (ACOVE) and Prescribing Indicators in Elderly Australians (PIEA) (31). However, none of these studies analyzed DRPs in people with dementia specifically.

2. Objectives

The objective of this study was to investigate the prevalence of DRPs among elderly people with dementia, by using STOPP/START. The objective was also to compare number and type of DRPs identified by STOPP/START with DRPs identified by clinical pharmacists among the same population. The questions that will be answered are:

- What is the prevalence of DRPs among elderly people with dementia according to STOPP/START?
- Is there a difference between the number of DRPs identified by STOPP/START compared with DRPs identified by the medication reviews performed by clinical pharmacists?
- What kind of differences in DRPs can be identified between the different methods in elderly people with dementia?

3. Method

3.1 Subjects and settings

A randomized controlled intervention study (RCT) performed between January 9, 2012 and December 2, 2014, investigated the prevalence of rehospitalization due to DRPs after medication reviews performed by three clinical pharmacists. The study was performed at Norrlands University Hospital in Umeå and Skellefteå hospital. The investigated people were people ≥ 65 years old with dementia or cognitive impairment. Four hundred and sixty people were randomized to either an intervention group or a control group. In the present study, only the people in the intervention group from the RCT were analyzed. Of the 230 people in the intervention group, 18 died and were therefore excluded from the study, leaving 212 peoples' data to be analyzed. The people in the intervention group had their medication lists reviewed by the clinical pharmacists (20).

3.2 Medication reviews

A previous study described the presence and type of DRPs found by the clinical pharmacists among the intervention group in the RCT. The pharmacists identified DRPs in 66.0 % of the people and a total of 310 DRPs. Of the 212 people, at least one DRP was identified in 140 of them. The most common DRPs identified in the study was inappropriate prescribing and the most common action by the clinical pharmacists was discontinued of drugs. The study also showed that DRPs were most common among people with polypharmacy and people with a history of stroke (6).

In the previous study three pharmacists used information about the peoples' drugs, medicinal history and lab values to be able to perform medication reviews. The medication reviews included both explicit- and implicit criteria and were performed without talking to the people, so no information about OTC drugs were received. The pharmacists did also participate in the ward rounds where DRPs identified were discussed with the prescribing doctor. The medication reviews are in detail described in Pfister et al (6).

3.3 STOPP/START

In the present study, only people from the intervention group were analyzed. Data regarding drugs, lab values, summary of medical history and diagnoses were available from the RCT in the previous study. All prescribed drugs to all people were checked twice by using STOPP/START.

STOPP includes 80 criteria, which indicate drugs that should be withdrawn for some people or some indications/combinations. START includes 34 criteria, which indicate drugs which should be prescribed for a specific indication (28).

Because of some lacking data about the people, some items on STOPP/START were excluded in this study. The following criteria were excluded: STOPP A1, A2, F2, J3 and START E5, F1, I1 and I2 (see appendix 9.1 and 9.2).

To be able to compare the DRPs identified in the present study with the DRPs identified in the study with the clinical pharmacists, DRPs were divided in to eleven categories. The categories used in the present study was the same as the DRPs in the study with the clinical pharmacists; suspected adverse drug reaction, dosage too high, dosage too low, ineffective/inappropriate drug, interaction, monitoring need, needs additional drug therapy, noncompliance, transition error and unnecessary drug therapy. Each criteria in STOPP/START was categorized to one of these categories (see appendix 9.3).

3.4 Ethics

This study is accepted by the Regional Ethical Review Board in Umeå, Sweden, (registration number 2011-148-31 M).

3.5 Statistics

Data of various associated factors with DRPs were analyzed by simple logistic regression analysis in Statistical Package for the Social Sciences (SPSS). The factors that were analyzed were age, gender, type of dementia, number of drugs prescribed, type of living, Mini Mental State Examination (MMSE), creatinine clearance and medical history of the people. Significant factors from the simple logistic regression analysis were further analyzed with multiple regression analysis in SPSS. The results were presented as odds ratio (OR). The confidence interval (CI) used were 95 %, and the P-value < 0.05.

3.6 Motivation to choose the method

The people were chosen from the randomized controlled intervention study since data from medication reviews by clinical pharmacists were already available, which was necessary to be able to compare number of DRPs identified by the different methods. STOPP/START was chosen because it has previously been observed that this list has evidence to reduce DRPs in a study were STOPP/START, Beers criteria, Mimica, ACOVE and PIEA was compared (31). Previous research has established that STOPP/START is able to identify 19 % of DRPs identified by communal pharmacists in elderly people (2). The present study will investigate similar objectives but among people with elderly people with dementia which as far as the author know, not has been investigated before.

4. Results

4.1 Characteristics of study population

Two hundred and twelve people were included in the study. Of the 212 people, 133 (62.7 %) were women. The people had a mean age of 83.1 ± 6.6 years and were prescribed 8.4 ± 3.6 drugs in average. The most common type of dementia was Alzheimer's dementia (30.2 %) and vascular dementia (19.8 %). Seventy-two persons (34.0 %) were diagnosed with heart failure and 62 persons (29.2 %) with cardiac arrhythmia (see table 1).

Table 1: Characteristics of study population.

	All people
Cases, n	212
Women, n (%)	133 (62.7)
Age mean \pm SD	$83,1 \pm 6.6$
Number of drugs prescribed \pm SD	8.4 ± 3.6
Type of dementia	
Alzheimer's dementia, n (%)	64 (30.2)
Vascular dementia, n (%)	42 (19.8)
Lewy Body dementia, n (%)	5 (2.4)
Other, n (%)	101 (47.6)
Type of living	
Living at home, n (%)	146 (68.9)
Nursing home, n (%)	66 (31.1)
MMSE (0–30) \pm SD	19.6 ± 4.8
Creatinine clearance, (mL/min)	53.6 ± 21.9
Medical history	
Heart failure, n (%)	72 (34.0)
Cardiac arrhythmia, n (%)	62 (29.2)
Diabetes mellitus, n (%)	61 (28.8)
Stroke, past, n (%)	16 (7.5)

SD = standard deviation

4.2 DRPs identified by STOPP/START

In total, 326 DRPs were identified by STOPP/START. The number of DRPs identified by STOPP was 224, and 132 by START. Grouping of these DRPs are described in more detail in appendix 9.4 (see table 6 and 7). The number of DRPs identified by STOPP added with DRPs identified by START exceeds the total number of DRPs identified by STOPP/START. The explanation for this is that some DRPs have been categorized into more than one STOPP/START criteria, but is counted as only one DRP in total. The most common DRPs identified by STOPP were hypnotic Z-drugs (25.0 %). The most common DRPs identified by STOPP were benzodiazepines (14.7 %) and neuroleptic drugs (8.4 %) (see table 2).

The most common DRPs identified by START were “statin therapy in people with a documented history of coronary, cerebral or peripheral vascular disease” (20.5 %), followed by “ACE inhibitor with systolic heart failure and/or documented coronary artery disease” (12.9 %) (see table 3).

Table 2: The most common DRPs identified by STOPP criteria.

STOPP criteria	Number of DRPs
K4: Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia), n (%)	56 (25.0)
K1: Benzodiazepines (sedative, may cause reduced sensorium, impair balance), n (%)	33 (14.7)
K2: Neuroleptic drugs (may cause gait dyspraxia, parkinsonism), n (%)	19 (8.5)
D8: Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment), n (%)	13 (5.8)
A3: Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimization of monotherapy within a single drug class should be observed prior to considering a new agent), n (%)	10 (4.5)
D5: 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), n (%)	10 (4.5)
J1: Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia), n (%)	10 (4.5)

DRPs = Drug related problems

Table 3: The most common DRPs identified by START criteria.

START criteria	Number of DRPs
A5: 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, n (%)	27 (20.5)
A6: Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease, n (%)	17 (12.9)
A7: Beta-blocker with ischaemic heart disease, n (%)	15 (11.4)
C3: Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine), n (%)	15 (11.4)
E2: Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy, n (%)	15 (11.4)
A3: Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease, n (%)	10 (7.6)
E4: 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), n (%)	8 (6.1)

DRPs = Drug related problems

4.3 Classification of DRPs identified by STOPP/START versus clinical pharmacists

The clinical pharmacists identified 310 DRPs among the 212 people (6), while STOPP/START identified 326 DRPs. After distributing all DRPs according to START/STOPP into categories (see appendix 9.3), the most common type of DRPs identified by the clinical pharmacists were “ineffective/inappropriate drug” (17.4 %), and “unnecessary drug therapy” (17.4 %). The most common type of DRPs identified by STOPP/START were “ineffective/inappropriate drug” (56.4 %), followed by “needs additional drug therapy” (39.3 %) (see table 4).

Table 4: Classification of DRPs identified by clinical pharmacists compared with DRPs identified by STOPP/START.

Type of DRPs	Identified by clinical pharmacists (n = 310)*	Identified by STOPP/START (n = 326)
Suspected adverse drug reaction, n (%)	41 (13.2)	-
Dosage too high, n (%)	44 (14.2)	-
Dosage too low, n (%)	14 (4.5)	-
Ineffective/inappropriate drug, n (%)	54 (17.4)	184 (56.4)
Interaction, n (%)	23 (7.4)	1 (0.31)
Monitoring need, n (%)	13 (4.2)	1 (0.31)
Needs additional drug therapy, n (%)	37 (11.9)	128 (39.3)
Noncompliance, n (%)	4 (1.3)	-
Transition error, n (%)	26 (8.4)	-
Unnecessary drug therapy, n (%)	54 (17.4)	12 (3.7)

DRPs = Drug related problems

* These results are already published (6).

4.4 Associated factors

According to the simple logistic regression analysis of STOPP/START, age, number of drugs prescribed, type of living and heart failure were significant factors associated with DRPs. Of DRPs identified by the clinical pharmacists, number of drugs prescribed and past stroke were significant factors according to the simple analysis. The only significant factor in the multiple logistic regression analysis associated with DRPs according to STOPP/START was number of drugs prescribed [OR = 1.208; 95 % CI (1.083-1.346)]. In the study with the clinical pharmacists, number of drugs prescribed, and previous stroke were significant factors associated with DRPs [OR = 1.241; 95 % CI (1.122-1.374)] respectively [OR=4.306; 95 % CI (1.685-11.005)] (see table 5).

Table 5: Characteristics of study population with and without DRPs identified by STOPP/START versus by clinical pharmacists.

	STOPP/START				Clinical pharmacists*			
	With DRP	Without DRP	Simple OR (95 % CI)	Multiple OR (95 % CI)	With DRP	Without DRP	Simple OR (95 % CI)	Multiple OR (95 % CI)
Cases, n (%)	153 (72.2)	59 (27.8)			140 (66.0)	72 (33.9)		
Women, n (%)	99 (64.7)	34 (57.6)	1.348 (0.739-2.490)		88 (62.9)	45 (62.5)	1.015 (0.564-1.827)	
Age mean \pm SD	83.7 \pm 6.3	81.6 \pm 7.1	1.049 (1.002-1.099)	1.046 (0.996-1.097)	83.7 \pm 6.6	82.0 \pm 6.3	1.042 (0.997-1.088)	1.041 (0.994-1.090)
Number of drugs prescribed \pm SD	9.1 \pm 3.5	6.8 \pm 3.2	1.245 (1.123-1.380)	1.208 (1.083-1.346)	9.3 \pm 3.4	6.8 \pm 3.4	1.225 (1.137-1.385)	1.241 (1.122-1.374)
Type of living								
Living at home, n (%)	97 (63.4)	49 (83.1)	Reference		91 (65.0)	55 (76.4)	Reference	
Nursing home, n (%)	56 (36.6)	10 (16.9)	2.829 (1.329-6.022)	2.017 (0.905-4.4495)	49 (35.0)	17 (23.6)	1.742 (0.94-3.321)	
MMSE (0–30) \pm SD	19.4 \pm 5.0	20.1 \pm 4.1	0.969 (0.878-1.068)		18.9 \pm 4.8	20.7 \pm 4.5	0.923 (0.842-1.013)	
Creatinine clearance, (mL/min), \pm SD	51.9 \pm 22.5	57.9 \pm 19.8	0.988 (0.975-1.001)		52.8 \pm 22.3	55.0 \pm 21.1	0.995 (0.983-1.008)	
Medical history								
Heart failure, n(%)	59 (38.6)	13 (22.0)	2.221 (1.107-4.456)	1.446 (0.677-3.089)	50 (35.7)	22 (30.6)	1.263 (0.687-2.322)	
Cardiac arrhythmia, n (%)	50 (32.7)	12 (20.3)	1.901 (0.927-3.900)		40 (28.6)	22 (30.6)	0.909 (0.488-1.692)	
Diabetes mellitus, n (%)	45 (29.4)	16 (27.1)	1.120 (0.572-2.191)		43 (30.7)	18 (25.0)	1.330 (0.699-2.530)	
Stroke, past, n (%)	40 (26.1)	10 (16.9)	1.735 (0.803-3.745)		44 (31.4)	6 (12.0)	5.042 (2.032-12.509)	4.306 (1.685-11.005)

DRP = Drug Related Problem, SD = Standard Deviation, OR = Odds Ratio, CI = Confidence Interval, MMSE = Mini Mental State Examination

The multivariate model includes significant variables as independent variables; for STOPP/START; number of medications at randomization, heart failure, type of living and age, for clinical pharmacists: number of medications at randomization, stroke and age (borderline significant).

* These results are already published (6).

5. Discussion

5.1 Summary of the result

DRPs according to STOPP/START in elderly people with dementia were identified in 72.2 % of the people, compared to 66.0 % of the people identified by the clinical pharmacists among the same population. The number of DRPs identified by STOPP/START compared with the number of DRPs identified by the clinical pharmacists was quite equal, 326 versus 310. The types of DRPs identified with the different tools differed however markedly. DRPs according to STOPP/START were mainly categorized as “ineffective/inappropriate drug” (56.4 %) or “needs additional drug therapy” (39.3 %), whereas the most common categories of DRPs identified by clinical pharmacists were “unnecessary drug therapy” (17.4 %), “ineffective/inappropriate drug” (17.4 %) and “dosage too high” (14.2 %).

5.2 Discussion

The prevalence of DRPs, 72.2 % according to STOPP/START, indicates that DRPs are common among elderly people with dementia. A systematic review from 2016 states that DRPs were identified by STOPP/START in 32.4-66.8 % of elderly people \geq 65 years. The review found that people living in nursing homes had the highest proportion of DRPs, 66.8 % (29, 32). The proportion of DRPs identified among people living in nursing homes was quite equal to the proportion of DRPs identified by STOPP/START in the present study although most people were living at home. In the population of the present study, 31.1 % of the people were living in nursing homes, which means that most people were living at home. The presence of dementia is probably contributing to a higher prevalence of DRPs. Of DRPs identified by STOPP, 5.3 % was “anticholinergics/antimuscarinics in people with delirium or dementia”, which could be one reason why more DRPs were identified among people with dementia in the present study compared with people in nursing home in the study mentioned above (32).

To identify DRPs is an important assignment in healthcare in order to improve peoples' drug therapy. Whether STOPP/START is adequate for this assignment is not fully investigated. In the present study, STOPP/START identified quite equal number of DRPs compared with medication reviews by the clinical pharmacists. However, the types of DRPs differed markedly between the different methods. DRPs identified by clinical pharmacists were distributed in several categories, whereas STOPP/START mainly identified DRPs in a few categories. That STOPP/START does not identify all DRPs is found in a previous study, where STOPP/START version 1 was compared with medication reviews performed by communal pharmacists. The study found that only 19 % of all DRPs identified by the communal pharmacists were identified using STOPP/START (2).

One type of DRPs not identified by STOPP/START but identified by the clinical pharmacists in the present study was DRPs regarding transition error (8.4 % of the DRPs). Transition error is a common problem were transition of a persons' drug list from inpatient care to primary care, or contrariwise, from primary care to inpatient care is inaccurate. An American study has shown that 70 % of people discharged from hospital had at least one transition error (33). These errors can lead to incorrect medications, incorrect dose, abrupt withdrawal of drugs that should be withdrawn gradually etcetera and cause a lot of suffering for the person. This can also contribute to a longer duration at the hospital and more frequent visits to the hospital which, in addition, is a great cost to the society (33).

A second type of DRPs not identified by STOPP/START but identified by the clinical pharmacists in a few cases was DRPs regarding noncompliance/non-adherence to drugs (1.3 % of the DRPs). Non-adherence occurs in 11-42 % according to different systematic reviews in people with dementia or cognitive impairment (34, 35). The prevalence differs greatly between the studies since different methods in measuring adherence are used. The communal pharmacists in the study mentioned above interviewed the people about their medications, and the main part of the DRPs were identified this way (2). The lack of

interviews was a reason to the fact that a lower proportion of DRPs according to STOPP/START was identified. In the present study, the clinical pharmacists did not perform interviews with the people. The reason for this was that the people suffered from dementia or cognitive impairment. Interviews with patients and/or their relatives would probably contribute to more DRPs identified by clinical pharmacists in relation to DRPs identified by STOPP/START, and play an important role in identifying problems regarding adherence. In several populations, studies have shown that non-adherence increases the rate of hospitalizations (36-38).

A third type of DRPs not identified by STOPP/START but identified by the clinical pharmacists was DRPs regarding dosage too high or dosage too low (14.2 % respectively 4.5 % of the DRPs). Dose adjustment because of impairment in renal function is usually necessary in elderly people. A study on the same population as in the present study found that 34 % of DRPs were because of too high doses in relation to renal function (39). Impairment in renal function affect the elimination of many drugs, which increase the risk for adverse effects of drugs and even toxicity if a drug has narrow therapeutic index (39, 40). Except dose adjustments because of impairment in renal function, other factors may be the reason why a dose adjustment is necessary. Dose adjustments can also be necessary because of impairment in liver function, drug interactions or increased part of body fat for example (4, 5).

The clinical pharmacists did also identify DRPs regarding monitoring lab values, adverse drug reactions and dosage too low, which STOPP/START in very few cases considered.

One reason why STOPP/START identified a lot more DRPs than the clinical pharmacists did in the categories “ineffective/inappropriate drug” and “needs additional drug therapy” (see table 4), can be explained by differences in treatment guidelines between Västerbotten county council and Europe as whole, where STOPP/START is developed. The most frequent DRPs identified by STOPP were “hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon” (25.0 % of DRPs identified by STOPP) and “benzodiazepines” (14.7 % of DRPs identified by STOPP). In Västerbotten treatment guidelines, the first line treatment for sleep disturbances is zopiclone, and the second line treatment for anxiety is oxazepam (3). In STOPP, where zopiclone and benzodiazepines are classified as inappropriate drugs, the different guidelines are contradictory and contribute to more DRPs identified by STOPP/START than by the clinical pharmacists.

The most frequent DRP identified by START is “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” (20.5 % of DRPs identified by START). In Västerbottens treatment guidelines, it is stated that lipid lowering drugs generally has bad evidence in people > 80 years, and the guidelines refers further to the guidelines of The National Board of Health and Welfare for cardiac care respectively the prevention guidelines of European Society of Cardiology (3, 41, 42) The difference in recommendations between the guidelines may contribute to less prescription of statins in Västerbotten county council among people > 80 years, and thus to the difference found between the number of DRPs according to STOPP/START and according to clinical pharmacists regarding this criteria.

Another study on the same study population as in the present study, is the RCT mentioned in the introduction (20). In this population, 41 % of rehospitalizations were due to DRPs. Of the DRPs related to rehospitalizations, 45.5 % was occurred by adverse drug reactions, 17.5 % because of incorrect dose, 10.6 % because of non-adherence, and 6.9 % of drug interactions (20). Costs saved by the intervention has been calculated to 290 Euro per person during 180 days (43). Comparing this cost with cost saved by reviews by STOPP/START in a study population in people \geq 65 years, approximately 154 Euro in 180 days per person would be saved (44). Due to the differences in costs and the high prevalence of DRPs that STOPP/START not are able to identify, STOPP/START does

not seem to be a complete tool to detect DRPs in elderly people with dementia. However, STOPP/START could be a great tool if consideration to its weakness is given.

In the multivariate regression analysis, the only significant factor associated with number of DRPs according to both STOPP/START and the clinical pharmacists were number of drugs prescribed. In the study with the clinical pharmacists, stroke was also an associated factor (6). A previous study have shown that clinically relevant drug-drug interactions in the same study population also have number of drugs prescribed as an associated factor with DRPs (45). Considerably more interactions were identified by the clinical pharmacists than by STOPP/START. In addition, studies in other populations has shown that number of drugs prescribed is associated with DRPs (46-48). Since number of drugs prescribed seems to be a common associated factor with DRPs, different methods in more careful prescribing should be used in order to decrease number of DRPs.

After literature search in PubMed and according to the review of STOPP/START from 2016 (29), it was concluded that there are limited studies of STOPP/START in people with dementia.

5.3 Evaluation of the methods

In earlier studies, STOPP/START has only been investigated in elderly people in general, and not exclusively in elderly people with dementia. That only people with dementia or cognitive impairment was investigated in the study with STOPP/START makes the study unique and answer questions that have not been answered before.

In order to get a higher reliability of the method, all peoples' drug lists were double-checked with STOPP/START after the first review of all people. This method was used so no DRPs would be missed/different judgement would be performed after review of a lot of people.

One bias is lack of data of the people, which either can overestimate or underestimate the number of DRPs identified. One DRP according to START is for example "vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation". The reason the people is not prescribed anticoagulation can be due to dementia or high risk of bleeding. These reasons may not be available in the extract from the journals, and will therefore be registered as a DRP although there is a contraindication. In contrast, STOPP/START can fail to identify DRPs also because of lacking data of the person. Failing to identify DRPs can occur for example in a person with depression that should be prescribed non-tricyclic antidepressants (non-TCA), but the extract from the journal give no information about depression. Another bias because of lacking data of the people is that START criteria does not consider if the person already has tried the drug, regardless to the reason the person has stopped the treatment.

In the previous mentioned study with the communal pharmacists, the most common DRP was "no indication apparent" (2). This criteria was excluded in the present study because lacking data of the people. If this criteria had been included in the present study, the number of DRPs identified by STOPP/START had probably been higher.

5.4 Evaluation of STOPP/START

STOPP/START version 2 is, as mentioned in the introduction, revised from STOPP/START version 1 which was developed from an expert panel in UK and Ireland. Even though STOPP/START version 2 is revised by experts in 13 countries in Europe, the main part of the criteria is originally developed from guidelines in UK and Ireland (28). The guidelines differ between UK/Ireland and Sweden, as well as the guidelines differ even between regions in the same country. Even though 13 countries have been involved in revising STOPP/START, it is not possible to agree with all treatment guidelines from all countries in Europe. STOPP/START version 2 consists of 31 % more criteria compared with version 1 and are thereby able to identify more DRPs than version 1 (28). An idea to

make the guidelines more agreeable is to revise the guidelines in agreement with every region's guidelines. However, the revised guidelines may still need to be combined with other tools to identify higher proportion of DRPs.

STOPP/START is not specifically developed to people with dementia, only to elderly people in general. People with dementia and other co-morbidities generally requires more complex treatment, and because of a lot of DRPs, more disease specific tools must be developed to identify DRPs in elderly people with dementia.

STOPP/START is an explicit criteria and are thereby less time consuming than implicit criteria and would probably save a lot of time and costs compared with exclusively medication reviews by clinical pharmacists given the same DRPs were able to be identified. STOPP/START has been showed to decrease drug costs in elderly people due to less prescribed drugs (49). A problem is that neither STOPP/START nor other explicit criteria has been proved to identify the majority of DRPs identified by clinical pharmacists. Thus, STOPP/START criteria could be used as a complement to medication reviews by clinical pharmacists, since the result in the present study showed that different type of DRPs was identified with the different tools. By this method, money and health could possibly be saved due to less side effects and unnecessary/inappropriate drugs prescribed. A combination of explicit criteria and implicit criteria performed by clinical pharmacists seems like a good combination, since more DRPs probably would be identified, and the clinical pharmacists can do an individual assessment were deviation from the explicit criteria are necessary and customize to treatment guidelines in the specific country or region. However, this must be studied in order to investigate if this combination is advantageous.

Even though STOPP/START does not replace medication reviews by clinical pharmacists, the present study clearly shows a problem with DRPs in elderly people with dementia. More research and development of tools to prevent DRPs in people with dementia is necessary. To manage development of more effective tools, more comparative studies between DRPs identified by clinical pharmacists and explicit tools in people with dementia are necessary to detect which areas in identify DRPs that is missing in relation to DRPs identified by clinical pharmacists.

Alternative ways of improving tool detecting DRPs in people with dementia, is to combine STOPP/START with other tools, for example interaction systems, to be able to identify a greater proportion of the people DRPs. Another way is to combine several explicit tools. STOPP/START has, as mentioned in the introduction, been used together with Beers criteria were a higher proportion of DRPs was identified compared with only STOPP/START (30). Since STOPP/START is only a part of an overall picture of a person's DRPs, a possible alternative could be that clinical pharmacists use STOPP/START as a part a medication review, to make an individual assessment in connection with knowledge and current guidelines.

6. Conclusion

The prevalence of at least one DRP in elderly people with dementia according to STOPP/START was found to be 72.2 %. The number of DRPs identified by STOPP/START was quite equal to the number identified by clinical pharmacists. However, different types of DRPs was identified with the different methods.

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9. Appendix

9.1 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.
2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
3. 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

1. 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).
4. Beta blocker with bradycardia ($< 50/\text{min}$), type II heart block or complete heart block (risk of complete heart block, asystole).
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).
7. Loop diuretic for dependent ankle 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).
8. Thiazide diuretic with current significant hypokalaemia (i.e. serum $\text{K}^+ < 3.0 \text{ mmol/l}$), hyponatraemia (i.e. serum $\text{Na}^+ < 130 \text{ mmol/l}$) hypercalcaemia (i.e. corrected serum calcium $> 2.65 \text{ mmol/l}$) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)
9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people)
11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.
12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. $> 6.0 \text{ mmol/l}$ – serum K should be monitored regularly, i.e. at least every 6 months).
13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP $< 90 \text{ mmHg}$, or concurrent nitrate therapy for angina (risk of cardiovascular collapse)

Section C: Antiplatelet/Anticoagulant Drugs

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).
3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).

4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)
5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)
6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).
7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).
8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).
9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).
10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).
11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)

Section D: Central Nervous System and Psychotropic Drugs

1. TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
2. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).
3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenazine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
4. 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).
5. 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).
6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms)
7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),
8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
9. 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).
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
11. 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)

1. 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)

3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m² (risk of bleeding)

4. NSAID's if eGFR < 50 ml/min/1.73m² (risk of deterioration in renal function).

5. Colchicine if eGFR < 10 ml/min/1.73m² (risk of colchicine toxicity)

6. Metformin if eGFR < 30 ml/min/1.73m² (risk of lactic acidosis).

Section F: Gastrointestinal System

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).

2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).

3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).

4. 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

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).

2. 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).

3. 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).

4. 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

1. 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).

2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).

3. 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)

4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).

5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).

6. 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) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)
8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)
9. 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

1. 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).
2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)

Section J. Endocrine System

1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure)
3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).
5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
6. 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).
3. 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 ≥ 20 mmHg (risk of syncope, falls).
4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Section L: Analgesic Drugs

1. 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).
2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
3. 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)

9.2 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

1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
2. 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.
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
4. 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.
5. 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.
6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.
7. Beta-blocker with ischaemic heart disease.
8. Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.

Section B: Respiratory System

1. Regular inhaled b2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV₁ <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
3. 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

1. 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.
3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.
5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
6. 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

1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.
2. 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.

2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.
3. 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).
4. 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).
5. 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).
6. 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

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

Section G: Urogenital System

1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
2. 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

1. 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

9.3 Categorization of STOPP/START criteria

Dosage too high

STOPP: C1

Dosage too low

Ineffective/inappropriate drug

STOPP: B1, B2, B4, B5, B6, B7, B8, B9, B10, B11, B13, C2, C3, C7, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, D12, D14, E1, E2, E3, E4, E5, F1, F3, G1, G2, G3, G4, H1, H2, H3, H4, H5, H6, H7, H8, H9, I1, I2, J1, J2, J4, J5, J6, K1, K2, K3, K4, L1, L2, L3

Interaction

STOPP: B3, C10, C11

Monitoring need

STOPP: B12

Noncompliance

Transition error

Suspected adverse drug reaction

Unnecessary drug therapy

STOPP: A3, C4, C5, C6, C8, C9, D13, F4, N

Needs additional therapy

START: A1, A2, A3, A4, A5, A6, A7, A8, B1, B2, B3, C1, C2, C3, C4, C5, C6, D1, D2, E1, E2, E3, E4, E6, E7, G1, G2, G3, H1, H2

9.4 DRPs identified in different categories of STOPP/START

Table 6: DRPs identified by STOPP.

Categories of STOPP	Identified by STOPP (n = 224)*
A: Indication of medications	10 (4.5)
B: Cardiovascular system	11 (4.9)
C: Antiplatelet/Anticoagulant Drugs	2 (0.9)
D: Central Nervous System and Psychotropic Drugs	43 (19.2)
E: Renal system	3 (1.4)
F: Gastrointestinal system	-
G: Respiratory system	2 (0.9)
H: Musculoskeletal System	2 (0.9)
I: Urogenital System	7 (3.1)
J: Endocrine System	15 (6.7)
K: Drugs that predictably increase the risk of falls in older people	116 (51.8)
L: Analgesic Drugs	13 (5.8)
N: Antimuscarinic/Anticholinergic Drug Burden	-

DRPs = Drug related problems

Table 7: DRPs identified by START .

Categories of START	Identified by START (n = 132)*
A: Cardiovascular system	82 (62.1)
B: Respiratory system	1 (0.08)
C: Central Nervous System & Eyes	15 (11.4)
D: Gastrointestinal System	-
E: Musculoskeletal System	28 (21.2)
G: Urogenital System	-
H: Analgesics	6 (4.5)

DRPs = Drug related problems

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