

BMJ Open Importance of potentially inappropriate medications, number of chronic conditions and medications for the risk of hospitalisation in elderly in Sweden: a case-control study

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ABSTRACT

Objectives This study aimed to investigate the importance of potentially inappropriate medications, number of medications and chronic conditions for the risk of hospitalisation among an elderly population.

Design This is a case-control study.

Setting Population-based study in 2013 of all individuals aged 75 years and older (17 203) in the county of Blekinge in the southeast of Sweden.

Participants A total of 2941 individuals were included who had at least one hospitalisation to a medical, geriatric and palliative, or orthopaedic ward during 2013. From this total, 81 were excluded because of incomplete data or absence of controls. In total, 5720 patients were included and formed 2860 risk sets matched on age and gender.

Primary and secondary outcome measures Conditional logistic regression was used to analyse the odds for hospitalisation according to use of potentially inappropriate medication (PIM), number of chronic conditions and medicines using univariate and multivariate models. PIM was defined as long-acting benzodiazepines, tramadol, propiomazine and medicines with anticholinergic effect.

Results The univariate analysis for use of PIM showed a significant association with hospitalisation (OR 1.54, 95% CI 1.30 to 1.83). For the number of chronic conditions, the OR was increased and was significant from two or more chronic conditions, and for the number of medicines from the use of five or more medicines, in the univariate analysis. Use of PIM has no association with hospitalisation in the full model. The number of chronic conditions and medicines in the full models continued to have strong associations for hospitalisation, from five to seven chronic conditions (OR 1.86, 95% CI 1.49 to 2.33) and use of five to nine medicines (OR 1.46, 95% CI 1.21 to 1.77) at the same time.

Conclusion The number of chronic conditions and medications are important for the odds of hospitalisation, while the use of PIM, according to the definition used in this study, was no significant in the full model.

INTRODUCTION

The number of elderly people is rapidly increasing in the world. Better living conditions, advances in medical practice and

Strengths and limitations of this study

- Case-control study combining individual factors from two data sources for the population of a Swedish county.
- The study county had one medical record system for all care, both primary and secondary, which gives almost total coverage of information on diagnoses.
- Information on medication came from the county councils register on dispensed medicines for all inhabitants in Blekinge but use of 'over-the-counter' medications and information that the patients had actually taken the medicines were unknown.
- The interaction between number of chronic conditions and number of medications can lead to over-estimating the effect that the number of medications has on hospitalisation, compared with the number of chronic conditions.
- In this study, a limited list of potentially inappropriate medications, including long-acting benzodiazepines, tramadol, propiomazine and medicines with anticholinergic effect, was used.

drug development have all contributed to increased life expectancy. Estimations from demographic data indicates that 22% of the global population will be older than 65 by 2050.¹

With an ageing population, the use of medicines is increasing. Higher prevalence of multimorbidity as a result of longer life expectancy, advances in drug development and an increased specialisation of the medical profession are some explanations for this increase.² Multimorbidity, the coexistence of two or more chronic conditions at the same time in one person, is increasing with age and is one of the great challenges facing healthcare systems in the near future. It is associated with reduced quality of life, higher mortality, polypharmacy and high treatment burden.^{2,3} The development of new treatment opportunities,

both surgical and medical, has led to more complex treatment regimes. Polypharmacy is mostly defined as the use of five or more prescribed drugs at the same time. With polypharmacy, the risk of drug–drug interactions increases, and thereby the risk for adverse drug reaction (ADRs) and drug-related problems (DRPs) in elderly increases. The more complex the drug treatment, the more challenging it becomes to evaluate the risk–benefit ratio for treatments in elderly patients due to a lack of evidence. The knowledge about interactions are between medicines A and B, and there is very little existing knowledge about how medicine C interacts.⁴

Age-related physiological changes, higher proportion of fat in relation to body water or decreased renal function alter the pharmacokinetics and pharmacodynamics properties of medicines. Therefore, elderly people are more sensitive to certain medications and their effects, for example, drugs that are lipophilic or have a high renal clearance. Some drug treatments can therefore be potentially inappropriate in the elderly that are appropriate for younger or middle-aged patients.¹⁵

The term potentially inappropriate medication (PIM) is commonly used for these medications and is generally defined as medications that have side effects, that when used by older patients, outweigh the clinical benefits of the drug. Particularly when there are safer or more effective alternatives.⁶ The use of PIM in the elderly is associated with increased risk of ADRs. A majority of ADRs are type A reactions, which means that they originate from the pharmacological properties of the medication and are therefore predictable and preventable to a certain level.^{7–11} Many studies have analysed the risk of ADRs and DRPs in an elderly population and found that risk factors such as polypharmacy and use of PIM increase the risk.^{1 7 8 11 12} Polypharmacy is mostly defined as the use of five or more prescribed drugs at the same time and increases the risk of DRPs due to increased complexity of the medication treatment.⁴

ADRs can cause unplanned hospitalisations in elderly people, unnecessary suffering for patients and lead to larger costs for the healthcare system. It is estimated that about 10%–30% of all unplanned admissions for all ages are drug related and that the risk increases with age.^{7 8 11 12}

The cause of a drug-related hospitalisation is multifaceted and complex. There are several steps in the prescribing process where, for different reasons, it can go wrong and cause an ADR in a patient. Some of the most common causes are communication problems between the prescriber and the patient, knowledge gaps about medications and/or patient medical history.¹⁰

To reduce the risk of ADR in the elderly caused by PIM, different recommendations have been developed regarding PIM and how to handle them clinically. Some of the most used recommendations and definitions of PIM are Beers criteria and the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria.^{13 14} Sweden, among other countries, has made national recommendations to take country-specifics into

consideration regarding the definition of PIM. In the Swedish National Board of Health and Welfare's report 'Quality indicators for good drug therapy in elderly', the Swedish recommendations are specified. The indicators cover a range of different quality indicators for drug treatment in elderly. Some examples of indicators are medications not to use, inappropriate dosage and polypharmacy in the elderly. The indicator 'Medicines that should be avoided unless there are special reasons' is mostly defined as PIM in different quality criteria to evaluate medication use in elderly in Sweden.⁶

A large focus in recent years in Sweden has been on decreasing the use of PIM in order to prevent ADRs and DRP. Many county councils have different prescribing indicators to reduce the prescribing and use of different PIM. PIMs have been used as a proxy for decreasing drug-related morbidity and drug-caused hospitalisations in elderly. The aim of this study was to analyse the use of PIM, number of chronic conditions and number of medications as useable risk factors concerning hospitalisation. We analysed the association between use of PIM, number of chronic conditions and number of medications for unplanned hospitalisation in elderly patients.

METHODS

Study design

This study was a case–control study to analyse the use of PIM, number of chronic conditions and number of medications, and their association with unplanned hospitalisations in patients aged 75 years or older in Blekinge County, Sweden. The study was based on register data from both primary and secondary care in Blekinge County Council.

Setting

Blekinge is located in the south eastern corner of Sweden. It is one of the smallest counties in Sweden with only 152 315 inhabitants in 2013. We included individuals aged 75 or older that were registered to a primary care centre in Blekinge during 2013. In Sweden, almost all inhabitants are registered to a primary care centre. All primary care is funded by the county council through a specific county council tax. Both public (operated by the county council) and private care centres were included in the study. Nine (41%) of the primary care centres in Blekinge 2013 were private.

Study population

We included the first hospitalisation during 2013 to a medical, geriatric and palliative, or an orthopaedic ward for individuals 75 years and older in Blekinge County. Each case was matched to a control 1:1 in the population by age (birth year) and gender. Each matched case and control formed a risk set. The date of the first unplanned hospitalisation for each case was set to be the index date for each risk set.

Potential inappropriate medication

PIM was identified according to the Swedish National Board of Health and Welfare's report 'Quality indicators

for good drug therapy in elderly'.⁶ The purpose of the indicators is to facilitate the follow-up of medical treatment. We used the indicator 1.1, 'Medicines that should be avoided unless there are special reasons'. As the name states, it is medicines that should be avoided in patients, 75 years and older, unless there are special reasons because of the higher risk of side effects. If prescribed, the prescriber should have a well-founded indication, and the treatment should be evaluated in regular intervals. This indicator has been used in the past few years in both national and local quality indicators in Sweden for drug treatment in elderly. The following drug groups and substances are included in the definition in the 2010 version of 'Medicines that should be avoided unless there are special reasons': long-acting benzodiazepines, tramadol, propiomazine and medicines with anticholinergic effect (table 1). The proportion of patients using them should be low. All mentioned medications have well-known side effects in the elderly due to age-related physiological changes. Among others, they can result in side effects such as day-fatigue, confusion or impaired balance.⁶

Number of chronic conditions

To measure multimorbidity, we used a method developed by Calderón-Larrañaga *et al* at the Ageing Research Centre in Stockholm.³ They analysed the full list of diagnoses classified by International Classification of Diseases version 10 (ICD-10) codes on a four-digit level to define if a diagnosis is chronic or not in an elderly population. To determine if a condition is chronic or not, the following key features were identified and discussed concerning their pertinence and suitability in older populations: duration, course, reversibility, treatment and consequences. They were then grouped into 60 groups of chronic conditions. We applied their definition and list on chronic conditions to estimate the multimorbidity in the study population.³ Multimorbidity was then estimated by counting the number of chronic conditions in each patient. All information about diagnoses for a 2-year period (2011–2012) was obtained from the electronic medical record database from the county council in Blekinge. Diagnoses from both primary and secondary care centres were included. Five intervals were then created for the number of chronic conditions (no chronic conditions, one, two to four, five to seven, and eight or more) for the statistical analyses.

Use of medications

Information about the use of prescribed dispensed medicines was obtained from the county councils register on dispensed medicines for all inhabitants in Blekinge, which was received from the Swedish eHealth Agency. The register contains the same data on prescribed medicines as the Prescribed Drug Register at the Swedish National Board of Health and Welfare, a national register with patient level data on all dispensed prescriptions. However, the coverage is restricted to the residents in the

Table 1 Potential inappropriate medication according to Swedish National Board of Health and Welfare's definition 2010

Groups	Substance	ATC code
Long-acting benzodiazepines	Diazepam	N05BA01
	Nitrazepam	N05CD02
	Flunitrazepam	N05CD03
Tramadol	Tramadol	N02A×02
Propiomazine	Propiomazine	N05CM06
Drugs with anticholinergic effect	Glycopyrronium bromide	A03AB02
	Atropine	A03BA01
	Hyoscyamine	A03BA03
	Butyl scopolamine	A03BB01
	Methyl scopolamine	A03BB03
	Scopolamine	A04AD01
	Disopyramide	C01BA03
	Oxybutynin	G04BD04
	Tolterodine	G04BD07
	Solifenacin	G04BD08
	Darifenacin	G04BD10
	Fesoterodine	G04BD11
	Morphine and spasmolytic	N02AG01
	Ketobemidone and spasmolytic	N02AG02
	Trihexyphenidyl	N04AA01
	Biperiden	N04AA02
	Levomepromazine	N05AA02
	Chlorprothixene	N05AF03
	Clozapine	N05AH02
	Hydroxyzine	N05BB01
	Clomipramine	N06AA04
	Amitriptyline	N06AA09
	Nortriptyline	N06AA10
	Maprotiline	N06AA21
	Dimenhydrinate	R06AA02
	Dexchlorpheniramine	R06AB02
Chlorpheniramine	R06AB04	
Alimemazine	R06AD01	
Promethazine	R06AD02	
Promethazine combinations	R06AD52	
Cyproheptadine	R06A×02	

ATC, anatomical therapeutic and chemical.

county. The register does not contain information on use of 'over-the-counter' medications or illicit medication use.¹⁵

In Sweden, prescribed medicines are generally prescribed for a 3-month period within the high cost threshold for medicines. Therefore, a 3-month period was used to construct a virtual medicine list on prescribed

collected medicines. The date a case was admitted to hospital was the index date for each risk set (matched case and control). If the same drug was dispensed more than once, it was counted only once. Since the county councils register of dispensed medicines does not contain the dose text, we used defined daily dose (DDD) to calculate the duration of the drug exposure for every individual. We assumed 0.9 DDD for regularly used medicines based on calculations for regularly used medicines in an elderly population.¹⁶ Medicines were classified according to the anatomical therapeutic and chemical (ATC) system.¹⁷ From the constructed medication list, the number of medicines and use of PIM according to the stated definition was calculated on each index date. For the statistical analysis, the number of medicines was categorised into five intervals (no medication, 1 to 4, 5 to 9, 10 to 14, and 15 or more) based on definition for polypharmacy.⁴

Statistical analysis

Descriptive demographic statistics and analyses were made with cross-tabulations and χ^2 test. A p value < 0.05 was considered statistically significant. Test of trend was used to analyse use of PIM according to the number of chronic conditions and number of medications.¹⁸ To analyse the OR for the hospitalisation in patients, we used conditional logistic regression and we created five different models to analyse the importance of the outcome variables. Models A to C were univariate analyses for each included variable; model D adjusted for the number of chronic conditions; model E adjusted for the number of chronic conditions and number of medicines. The results are presented as OR with 95% CI. All statistical analyses were performed with STATA V.14 (Stata Corporation, Texas, USA).

Ethical considerations

Data in the present study are based on anonymised information provided by the County Council of Blekinge. They provided anonymised information for research purposes once the study had been vetted and approved by the Regional Ethical Review Board according to Swedish ethical review regulations. Due to the requirement of anonymised data, each individual could not be asked for consent to participate; active refusal of participation was instead applied. This was done by publishing information about the planned study in the Swedish local newspapers 'Sydöstran' and 'Blekinge Läns Tidning'. The advertisement outlined the study and contained information on how to contact the data extractor in Blekinge County Council by phone, email or mail in order to opt out of the study. The data manager was then responsible for ensuring that those who opted out were excluded before any data were delivered to the research manager (first author).

Patient and public involvement

There was no patient or public involvement in the development or the conducting of the study. The results are being presented at a public defence as a part of a doctoral thesis.

RESULTS

There were 2941 patients with at least one hospitalisation to a medical, geriatric and palliative, or orthopaedic ward during 2013 and 2860 of these patients were included in the study. Of 81 cases excluded, 78 were excluded because of incomplete data and 3 because of absence of controls. In total, 5720 individuals were included and formed 2860 risk sets. There were 3314 (58%) women and 2406 (42%) men, with a mean age of 84 years. The mean age in women was 85 years, and in men, it was 83 years. In 87% of the cases, the patients were admitted to a medical ward, 13% to an orthopaedic ward and only 14 patients (0.49%) to the geriatric and palliative ward. In the descriptive analysis, age was categorised into four groups: 75–<80, 80–<85, 85–<90 and ≥ 90 (table 2). The χ^2 test shows that there is a significant difference between controls and cases in the number of chronic diagnoses and number of medicines. Use of PIM was increasing with the increase of the number of chronic conditions but not as much as with increasing the number of medicines (table 3). In the univariate analysis of hospitalisation during use of PIM, the OR was 1.54 (95% CI 1.30 to 1.83) (table 4). In the univariate analysis for the number of chronic conditions, the OR was significant from two to four chronic conditions (OR 1.27, 95% CI 1.04 to 1.56) and then continued to increase. The number of medicines has the strongest association for hospitalisation in the univariate analysis and the OR increased exponentially for each interval of the number of medicines 5 to 9 medicines (OR 1.86, 95% CI 1.55 to 2.90), 10 to 14 medicines (OR 3.10, 95% CI 2.44 to 3.93), ≥ 15 medicines (OR 6.93, 95% CI 4.25 to 11 to 30). When the number of chronic conditions was added to the model, the association for hospitalisation during use of PIM decreased to OR 1.39, 95% CI 1.16 to 1.66. For the number of chronic conditions, the association was significant from two to four chronic conditions (OR 1.26, 95% CI 1.03 to 1.54) and was doubled for five to seven chronic conditions (OR 2.30, 95% CI 1.86 to 2.85) and for greater than or equal to eight chronic conditions (OR 3.94, 95% CI 3.08 to 5.04). In the full model, the use of PIM was not significant. The number of chronic conditions was significant from five to seven chronic conditions (OR 1.86, 95% CI 1.49 to 2.33) and for greater than or equal to eight chronic conditions (OR 2.70, 95% CI 2.08 to 3.51). The strongest association for hospitalisation in the full model was the number of medicines. For five to nine medicines used at the same time, the OR was doubled for each interval of the number of medicines; five to nine medicines; OR 1.86 (CI 95% 1.55 to 2.90). Ten to 14 medicines, OR 3.10 (95% CI 2.44 to 3.93). Fifteen and more medicines, OR 6.93 (95% CI 4.25 to 11 to 30).

DISCUSSION

The number of chronic conditions and medicines had the strongest association to hospitalisation in elderly patients in this study. Use of PIM, as defined here, was

Table 2 Descriptive table of the study population

Variables	Category	Control (%)	Case (%)	Total (%)	P value
	Total	2860	2860	5720	
Age	75–<80	738 (27.38)	738 (27.38)	1476 (25.80)	
	80–<85	831 (29.06)	831 (29.06)	1662 (29.06)	
	85–<90	711 (24.86)	711 (24.86)	1422 (24.86)	
	≥90	580 (20.28)	580 (20.28)	1160 (20.28)	
Gender	Male	1657 (57.94)	1657 (57.94)	3314 (57.94)	
	Female	1203 (42.06)	1203 (42.06)	2406 (42.06)	
Use of PIM	No use of PIM	2618 (91.54)	2503 (87.52)	5121 (89.53)	
	Use of PIM	242 (8.46)	357 (12.48)	599 (10.47)	0.001
Chronic conditions, n	0	324 (11.33)	195 (6.82)	519 (9.07)	
	1	408 (14.27)	278 (9.72)	686 (11.99)	
	2–4	1285 (44.93)	986 (34.48)	2271 (39.70)	
	5–7	619 (21.64)	865 (30.24)	1484 (25.94)	
	≥8	224 (7.83)	536 (18.74)	760 (13.29)	0.001
Medicines, n	0	422 (14.76)	290 (10.14)	712 (12.45)	
	1–4	1348 (47.13)	917 (32.06)	2265 (39.60)	
	5–9	896 (31.33)	1157 (40.45)	2053 (35.89)	
	10–14	172 (6.01)	390 (13.64)	562 (9.83)	
	≥15	22 (0.77)	106 (3.71)	128 (2.24)	0.001

PIM, potential inappropriate medicine.

non-significant for hospitalisation in the full model with the number of chronic conditions and number of medicines. However, use of PIM was associated with increased number of chronic conditions, and to a higher degree, an increased number of medicines. The association to hospitalisation for number of chronic conditions and

number of medicines was increased from five or more for both variables. The findings from this study indicate that the focus has to shift from only deprescribing of PIM to more optimisation of the medicine treatment, including care optimisation in each individual patient according to the number of chronic conditions and treatment phase (preventive, curative or palliative treatment).

Table 3 Descriptive analyses of the use of potentially inappropriate medicine, number of chronic conditions and number of medicines.

Variables	Total number	Use of PIM (%)	P for trend
Chronic conditions, n			
0	519	34 (6.55)	
1	686	63 (9.18)	
2–4	2271	196 (8.63)	
5–7	1484	185 (12.47)	
≥8	760	121 (15.92)	<0.001
Drugs, n			
0	712	0 (0)	
1–4	2265	130 (5.74)	
5–9	2053	266 (12.96)	
10–14	562	151 (26.87)	
≥15	128	52 (40.63)	<0.001

PIM, potential inappropriate medicine.

Strengths and limitations

Previous studies have found that the use of PIM is a risk factor for hospitalisation.^{19–21} Our results show a more complex picture where the number of chronic conditions and the number of medicines have a large share. This can be due to the definition of PIM used in this study that differs from some of them in PRISCUS list, Beers' and the STOPP criteria.^{22–24} Our definition from the Swedish National Board of Health and Welfare is stricter in its definition and includes fewer drugs and drug classes than the other definitions.⁶ For example, we do not include non-steroidal anti-inflammatory drug (NSAID) or cardiovascular drugs except for disopyramide. Our definition of PIM is commonly used in Sweden as an indicator for quality of drug treatment in elderly, both nationally and by local councils and is therefore relevant in this setting. This means that our results cannot be directly translated to other settings where the definition is wider.

The information on medicines in the study was register data from the county councils register that includes prescribed and pharmacy dispensed medicines for all

Table 4 OR of hospitalisation, model A to C, are univariate analyses, model D includes PIM and number of chronic conditions and model E includes PIM, number of chronic conditions and number of medicines

Variables	Model A OR (95% CI)	Model B OR (95% CI)	Model C (95% CI) ³	Model D OR (95% CI)	Model E OR (95% CI)
No use of PIM	1			1	
Use of PIM	1.54 (1.30 to 1.83)*			1.39 (1.16 to 1.66)*	1.09 (0.90 to 1.33)
Chronic conditions, n					
0		1		1	1
1		1.12 (0.88 to 1.42)		1.11 (0.88 to 1.41)	1.09 (0.86 to 1.39)
2–4		1.27 (1.04 to 1.56)*		1.26 (1.03 to 1.54)*	1.15 (0.93 to 1.41)
5–7		2.35 (1.90 to 2.90)*		2.30 (1.86 to 2.85)*	1.86 (1.49 to 2.33)*
≥8		4.06 (3.18 to 5.19)*		3.94 (3.08 to 5.04)*	2.70 (2.08 to 3.51)*
Medicines, n					
0			1		1
1–4			0.99 (0.82 to 1.18)		0.89 (0.74 to 1.08)
5–9			1.86 (1.55 to 2.22)*		1.46 (1.21 to 1.77)*
10–14			3.10 (2.44 to 3.93)*		2.05 (1.59 to 2.66)*
≥15			6.93 (4.25 to 11.30)*		3.84 (2.30 to 6.44)*

*Significant.

PIM, potential inappropriate medicine.

the inhabitants in Blekinge. We were not able to assess the use of illegal drugs or over-the-counter drugs in this study. Data from the Medical Products Agency indicate that 11% of the Swedish population bought prescription drugs from non-approved pharmacies during 2011.²⁵ By constructing a medicine list on collected prescribed drugs from the index date of hospitalisation and 3 months back for each risk set, it has allowed us to determine as close as possible to what the patient was likely to be using. On the other hand, there is a possibility that we are missing medications used as needed because they are collected more rarely than every 3 months. We were also unable to take compliance into consideration when determining use of PIM.

Multimorbidity in the study population was measured by the number of chronic conditions and is dependent on the quality of registration of the diagnoses.³ The recording of diagnoses in this study has not been validated. During 2013, Blekinge did not use any multimorbidity measurement method for reimbursement in healthcare, and therefore, the risk of up-coding in diagnoses is low. It is more likely that there was an under-registration. We used registered diagnoses from a 2-year period and from both primary and secondary care centres to get as close to total coverage as possible. Another Swedish study has found that 75% of the total population in Blekinge County had at least one diagnosis registered during a 3-year period in primary care.²⁶ The time gap between the collection of diagnoses (2011–2012) and when the index date accrues for each risk set (2013) means there is a risk for underestimating the number of chronic conditions. For example,

if a risk set had index date in the last 2 months of 2013, there is almost a year gap between the index date and the date of collection of diagnoses.

Other multimorbidity estimates are constructed by giving different diagnoses a weight to how much the diagnosis contributed to need of care or cost.²⁷ In our definition of chronic conditions, all diagnoses contribute the same to the morbidity burden and are more an expression of the complexity of care in the patient than need of care.

The cases in this study had a higher prevalence of number of chronic conditions and number of medications than the controls. Therefore, we cannot exclude the presence of selection bias in our study. Confounding by indication may be present in our study, although we only include use of PIM, number of medicines and number of chronic conditions. Number of medications can be a confounder for specific medications that cause hospitalisation. They can also cover the effect by PIM since PIM is included in number of medications.

There is also an interaction between number of chronic conditions and use of medications. With the increase of number of chronic conditions in a patient come further increase in medication use. The risk that one of these medications is then a PIM increases. This can lead to overestimating the effect of the number of medications on the outcome.

This study does not include information on the patient's socioeconomic status. Socioeconomic factors such as educational level or income level are known risk factors for morbidity and increased use of medication.²

A low educational level is often related to an increased use of medications and inappropriate drug use also in the elderly.^{28 29} The absence of adjustment for educational level or income level in this study is a limitation.

Blekinge County is a small county in Sweden both in terms of population and area and has a relatively simply organised healthcare service, which makes it easy to include data from primary care, both public and private, and secondary care centres. Our results are applicable to elderly populations in similar settings.

Implications for clinical practice

Our results are interesting since other studies have shown that use of PIM increases the risk for hospitalisation.^{19–21} However, our results indicate that number of medications and number of chronic conditions are better predictors for hospitalisations in elderly than the use of PIM. With increasing number of medicines and, to a lesser degree, the number of chronic conditions, the chance of having a PIM prescribed or a drug–drug interaction increases and is a known risk factor for ADEs and DRP.^{5 30 31} And with increasing age and multimorbidity, the prevalence of polypharmacy increases.² The risk–benefit ratio for treatment becomes more complex to evaluate, and physiological changes that affect pharmacokinetics and pharmacodynamics can appear fast in an elderly patient.^{1 32} The result of increasing risk of hospitalisation with increasing number of medicines and chronic conditions is confirmation of this.

Previous studies have also shown that patients with chronic diseases and with low continuity of care use more out-of-hours primary care than other patients.^{33 34} Causes for polypharmacy and inappropriate prescribing are many, for example, number of prescribers, communication failures and knowledge gaps at the prescriber level about the patient or the medication.^{10 35} For number of medications, polypharmacy can cover many other risk factors, such as underuse or overuse and inappropriate prescribing in elderly according to Kujipers *et al.*³⁶ They showed that patients with polypharmacy (defined as using four or more medications) were undertreated in 42.9% of cases compared with those receiving fewer medicines (13.5%). The theory is that fear of causing ADEs is contributing to underprescribing by prescribers in patients with polypharmacy.³²

The most common drugs causing ADEs are drugs that have well-documented positive effects on reducing risk of morbidity and mortality in elderly. The most common drugs causing ADEs are antiplatelet, anticoagulants, diuretics, NSAIDs, antidepressants and antibacterial preparations for systemic use.^{37 38} This is not surprising as all mentioned drugs are potent with a good effect in preventing morbidity when used with the right patient, at the right time and at the right dosage. However, when used inappropriately, they can cause ADEs, especially in the elderly due to their frailty.^{8 12} The majority of these drugs are not included in the definition of PIM used here. Together with our results, this indicates that deprescribing

PIM in the elderly has to be supplemented with systematic methods for evaluating the whole medical treatment in the individual to reduce the risk for hospitalisation.

New approaches are needed to improve quality of drug treatment in the elderly and possibly coordination with other care interventions. Our results indicate that the healthcare system needs to improve the care of patients with multimorbidity, polypharmacy and use of PIM. The term appropriate polypharmacy needs to be embraced and in clinical practice it is defined as evidence-based prescribing and medicine optimisation. What it means is that when choosing treatment, the dosages are adjusted to the patient's physiological conditions.³²

However, only using number of medicines as an indicator for the assessment of drug-related problems has been shown to have limited value in clinical practice.⁴ When combining number of medications, number of chronic morbidities and use of medications with high risk of ADE, the clinical advantage increases. Different methods have been tested to improve drug treatment in elderly. Implementing the STOPP criteria in a hospital setting reduced the number of ADE in a study from Cork University Hospital.³⁹ The STOPP criteria are wider in its definition for PIM than in this study. The STOPP criteria are a collection of indicators to detect and stop potentially inappropriate prescribing. The complete collection of quality criteria in “Quality indicators for good drug therapy in elderly” can be used in the same way.⁶ However, evaluating the effect is more complex than measuring the use of PIM when evaluating quality of care in the elderly on a population level. There are several studies showing that using a systematic method, such as medication review, in multiprofessional teams reduces the prevalence of potentially inappropriate prescribing, the use of PIM and medication cost. It is a method developed not to focus on specific risk medication but a systematic approach to optimise a patient's medical treatment as a whole; diagnoses, medicines and patient's physical conditions, for example, kidney function.^{40–42} The method is more complex to evaluate on a population level, but the clinical effect is greater.

When developing new indicators for evaluating quality of medication use in elderly, our results strongly indicate that focus should shift from only deprescribing PIM to include total medicine optimisation for each individual.

Future research

There are many studies done on the topic of pharmaceutical review or information interventions to improve pharmaceutical care in elderly.^{40 41 43} A new structure needs to be established around the elderly with multimorbidity and/or polypharmacy to improve the pharmacology care. Polypharmacy is a large risk factor for ADE and hospitalisations. However, to find patients in need for a medical review before an ADE, multimorbidity also needs to be considered. More focus needs to be on the appropriate drug treatment in relation to the individual patient, instead of potentially inappropriate treatment in general.

Future healthcare systems need to step up the care for the elderly to be able to handle the challenges of a complex drug treatment in a patient with multimorbidity. Future research needs to investigate different models to manage the complexity that surrounds the elderly patient. For example, analysing multiple interventions that one-by-one have little impact on the risk but together can increase the quality of drug treatment.

CONCLUSION

The number of medications and the number of chronic conditions are strong risk factors for hospitalisation. PIMs (defined as long-acting benzodiazepines, medications with anticholinergic effect, tramadol and propiomazine) do not have an increased OR for hospitalisation in relation to the number of chronic conditions and number of medications. This study confirms what previous studies have found, that there are multiple causes to ADEs and drug-related hospitalisations. Focus must shift from only deprescribing PIM to evidence-based prescribing and medicine optimisation in patients with use of PIM, polypharmacy and high multimorbidity. The healthcare structure needs to support implementation of methods that facilitate follow-up of drug treatments in the elderly more frequently and gives the healthcare personnel the right conditions.

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