Wien Klin Wochenschr (2008) 120: 733–741
DOI 10.1007/s00508-008-1089-z
Printed in Austria

Wiener klinische Wochenschrift
The Middle European Journal of Medicine

Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria

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Received February 28, 2008, accepted after revision September 1, 2008

Polypharmakotherapie und unangemessene Verschreibung bei älteren internistischen Patienten in Österreich

Zusammenfassung. *Ziele der Studie:* 1. Bestimmung der Prävalenz von Polypharmakotherapie und unangemessenem Arzneimittelgebrauch bei älteren internistischen Patienten in Österreich; 2. Einschätzung deren Bedeutung für das Auftreten von unerwünschten Arzneimittelwirkungen; 3. Suche nach Prädiktoren für das Auftreten von unerwünschten Arzneimittelwirkungen bei einer älteren Patientenpopulation.

Methodik: In einer monozentrischen Kohortenstudie wurden über 3 Monate alle neu aufgenommenen Patienten ≥75 Jahren eingeschlossen. Die Aufnahmemedikation wurde durch ein multidisziplinäres Team bestehend aus Krankenhausapothekern und Internisten auf ihre angemessene Anwendung hin analysiert und überprüft, ob eine unerwünschte Arzneimittelwirkung aufgetreten war.

Ergebnisse: Es wurden insgesamt 543 Patienten analysiert (Altersmedian 82 Jahre, 60,2% Frauen). Die mittlere Medikamentenanzahl bei Aufnahme betrug 7,5 ± 3,8. Frauen nahmen signifikant mehr Medikamente ein als Männer (7,8 vs. 6,8, p = 0,013). 58,4% der Patienten erfüllten das gewählte Kriterium für Polypharmakotherapie (>6 Medikamente). Folgende Faktoren waren mit Polypharmakotherapie assoziiert: weibliches Geschlecht, Pflegebedürftigkeit, hohe Anzahl an Entlassungsdiagnosen und ein hoher Punktwert auf der Charlson Komorbiditäts-Skala. Verzichtbare Medikamente wurden bei 36,3% aller Patienten gefunden, Medikamente, die für alte Menschen inadäquat sind, bei 30,1%, Doppelverordnungen bei 7,6%, Fehldosierungen bei 23,4% und potenzielle Medikamenteninteraktionen bei 65,8%. Unerwünschte Arzneimittelwirkungen wurden bei 97/543 Patienten gefunden (17,8%). In 56,7% der Fälle war die unerwünschte Arzneimittelwirkung Grund für die stationäre Aufnahme und bei 18,7% war eine Arzneimittelinteraktion sehr wahrscheinlich an der Entstehung beteiligt. Risikofaktoren für unerwünschte Arzneimittelwirkungen waren weibliches Geschlecht, Polymorbidität, Niereninsuffizienz und unangemessener Arzneimittelverordnung.

Schlussfolgerung: Polypharmakotherapie, unangemessene Verschreibung und unerwünschte Arzneimittelwirkungen sind bei älteren internistischen Patienten in dem untersuchten österreichischen Zentrum vergleichbar häufig wie in anderen westlichen Ländern. Zur Verbesserung der Arzneimittelsicherheit bei dieser Hochrisikogruppe erscheint uns eine bessere Verschreibungsqualität bedeutsamer als eine Verminderung der Medikamentenanzahl.

Summary. *Objective:* The aim of the study was to assess the prevalence of polypharmacy and inappropriate drug use in elderly internal-medicine patients in one Austrian center and to define the impact of these and other identified predictors on the occurrence of adverse drug events.

Methods: All patients ≥75 years admitted to selected internal wards of a university hospital were included in a monocentric prospective cohort study over a period of three months. The pre-admission medication of the patients was analyzed with respect to appropriateness by a multidisciplinary team consisting of pharmacists and physicians trained in internal medicine. The medication was evaluated for the occurrence of adverse drug events.

Results: A total of 543 patients were analyzed (median age 82 years; 60.2% female). The mean number of drugs taken was 7.5 ± 3.8, with women taking significantly more drugs than men (7.8 vs. 6.8, $P = 0.013$). Overall, 58.4% of the patients fulfilled the given criteria for polypharmacy (>6 drugs). The following factors were associated with polypharmacy: female sex, need for

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nursing care, high number of discharge diagnoses and high Charlson comorbidity score. Unnecessary drugs were found prescribed in 36.3% of all patients, drugs to avoid (Beers criteria) in 30.1%, duplication in 7.6%, wrong dosage in 23.4% and possible drug-drug interactions in 65.8%. Adverse drug events were identified in 17.8% of the patients (97/543), among whom the adverse drug event was the reason for hospital admission in 56.7% of the cases and a drug-drug interaction was involved in 18.7%. Risk factors for adverse drug events were female sex, polymorbidity, renal dysfunction and inappropriate prescribing.

Conclusion: Polypharmacy, inappropriate prescribing and adverse drug events were highly prevalent in a cohort of elderly internal-medicine patients in Austria. To improve drug safety in this high-risk population, appropriate prescribing might be more important than simply reducing the number of prescribed drugs.

Key words: Polypharmacy, inappropriate prescribing, elderly, adverse drug events, Austria.

Introduction

Previous studies have shown that inappropriate medication, low adherence to medication regimes and errors in monitoring lead to adverse drug events (ADEs), significant morbidity and mortality, and increased costs [1–3].

"Appropriate medication" refers to good quality prescriptions; "inappropriateness" is defined as drug usage that poses more risk than benefit to a patient [4]. Inappropriateness includes *underprescription* (withholding) of needed drugs, *overprescription* of drugs that are not needed or simply the use of too many drugs (Polypharmacy), and *misprescription*, which consists of wrong dosages, duplication, prescription of drugs that might provoke severe interactions, and the use of drugs that should be avoided [4].

The elderly are at particular risk for inappropriate prescribing. Because of the increasing incidence of chronic diseases in older persons, polypharmacy is highly prevalent in this population [4, 5]. The use of multiple drugs increases the risk of inappropriate prescribing and significantly lowers adherence to drug regimes [2, 6]. The physiologic changes in pharmacokinetics and pharmacodynamics in old age often go together with polypharmacy and contribute to a 2–3-fold higher risk of ADEs in the elderly [7, 8].

In Austria, people of 75 years of age or older account for 8% of the total population and it is estimated that this percentage will increase to 14% by 2050 [9]. Thus, drug-related problems will be of increasing significance in clinical practice.

The prevalence and reasons for polypharmacy and inappropriate drug use and the impact of these on ADEs in the elderly have not been previously evaluated in Austria. We therefore conducted this monocentric cohort study to analyze the prevalence of and predictors for polypharmacy and inappropriate drug use and their clinical impact in medical patients ≥75 years of age.

Patients, materials and methods

Subjects and data

All patients aged ≥75 years newly admitted to the departments of gastroenterology and cardiology at the Paracelsus Medical University Salzburg were eligible for the study and were screened over a period of three months (20.2.–15.5.2007). Most acute medical admissions at our hospital are transferred to these two departments, which comprise seven wards with 166 internal beds and one intensive care unit with 13 beds. We did not include patients with known neoplasia, because they are looked after in the oncology/hematology department, which did not participate in the study.

Patients were identified from the admission books by two trained study nurses on the wards every day. Demographic (age, sex), clinical (height, weight, reason for admission) and social data, as well as patients' medication and laboratory results (serum creatinine, hemoglobin, sodium, potassium, bilirubin, ALAT, INR, TSH) were collected from the medical charts and entered on a standardized case report form. To assess patients' cognitive abilities and the need for nursing care, the study nurses interviewed the patients themselves, or their care givers, and the medical staff.

All data were checked by a physician (TM) for plausibility and then entered on an Excel™ data sheet. After discharge, data on the duration of hospital stay, the final diagnoses and discharge medication were added.

Definitions

Number of drugs and category: Medication on admission and at discharge was checked for the active components. Drugs without a systemic action (e.g. artificial tear fluid) or drugs not taken at regular intervals during the two weeks before admission were excluded from the analysis. We did not ask about over-the-counter drugs because patients' knowledge and statements regarding these drugs appeared to be inconsistent. In addition to the total number of drugs, we classified the medication into 20 categories for better evaluation: ACE inhibitors, diuretics, betablockers, cardiac glycosides, amiodarone, statins, non-opioid analgesics, opioid analgesics, antiplatelet drugs, oral anticoagulants, antidepressants or antipsychotic drugs, benzodiazepines, anti-parkinson drugs, carbamazepine or gabapentin, proton-pump inhibitors, allopurinol, levothyroxine, pentoxiphylline or ginkgo biloba, antidiabetic drugs, and bisphosphonates.

Polypharmacy: There is no accepted definition for polypharmacy. We chose >6 drugs as a cut off, in accordance with a recent North American study where the risk for inappropriate medication increased greatly at this threshold [5].

Unnecessary drugs: Several drugs with no proven or controversial benefit in long-term therapy were defined as unnecessary, according to well established data on national drug prescription [10]. These unnecessary drugs included ginkgo biloba and peripheral vasodilators such as pentoxiphylline for the treatment of dementia, β-adrenergic agents for elevating blood pressure or allopurinol in patients without a history of gout or excessively elevated uric acid (see supplementary Appendix 1 available at http://dx.doi.org/10.1007/s00508-008-1089-z).

Drugs to avoid: For this study, we used a modified Beers list as reference for drugs to avoid. This consensus-based list names several drugs that are inadequate in older adults in general or in specific conditions because of the existence of safer alternatives [11]. For example, amitriptyline and doxepin are not recommended as antidepressants because of their anticholinergic properties, fluoxetine should not be administered on a daily basis because of its long half-life and excessive CNS stimulation, and ferrous sulfate should not be given in

high doses (>325 mg/d) as it induces constipation. We modified the Beers list by accepting amiodarone and doxazosin as adequate drugs for elderly patients, whereas unlisted benzodiazepines such as flunitrazepam and bromazepam were considered to be inadequate because of their long half lives (see supplementary Appendix 2).

Duplication: The use of two or more medications of the same class, such as multiple laxatives or multiple benzodiazepines, was counted as drug duplication.

Wrong dosage: We screened every individual medication for significant dosage errors. Of special interest was the correct adaptation of dose to body weight and renal function: spironolactone > 50 mg or allopurinol > 100 mg in patients with renal failure (serum creatinine > 2 mg/dl), amiodarone > 100 mg in patients with body weight < 65 kg, high dose NSAID therapy (e.g. diclofenac > 150 mg/d) or high dose proton-pump inhibitor therapy without clear indication (pantoprazole or omeprazole > 20 mg/d) were considered as overdosed.

Adverse drug events: ADEs were recorded from the reports of the treating physicians or nurses, or by an active search in the charts (study nurses) and by checking all discharge letters (physicians in the study group: JS, EP). The given clinical information was screened for suspicious symptoms for ADEs (see supplementary Appendix 3). Laboratory results were routinely checked for electrolyte imbalances, elevated renal and liver enzymes and irregular TSH or coagulation values. Glycoside levels were not routinely tested, only in the case of suspected intoxication. QT prolongations were detected only when they were described in the final medical report.

All suspicious events were assessed, following well established criteria, by one of three physicians specialized in internal medicine (EP, TM, JS) [12]. The causality was assessed as certain, probable/likely, possible, unlikely or unclassified. Only the first three categories were included in the analysis. To assess the clinical relevance, every ADE was categorized as either (a) an accompanying event, when the ADE was not the reason for admission, or (b) leading to hospital admission, when the ADE was causative for the admission. ADEs were not analyzed further, except for screening drug-drug interactions.

Drug interactions: The drug portfolio of each patient was screened for potential drug-drug interactions (CD, WB). All known pharmacokinetic and pharmacodynamic interactions of moderate-to-severe clinical relevance were counted by the pharmacists, using a commercial database as the primary reference for the assessment. Medis© software [13] lists all available drugs in Austria with their known ADEs and drug-drug interactions and is based on the information on drug-drug interactions in the ABDA© database, which is mainly based on journals and books [14].

The study group published a small pocket booklet for practical use, where the most common and relevant drug interactions are shown in tables. The booklet was handed out to all physicians in the two participating departments as a bedside reference. Two pharmaceutical textbooks [15, 16] were used as references for the booklet and any uncertainties were clarified through open discussion and consensus among the members of the study group.

All detected ADEs were screened for causative drug interactions. If a causality was plausible (e.g. hyperkalemia in combined therapy with spironolactone and ACE inhibitors), it was simply postulated, because there is no practicable methodology for proof at the present time.

Health status: The individual health status of the patients was characterized from the number of discharge diagnoses and the Charlson comorbidity score (range 0–34), a score based on 18 chronic diseases [17].

Severe renal failure: Renal function was calculated using the Cockroft–Gault formula. A glomerular filtration rate < 30 ml/min was defined as severe renal failure.

Analyses

Two clinical pharmacists (CD, WB) analyzed and categorized the medication given on the case report form every day (correct dosage, duplication, possible drug-drug interactions, use of drugs to avoid, use of unnecessary drugs). Two physicians specialized in internal medicine (EP, JS) confirmed and evaluated the given clinical information, laboratory results and suspected ADEs. Uncertainties were clarified by interviewing the patients, the medical staff or the care givers, and finally determined by consensus among the study group members.

Statistics

All values were recorded on an MS-ECXEL© data sheet. Calculations were made by an independent statistician using SPSS© software. Means were compared using t-tests, proportions using the chi-squared test. The assumption of normal distribution for the sample means, a prerequisite for the t-test, is valid even if individual measurements are not normally distributed, since the means are based on more than 100 measurements (central limit theorem). The prerequisites for the chi-squared analysis of proportions (at least 5 cases in every cell) are also fulfilled. Spearman's rank correlation (rho) was used to measure the correlation of various attributes with polypharmacy or ADEs, since this does not require normal distribution of the data. Logistic regression was used for multivariate analysis of the dependence of polypharmacy on several variables.

Results

During the three-month screening period, there were 603 admissions of 543 patients 75 years of age or older. This age group represented 33.7% of all hospital admissions on the internal wards. Only the 543 first admissions were included in the study and data sheets were completed for 482 of these patients (88.8%). In some cases, information on height (5.3%), weight (2.2%) and sociodemographic variables (4.2%) was missing, mostly due to short hospital stays. Data on drugs at admission and discharge were almost complete (99.8%). The demographic and clinical data are given in Table 1.

Admission diagnoses

Using the charts, we identified 781 diagnoses that led to hospital admission in 543 patients: 334 patients had one diagnosis, 179 had two and 30 had three or more different diagnoses. The most common reasons for hospital admission were volume overload states (arterial hypertension, heart failure; 35%), chest pain (22.3%), planned procedures (15.7%) and arrhythmias or syncopes (22.3%), followed by worsening of general condition (11.6%) and nausea, constipation or diarrhea (10.1%).

Number and quality of drugs

At admission, we counted a total of 4061 prescriptions in 543 patients. The average number of drugs was 7.5 ± 3.8 (range 0–27). Women took significantly more drugs than men (7.8 ± 3.9 vs. 6.8 ± 3.6; $P = 0.013$).

The most commonly prescribed drugs were diuretics (62.2%), inhibitors of the ACE system (55.8%), platelet inhibitors (50.6%), proton-pump inhibitors (37.5%), be-

tablockers (36.5%), antidepressants and antipsychotic drugs (30.3%), benzodiazepines (25.5%), statins (24.5%) and oral anticoagulants (22.3%).

Some drugs were found to be significantly more often prescribed for women: diuretics (67% vs. 55.1%; $P < 0.005$), betablockers (55.1% vs. 40.2%; $P < 0.04$), antidepressant and antipsychotic drugs (34.6% vs. 24.1%; $P < 0.009$), benzodiazepines (32.1% vs. 15.7%; $P < 0.0005$), levothyroxine (19.9% vs. 6.9%; $P < 0.0005$) and bisphosphonates (8% vs. 2.3%; $P < 0.005$), whereas allopurinol was more common in men (19.4% vs. 6.1%; $P < 0.0005$).

Polypharmacy

In 58.4% of patients (317/543), more than six different medications were found at admission, all the analyzed drugs being significantly over-represented in these patients. It was not possible to name individual drugs that were characteristic in patients with polypharmacy; nevertheless, the highest correlations with polypharmacy were found with proton-pump inhibitors (*rho:* 0.316), diuretics (*rho:* 0.313), betablockers (*rho:* 0.240) and opioid analgesics (*rho:* 0.226), and the lowest correlations were with antiplatelet drugs (*rho:* 0.086). Clinical parameters and diseases associated with higher risk for polypharmacy are given in Table 2.

Unnecessary drugs

These were identified in 36.3% of patients (197/543) and in 6.8% of prescriptions (277/4061). The most common unnecessary drugs were pentoxiphylline (n = 52) and ginkgo biloba (n = 40), followed by allopurinol (n = 28), magnesium salts (n = 26), laxatives (n = 18), bladder spasmolytics (n = 16), prokinetics (n = 14), β-adrenergic drugs for low blood pressure (n = 11), herbal sedatives (n = 10), venous therapeutics (n = 9), herbal liver and cardiac therapeutics (n = 9) and herbal prostate therapeutics (n = 5).

Table 1. Patient characteristics

Number	543
Mean age (SD)	82.6 (± 5.0)
Female sex	327 (60.2%)
Admission acute/planned	444/99 (81.8%/18.2%)
Living alone	142 (27.3%)
Need for nursing care	238 (43.8%)
Living in a nursing home	92 (17.6%)
Need for help with eating	89 (17.0%)
Impaired cognitive abilities	84 (16.1%)
Mean number of discharge diagnoses (SD)	7.1 (± 2.6)
Mean Charlson comorbidity index (SD)	3.2 (± 2.0)
Mean BMI (SD)	25.32 (± 4.47)
BMI < 20	58 (11.4%)
Mean creatinine clearance* (ml/min) (SD)	44.92 (± 20.19)
Creatinine clearance* < 30 ml/min	122 (23.0%)

SD standard deviation; *BMI* body-mass index; *calculated with the Cockroft–Gault formula

Table 2. Correlation (Spearman) of polypharmacy

	Correlation with >6 drugs	*P* value
Age in quartiles	0.025	0.566
Female sex	0.100	0.020
Need for nursing care	0.142	0.001
Impaired cognitive abilities	0.079	0.072
Number of final diagnoses	0.230	<0.0005
Charlson comorbidity score	0.186	<0.0005
Special diseases:		
Heart failure	0.049	0.256
Coronary heart disease	0.055	0.203
Renal failure	0.085	0.048
Hypertension	0.087	0.042
Atrial fibrillation	0.061	0.155
Diabetes mellitus	0.181	<0.0005
Pain disease	0.119	0.005
Neoplasia	–0.072	0.097
COPD	0.079	0.065
Dementia	–0.004	0.926

COPD chronic obstructive pulmonary disease

The prescription of unnecessary drugs was significantly correlated with polypharmacy: prevalence among patients with >6 drugs was 48.1% and among patients with ≤6 drugs 19.9% ($P < 0.0005$, OR 3.73).

Drugs to avoid

Inadequate drugs, following the modified Beers criteria, were found in 30.1% of the patients (163/543) and 4.6% of prescriptions (187/4061). Women were found to have a much higher rate of inadequate drugs than men (38.0% vs. 18.1%). The most important inadequate drugs identified were benzodiazepines (n = 110), nifedipine (n = 23), amitriptyline (n = 10), ergotamine (n = 8), daily fluoxetine (n = 6), long-acting NSAIDs (n = 6) and oxybutynin (n = 5). Inadequate drug use was significantly correlated with polypharmacy: prevalence among patients with >6 drugs was 38.6% and among patients with ≤6 drugs 18.1% ($P < 0.0005$, OR 2.84).

Duplication

Double prescriptions were found in 7.6% of the patients (41/543) and 1.2% of the prescriptions (49/4061). Patients with polypharmacy had a significantly higher risk for duplication (12.6% vs. 0.4%, $P < 0.0005$, OR 32.6). The most common duplicated drugs were benzodiazepines and diuretics.

Wrong dosage

Incorrect drug dosage, namely overdosing, was found in 23.4% of the patients (127/543) and 3.8% of prescriptions (156/4061). Patients with polypharmacy had a signifi-

cantly higher risk for wrong dosage (31.0% vs. 12.8%, $P < 0.0005$, OR 3.05). In many cases, the overdosage occurred in patients with renal failure (300 mg allopurinol: n = 19, >50 mg spironolactone: n = 21) or low body weight (200 mg amiodarone: n = 16). Other common errors were overdoses of proton-pump inhibitors (n = 59), NSAIDs (n = 18), intoxication with cardiac glycosides (n = 3) and symptomatic opiate overdoses (n = 4).

Drug interactions

Potential drug-drug interactions were identified in 65.8% of patients (356/541) and in 22.6% of all drugs (919/4061). We found an almost linear association between the number of drugs prescribed and the mean number of potential drug interactions (Fig. 1). The majority of drug interactions were pharmacodynamic ones such as synergistic actions of benzodiazepines and opiates, amiodarone and beta-blockers, tramadol and serotonin reuptake inhibitors. Potential pharmacokinetic drug interactions such as acenocoumarol and celecoxib (protein-binding competition) or simvastatin and clarithromycin (inhibition of cytochrome p450 metabolism) were less prominent.

Outcome

The mean hospital stay was 10.1 ± 9.5 days. Overall, 5.7% of the patients (31/543) died in hospital. Polypharmacy and inappropriate prescribing were not associated with adverse outcome.

Adverse drug events

In total, 107 ADEs were identified at the time of admission in 17.8% of the patients (97/543) (Table 3), among whom the ADE was the reason for hospital admission in 56.7% (55/97). The most common ADEs were hemorrhages (n = 16), hyponatremia (n = 13), hypokalemia (n = 10) and bradycardia (n = 10). The most common causative drugs were diuretics, oral anticoagulants, NSAIDs, antiarrhythmics, antiplatelet drugs and psychotropic drugs. The occurrence of an ADE was significantly correlated with critical creatinine clearance (rho –0.15, $P < 0.0005$), female sex (rho 0.12, $P = 0.004$) and the number of discharge diagnoses (rho 0.08, $P = 0.039$). The occurrence of ADEs was also correlated with inappropriate prescribing: wrong dosing (rho 0.12, $P = 0.003$), potential drug-drug interaction (rho 0.12, $P = 0.003$) and the use of drugs on the Beers list (rho 0.09, $P = 0.035$). However, ADEs were not correlated with the number of drugs on admission (Fig. 2), the prescription of unnecessary drugs, age per year or low body-mass index.

In 18.7% of the ADE cases (20/107), the event was probably caused by a drug-drug interaction; thus, only 5.6% of all identified potential drug-drug interactions (20/356) led to a clinical event.

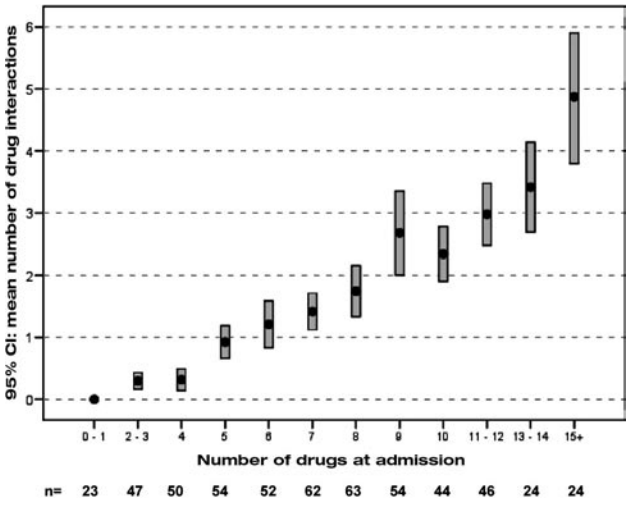

Fig. 1. Relationship between the number of prescribed drugs and the mean number of potential drug interactions

Discussion

We found that polypharmacy was highly prevalent (58.4%) in elderly internal-medicine patients in Salzburg. The definition of polypharmacy is vague. Some authors define it as "excessive and unnecessary drug use", others use definitions based on the number of drugs [9, 18]. In this study, we defined polypharmacy as prescription of >6 different drugs, because at this threshold the risk for inappropriate prescribing increases [5]. Polypharmacy was shown to be even more prevalent in our hospital (65%) when we used the more rigorous definition of >5 different drugs. Indeed, this study confirms that polypharmacy in old age is the rule rather than the exception.

The average number of drugs being taken by our elderly patients was 7.4. Similar numbers have been found in other western countries [5, 18]. Many patients also consume additional drugs without the knowledge of the treating physician; clearly there is no accordance with the recommendations of some authors not to take more than five different drugs [19].

There are many reasons for polypharmacy in the elderly. In our study, the most important risk factor was a patient-related one: polymorbidity. The more diagnoses and the higher the Charlson comorbidity score, the more drugs were found: thus, polymorbidity triggers polypharmacy.

Some diseases such as arterial hypertension, diabetes mellitus, renal failure and diseases associated with pain were significantly correlated with polypharmacy. Other authors have also found an association of polypharmacy with heart failure, dementia and cerebrovascular disease [18]. However, most of these diseases need to be treated with many different drugs and are also highly prevalent in the older population. According to current guidelines, a patient with diabetes, hypertension, heart failure and atrial fibrillation requires a minimum of six different drugs. Redefining thresholds (e.g. for blood pressure and cholesterol) and marketing new drugs (most of them without adequate testing in the older population) also promote polypharmacy. Poly-

Table 3. Observed adverse drug events

Involved organ system	n	Leading to admission	Drug-drug interaction	Involved drugs
Electrolytes	*25*	*12*	*6*	
Hyperkalemia	2	0	1	Spironolactone (2)
Hypokalemia	10	6	3	Hydrochlorothiazide (8), furosemide (2), torasemide (2), xipamide (2)
Hyponatremia	13	6	2	Hydrochlorothiazide (11), furosemide (2), xipamide (1), carbamazepine (1)
Cardiovascular	*23*	*16*	*5*	
Bradycardia	10	9	5	Beta-blocker (8), digoxin (5), digitoxin (1), amiodarone (1)
Cardiac glycoside overdosing	3	1	0	Digitoxin (2), digoxin (1)
QT prolongation, syncope	5	2	0	Amiodarone (2), propafenone (1), nitroglycerine (2)
Heart failure	5	4	0	Omitting drugs (3), NSAID (2)
Coagulation system	*18*	*9*	*0*	
Bleeding	16	9	0	Acenocoumarol (15), phenprocoumon (2), NSAID (1)
Over-anticoagulation	2	0	0	Acenocoumarol (2)
Central nervous system	*10*	*6*	*3*	
Anticholinergic syndrome, Agitation	2	2	2	Polypharmacy (trazodone+citalopram+flupentixol,1), SSRI (1), antipsychotic drugs (1)
Dyskinesias	2	0	0	Levodopa (1), gabapentin (1)
Falls, vertigo, severe cognitive impairment	5	3	1	Benzodiazepines (4), antipsychotic drugs (1)
Opiate withdrawal	1	1	0	Tramadol (1)
Kidney	*9*	*5*	*2*	
Hypovolemia, acute renal failure	9	5	2	NSAID (4), diuretics (4), ACE inhibitors (2), ciprofloxacin (1)
Gastrointestinal	*7*	*3*	*3*	
Obstipation, nausea	5	2	2	Fentanyl (3), tramadol (1), imatinib (1), polypharmacy (1)
Ulcer, diarrhea	2	1	1	NSAID (1), ciprofloxacin (1)
Endocrine	*7*	*2*	*0*	
Hypo/hyperthyreosis	5	1	0	Thiamazole (2), amiodarone (2), dye (1)
Hypoglycemia	1	1	0	Insulin (1)
Lactate acidosis	1	0	0	Metformin (1)
Others	*8*	*2*	*1*	
Neutro/pancytopenia	3	0	0	Enalapril (1), methotrexate (1), moxifloxacin (1)
Skin/mucosa	3	1	0	Beta-blocker (1), diclofenac (1), amiodarone (1)
General condition	1	1	1	Polypharmacy (27 different drugs)
Pulmonary	1	0	0	Beta-blocker (1)
Total	*107*	*55*	*20*	

SSRI serotonin reuptake inhibitors; *NSAID* non-steroidal anti-inflammatory drug

pharmacy can therefore also be interpreted as a problem of evidence-based medicine and medical progress. In the future, guidelines must address more the specific problems of older patients against the background of polymorbidity and polypharmacy.

Additional patient-related risk factors for polypharmacy were the need for nursing care and female gender. We consider that the high polymorbidity in patients with nursing requirements explains the polypharmacy in this subgroup, but it is less clear to us why women are more likely to have multiple drug regimes than men with comparable morbidity. In an in-depth analysis of this gender phenomenon, we found that women with few diagnoses had a significantly higher risk for polypharmacy than men with comparable morbidity, although in the more severely ill patients (number of discharge diagnoses >9 or Charlson comorbidity score >5) drug prescription rates were similar between the sexes. The fact that sedative and antidepressant drugs are prescribed twice as often in women suggests that polypharmacy in elderly women might be a consequence of social deprivation or a sign of a different attitude of doctors toward women [20].

Although not addressed in this study, polypharmacy is considered to be related to the prescribers and the healthcare system. Misinterpretation of drug side effects as a new disease or progression of a known disease and then treating with additional drugs is a well known phenomenon: the prescribing cascade. Furthermore, multiple prescribers and ineffective communication between healthcare providers and patients may lead to parallel prescribing and polypharmacy [5, 21]. In the fu-

ture, the use of electronic media such as the Austrian "ecard" might help to detect parallel consultation of more than one doctor and dangerous co-consuming of over-the-counter drugs.

We did not find a significant relationship between the number of prescribed drugs and ADEs, hospital mortality or length of hospital stay. Despite its well recognized economic impact and its causality for low adherence to drug regimes [3, 4] and underprescribing [22], polypharmacy itself does not appear to cause patients´ adverse outcome. Reducing the amount of medication is always worthwhile but it should not be the main target in improving drug safety in the elderly. Polypharmacy is sometimes unavoidable and can be appropriate when it is carefully managed and monitored.

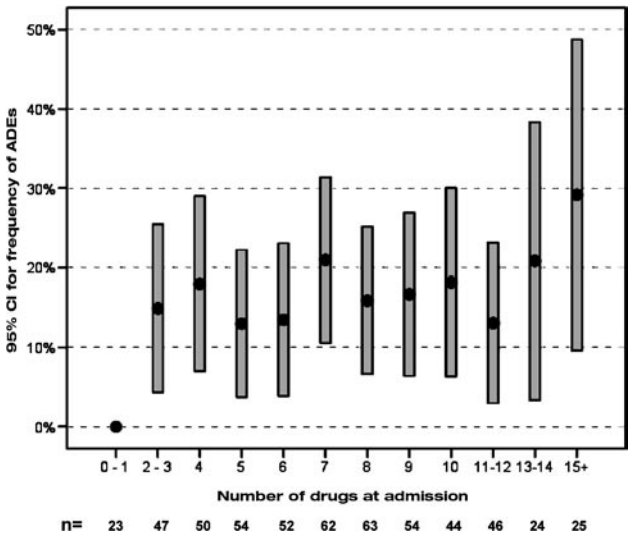

Fig. 2. Frequency of adverse drug events in relation to the number of drugs at admission

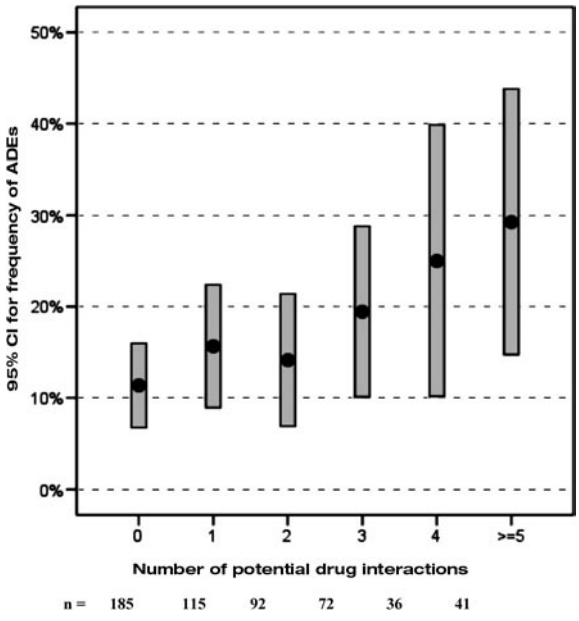

Fig. 3. Frequency of adverse drug events in relation to the number of potential drug-drug interactions at admission

Other authors have found a good correlation between the occurrence of an ADE and the number of prescribed drugs [23]; however, that particular study was in an ambulatory setting and with younger patients (mean age 52 years vs. 82.4 years) on far fewer drugs (average 1.5 vs. 7.4). We assume that in patients with polypharmacy the statistical association between ADEs and number of drugs is diluted by a higher number of given drugs.

In contrast to the plain number of prescribed drugs, we found inappropriate prescribing to be associated with adverse outcome: overdosage, the use of drugs to avoid and drug-drug interactions appear to be relevant risk factors for ADEs.

In most cases, overdosing occurs in patients with renal failure or low body weight. Adapting dosage to individual capacity for drug clearance is crucial in improving drug safety. This is highlighted by the fact that one quarter of our patients had a critical creatinine clearance. Knowledge of a patient's renal function and adequate adaptation of the dose is an absolute requirement for appropriate and safe prescribing.

The 36.6% prevalence of drugs to avoid (Beers list) in our elderly hospitalized population was similar to that in other European countries [2, 5, 18]. Prescription of drugs on the Beers list was the second most important factor associated with the occurrence of ADEs. However, those drugs were mostly not causative for the development of ADEs, a finding supported by a recent study of older patients in an emergency department [24]. Nevertheless, the presence of drugs to avoid on a patient's medication list appears to be a significant predictor of ADEs [25] and is therefore a useful indicator of poor prescribing quality. There might, however, be valid indications for the use of some drugs on the Beers list in the individual patient; for example, amiodarone in intractable arrhythmias or doxazosin in severe arterial hypertension. For that reason, the term "drugs to avoid" can be misleading. Several initiatives have been started to amend this list for current practice and the European drug market. In the future, controlled prospective studies should investigate whether withdrawal of these drugs has an impact on quality of life and life expectancy in elderly patients.

Drug-drug interactions were found to be a major cause of ADEs in our study and were highly prevalent (65%) in the investigated patients. The rate was lower (46%) in a larger European database, probably because the study population was younger and the average number of drugs prescribed was smaller [26]. We calculated that about 6% of the potential drug-drug interactions led to a clinical event. However, it is difficult to assess the probability of a drug-drug interaction causing an ADE with certainty, especially in the absence of discriminating criteria.

Nonetheless, not every potential drug-drug interaction will have a clinical impact and some drugs are definitely more critical than others in causing interactions;

for example, NSAIDs, diuretics, amiodarone, betablockers and benzodiazepines [28, 29].

In clinical routine, these drug relationships often remain undiscovered, as symptoms may be attributed to underlying diseases rather than to the drugs. Physicians need to be aware of drug-drug interactions and every prescription should be appropriately checked. As the topic is very complex and knowledge is expanding rapidly, effective electronic backup is needed for this purpose.

Our data and findings should be interpreted in the context of several important limitations. The major limitation of our study is its monocentric and time-limited study design. We exclusively recruited patients on seven wards in two internal medical departments and missed the patients with hematological, surgical, neurological or other problems (skin, eyes, etc.). Furthermore, we analyzed data exclusively in internal medical departments, therefore multimorbid patients with many prescribed drugs were over-represented in our sample. We found that 33% of the hospitalized patients in the two investigated departments were ≥75 years of age. In comparison, in 2006, taking Austria as a whole, 21% of all patients hospitalized for all indications were ≥75 years [8].

For the above reasons a selection bias is obvious and our findings cannot be generalized to the elderly Austrian population overall. However, our intention was not to review the national prescription data of elderly patients, but to analyze the extent and impact of polypharmacy and inappropriate prescribing on the outcome of elderly patients with multiple medical problems in our community. We therefore believe that it was feasible to use a time-limited sample in one of the biggest hospitals in Austria. Many other studies with comparable patient populations have found similar figures, confirming our conviction that our findings have a general meaning in this clinically and economically significant subgroup.

A further limitation of this study is that we did not evaluate over-the-counter drugs such as NSAIDs or herbal medicines that might be responsible for ADEs or drug-drug interactions. However, it is very difficult to determine this comedication in elderly patients with cognitive impairments or simply too many drugs to be remembered.

Lastly, drug assessment is difficult to standardize and therefore our decision-making process can be criticized. We did not use the method of blinded double data entry for decisions on potential ADEs and interactions. Decisions on the significance of potential interactions were made by the pharmacists of the study group on the basis of predefined parameters. The significance was discussed in the group only when there was doubt or a need for clarification. Because of the complexity of the topic there will always be a need for discussion of the relevance of an interaction or ADE; in the absence of feasible and well evaluated computer programs, we believe that drug assessment by two experienced pharmacists gives enough stability to the data to permit statistical comparisons.

Interdisciplinary teamwork with the support of electronic media has already shown that improvements are possible [30]. We feel that the commercially available electronic drug-interaction programs are of limited benefit because they give far too much information, especially in patients with polypharmacy. In our experience, the most practical way to assess a complex medication portfolio at present is through continuous discussion between clinical pharmacists and specially trained physicians.

In conclusion, polypharmacy was highly prevalent in patients ≥75 years of age who were admitted to the medical wards of our institution and was as common as in other European countries. According to our results, polypharmacy itself is not a major risk factor for ADEs. What was revealed to be far more important was the quality of prescribing: overdosing, the use of drugs to avoid and ignorance of drug-drug interactions were the most important reasons for adverse outcome in our study. Appropriate prescribing is thus the key issue in improving drug safety in the elderly.

Acknowledgements

This work was supported by grants from the local health insurance company (Salzburger Gebietskrankenkasse) and the Austrian Pharmacists Society (Österreichischer Apothekerverband). All statistic analyses were performed by Dr. Mynda Schreuer. The funding institutions had no influence on the analysis or interpretation of the data.

We wish to thank Elisabeth Wagner and Andrea Zarbl for their excellent work as study nurses and Prof. Walter Thimme for his valuable advice in preparing the manuscript.

Conflict of interest statement

No conflict of interest with any of the authors.

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