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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug-related hospital admissions among old people with dementia

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Abstract
Purpose Drug treatment associated problems are common and are the cause of a large proportion of hospitalizations in old people. People with dementia are especially at risk of drug-related problems. The objectives of this study were to assess the occurrence and character of drug-related problems that lead to acute hospital admissions among old people (≥65 years) with dementia or cognitive impairment.
Methods This study was conducted in orthopedic and internal medicine wards in two hospitals in Northern Sweden. Information about acute admissions was collected from the medical records. A total of 458 people aged 65 years or older with dementia or cognitive impairment were included in the study. The contribution of drug-related problems to each hospitalization was assessed.
Results Of 458 acute hospital admissions, 189 (41.3 %) were determined to be drug-related. The most common drug-related problem (86/189; 45.5 %) was an adverse drug reaction. In total, 264 drugs were judged to be involved in 189 drug-related admissions, of which cardiovascular (29.5 %) and psychotropic (26.9 %) drugs were the most commonly involved drug classes. The relationship between the drug-related problem and the admission was judged certain in 25 cases, probable in 78 cases, and possible in 86 cases. Drug-related admissions were more common among people taking more drugs ($p = 0.035$) and among younger patients ($p = 0.031$).
Conclusion Drug-related problems appear to be responsible for a major proportion of hospitalizations among old people with dementia or cognitive impairment. Targeted interventions such as education and medication reviews may be warranted to reduce drug-related problems.

Keywords Old people · Dementia · Drug-related problems · Drug-related hospitalizations

Introduction

A drug-related problem (DRP) has been defined as "an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome" [1]. The risk of DRPs increases with age due to age-related physiological and pathophysiological changes in organ function that affect the pharmacodynamics and pharmacokinetics of drugs. Patients with reduced renal function or impaired homeostatic mechanisms require dose adjustments to alleviate their increased risk of adverse drug reactions. Additionally, reduced levels of dopamine and acetylcholine in the brain increase sensitivity to antidopaminergic and anticholinergic drugs [2].

Problems associated with drug treatment can result in drug-related morbidity and contribute to a large proportion of hospital admissions; up to 30 % of hospital admissions have been directly related to DRPs among old people [3–6]. In general, increased age is associated with an increased risk of hospitalization [7] but other factors also contribute to higher admission rates. Polypharmacy (usually defined as taking five or more drugs daily) and use of potentially inappropriate drugs

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may increase the risk of hospitalization [6–10], and females have a greater risk of adverse drug reactions (ADRs) leading to hospitalization than males [11]. Moreover, dementia is associated with an increased risk of hospitalization [12]. A higher level of comorbidity among people with dementia [12] and an increased risk of acute organ dysfunction [13] together with other problems specific for this patient group, such as malnutrition [14], pose considerable challenges on drug therapy. Changes in brain neurotransmitter levels and alterations in the blood-brain barrier increase sensitivity to drugs and may lead to greater susceptibility to side effects [15–17]. In addition, cognitive impairment impacts compliance [18] due to problems with understanding instructions and remembering dosage and timing of drug administration. Finally, executive dysfunction may lead to difficulties in identifying, recognizing, and reporting adverse drug events.

Adverse drug reactions caused by cardiovascular drugs have been responsible for 36 % of hospital admissions related to drug problems [19], but CNS-active drugs are also frequently involved [6, 20]. Analgesic drugs, endocrine, and hematological agents are other common drug classes that can cause drug-related hospitalizations [7].

It is important to map drug-related hospitalizations to improve treatment outcomes and prevent unnecessary hospital admissions. To the best of our knowledge, the proportion of drug-related admissions in people with dementia or cognitive impairment has not been previously explored. The objective of the present study was to assess the frequency and type of drug-related problems that lead to acute hospital admissions in old people with dementia or cognitive impairment.

Methods

Subjects and settings

This study is based on the same population of old patients with dementia or cognitive impairment that were recruited for an intervention study that set out to investigate the impact of including a clinical pharmacist in the healthcare team on the rate of readmission (Gustafsson et al. (2016), unpublished). The patients in the present study represent the total study population (both intervention and control groups) of the intervention study at the time of index admission.

Patients admitted to the acute internal medicine ward and to the orthopedic ward at Umeå University Hospital, and patients from the medicine wards at the county Hospital in Skellefteå were included. Both hospitals are located in Västerbotten County in Northern Sweden. Eligible patients were aged 65 years or older and had dementia or cognitive impairment. Patients were considered to have cognitive impairment if sufficient information in the medical record related to memory, orientation, or executive function was noted before index hospitalization. In addition, patients in whom dementia was suspected and medical investigation had been commenced or would be initialized were included. In ambiguous or uncertain cases, patients were excluded. Between January 9, 2012, and December 2, 2014, 473 patients aged 65 years or older were invited to participate in the trial. Thirteen patients declined participation. Persons who withdrew from the intervention study before discharge (one person) and those with planned admissions (one person) were excluded. The final sample was 458 persons.

Procedures and definitions

Three experienced clinical pharmacists in the Department of Clinical Pharmacology at the Umeå University Hospital checked the medical records at the patients' index admission to the hospital (before an intervention was performed), to determine if this admission was drug-related or not.

Data associated with the patients' drug therapy were reviewed, using information taken from the patient's medication list, laboratory values, medical record notes from primary care, and from the actual admission, as well as from earlier contacts with healthcare providers in order to get the full medication history of the patient. In order to judge the probability that a certain drug may have caused or contributed to an acute admission, the time-relationship between intake of medicine and admission was assessed. In addition, it was checked whether any changes in the patients' medication list had been made shortly before admission.

The classification of admissions, *certain*, *probable*, *possible*, or *unlikely*/*un-assessable related to drugs*, were noted individually at first. Then, all admissions were discussed in the group of clinical pharmacists to come toward a consensus regarding classification of admissions.

Classifications of DRP

Drug-related problems were classified in seven subgroups according to a modified version of Cipolle et al. [21]: *ADR*, *dosage too high*, *dosage too low*, *ineffective drug*, *needs additional drug therapy*, *unnecessary drug therapy*, and *noncompliance.* Inappropriate drugs were added to the category *ineffective drugs*, and in addition, a further category was introduced, *interactions* (pharmacodynamic and pharmacokinetic). The drug-related problems were defined according to Table 1.

Criteria for causality assessment

The drug-related problems resulting in an ADR (ADR, dosage too high, ineffective drug/inappropriate drug, unnecessary drug therapy, needs additional drug therapy, noncompliance, and interactions producing too high therapeutic effect) were

Table 1 Classification of DRP

ADR: Adequate doses resulting in adverse drug reactions were classified as ADR.

Dosage too high: If the prescribed dose was too high in relation to the patient's renal function, liver function or age, resulting in an ADR, this was classified as dosage too high.

Dosage too low: If the prescribed dose was less then recommended leading to an exacerbation of symptoms, this was classified as dosage too low.

Ineffective/inappropriate drug: Inappropriate drugs according to explicit Swedish criteria [22] and inappropriate drug use according to renal function or disease leading to an ADR were classified as ineffective/inappropriate drug.

Needs additional drug therapy: If a patient were inadequate medicated resulting in an ADR or exacerbation of symptoms, this was classified as needs additional drug therapy.

Unnecessary drug therapy: If a patient had an unnecessary drug therapy resulting in an ADR, this was classified as unnecessary drug therapy.

Noncompliance: A deviation from the prescribed medications because of a choice, noncomprehension or forgetfulness leading to an ADR or exacerbation of symptoms, were classified as noncompliance.

Interactions: A drug interaction was defined as the modification of one drug by concomitant administration by another drug, producing loss of therapeutic effect (leading to exacerbation of symptoms) or too high therapeutic effect (leading to ADR).

DRP drug-related problem, *ADR* adverse drug reaction

Table 2 WHO criteria for causality assessment of ADR

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/unclassifiable: A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

WHO World Health Organization

assessed according to the World Health Organization (WHO) criteria for causality assessment regarding ADRs (Table 2).

Inadequate treatment (dosage too low, ineffective drug/inappropriate drug, needs additional drug therapy, noncompliance, and interactions producing loss of therapeutic effect) causing an exacerbation of the patient's condition were assessed according to the same WHO criteria with the following changes: the clinical event is changed to the exacerbation of symptoms and the time relationship to administration of the drug is changed to the time relationship between the start of inadequate treatment and the appearance of symptoms. The response to withdrawal of the drug is changed to the response to adjustment to an adequate dosage.

Data analysis

Simple logistic regression analyses were conducted to investigate the association between drug-related admission and different factors extracted from the medical record. These factors were gender, age, number of medications, type of ward, type of living, MMSE, creatinine clearance, and the patients' medical history. A multiple logistic regression analysis was conducted including significant variables from the simple models.

Results are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). P values <0.05 were considered statistically significant. All analyses were conducted using Statistical Package for the Social Sciences (SPSS) for Windows version 22.0.

Ethical considerations

This study was approved by the Regional Ethical Review Board in Umeå (registration number 2011-148-31M).

Results

The basic characteristics of the study population are summarized in Table 3. Drug-related problems caused or contributed to189 of 458 nonscheduled admissions (41.3 %). Of those 189 drug-related admissions, the relationship to a drug was deemed certain in 25 cases (Table 4), probable in 78 cases (Table 5), and possible in 86 cases (supplementary material Table 1). *ADRs* constituted 86/189 (45.5 %) of all drug-related admissions, making them the most common drug-related problem. *Dosage too high* (12.7 %) and *noncompliance* (10.6 %) were also frequently encountered problems. *Ineffective/inappropriate drug use* and *interactions* accounted for 10.6 and 6.9 % of the drug-related admissions. Other drug-related problems that potentially contributed to admissions

Table 3 Characteristics of study population with and without drug-related admission

	Drug-related admission	Nondrug-related admission	Simple OR (95 % CI)	Multiple OR (95 % CI)
Cases, *n* (%)	189 (41.3)	269 (58.7)		
Women, *n* (%)	114 (60.3)	172 (63.9)	0.857 (0.584–1.258)	
Age mean ± SD	82.4 ± 7.0	83.8 ± 6.2	0.968 (0.941–0.997)	0.969 (0.941–0.997)
Number of medications at admission ± SD	8.2 ± 3.4	7.4 ± 3.6	1.068 (1.012–1.126)	1.060 (1.004–1.119)
Type of ward				
Orthopedic ward, *n* (%)	20 (10.6)	41 (15.2)	Ref	
Medical ward, *n* (%)	169 (89.4)	228 (84.8)	1.520 (0.859–2.688)	
Type of living				
Living alone, *n* (%)	86 (45.5)	116 (43.1)	Ref	
Living in nursing home or at home with a relative, *n* (%)	103 (54.5)	153 (56.9)	0.908 (0.624–1.320)	
MMSE (0–30) mean ± SD	19.8 ± 4.8	19.9 ± 4.5	0.998 (0.932–1.069)	
Creatinine clearance (mL/min)	55.0 ± 24.7	54.4 ± 21.9	1.001 (0.993–1.009)	
Medical history				
Heart failure, *n* (%)	59 (31.2)	82 (30.5)	1.035 (0.692–1.548)	
Cardiac arrhythmia, *n* (%)	60 (31.7)	71 (26.4)	1.297 (0.862–1.953)	
Diabetes mellitus, *n* (%)	54 (28.6)	66 (24.5)	1.230 (0.808–1.873)	
Chronic obstructive pulmonary disease, *n* (%)	15 (7.9)	21 (7.8)	1.018 (0.510–2.030)	
Stroke, past, *n* (%)	52 (27.5)	53 (19.7)	1.547 (0.998–2.398)	1.508 (0.966–2.354)

Creatinine clearance was based on P-creatinine applying the Cockcroft-Gault equation. The multivariate model includes significant variables as independent variables: age, number of medications at admission and stroke (borderline significant)

CI confidence interval, *OR* odds ratio, *SD* standard deviation, *MMSE* Mini Mental State Examination (n = 157)

were as follows: *needs additional drug therapy* (6.3 %), *dosage too low* (4.8 %), and *unnecessary drug therapy* (2.6 %).

Cardiovascular drugs (29.5 %) and psychotropic drugs (27.3 %) were the drug classes that caused or contributed to hospital admissions most frequently. Other drugs that were identified to have caused or contributed to drug-related hospital admissions were analgesics, drugs for obstructive airway diseases, anticoagulants, and antidiabetics (Table 6). In total, 264 drugs were suspected to contribute to 189 drug-related admissions.

Drug-related admissions were more common among people taking a higher number of drugs (OR, 1.068 [95 % CI, 1.012–1.126]; P = 0.016) and less common with increasing age (OR, 0.968 [95 % CI, 0.941–0.997]; P = 0.028). There were no significant differences between patients with and without drug-related admissions regarding gender, living arrangement, or ward type. No correlations were seen between drug-related admissions and any specific medical history (Table 3). In a multivariate model with drug-related admission as the dependent variable and significant variables from Table 3 as independent variables (number of drugs at admission, age, and stroke [borderline significant]), number of drugs (OR, 1.060 [95 % CI, 1.004–1.119]; P = 0.035) and age (OR, 0.969 [95 % CI, 0.941–0.997]; P = 0.031) remained significant.

Discussion

The frequency of drug-related hospital admissions in old people with dementia or cognitive impairment was high in this study (41.3 %). This proportion is somewhat higher than reported previously among old people, for example, one study did report a prevalence of 30 % [6]. Physiological age-related changes [15–17] and other specific problems as noncompliance among people with dementia represent a challenge to drug therapy and may have contributed to the high prevalence of drug-related admissions seen in the present study.

The most common drug-related problems were *ADRs* in the present study. Other drug-related problems such as *dosage too high* and *noncompliance* were also encountered frequently. ADRs and noncompliance are reasons of drug-related hospital admissions seen in previous research as well [6]. Notably, cognitive impairment affects compliance [18], and in the present study, *noncompliance* accounted for 10.6 % of the drug-related admissions. Specifically, some people in this group had difficulties with inhalation technique. Patients with dementia or cognitive impairments may lack the ability to operate dry powder inhalers correctly, and therefore, the effectiveness of treatments for chronic obstructive pulmonary disease (COPD) or asthma may be reduced. It is possible that these drug-related admissions could have been prevented by

Table 4 Drug-related problems as a certain cause for or certain contributing to admission

Type of drug-related problem	Drugs involved (frequency)	Symptoms/diagnosis at admission	Comment
Adverse drug reaction	Amiodarone	Hypothyroidism	At admission TSH was 13 mlU/L and T4 15 pmol/L. Amiodarone was withdrawn.
	Ciprofloxacin	Entercolitis/clostridium	Cause of hospital admission was diarrhea caused by *clostridium difficile*. Therapy with ciprofloxacin was started a few days before admission.
	Enalapril, spironolactone	Acute renal failure	Drug therapy with enalapril and spironolactone was started a month before admission. Serum creatinine increased from 113 to 212 μmol/L and serum potassium from 4.6 to 5.5 mmol/L. At admission, spironolactone was withdrawn and enalapril dose was reduced.
	LMWH	Hematoma	
	Warfarin	Bleeding	Large bleed in right thigh. Warfarin was withdrawn.
	Warfarin	Bleeding	
Dosage too high	Insulin (2)	Hypoglycemia	
	Levothyroxine	Thyreotoxicos/atrial fibrillation	At admission T4 was 56 pmol/L and TSH 0.067 mlU/L. When the patient a few weeks before admission moved to a nursing home, the dose of levothyroxine was doubled because of a TSH 90 mlU/L (probably because of noncompliance at home).
	Metoprolol, digoxin	Bradycardia	Digoxin was prescribed 6 days before admission. The patient was admitted for loss of consciousness. Low heart rate at admission. Metoprolol was decreased from 100 mg daily to 50 mg daily. S-digoxin was 1.61 nmol/L. Digoxin was decreased from 0.13 mg daily to 0.13 mg five times a week.
Dosage too low	Insulin (2)	Hyperglycemia	
Ineffective/Inappropriate drug	Propiomazine	Sedation	Propiomazine was prescribed 8 days before admission. The patient was admitted because of hangover and daytime sedation.
Interaction	Warfarin + citalopram	Bleeding	Bleeding left forearm. Citalopram was prescribed 1 month before admission.
Needs additional drug therapy	Morphine	Obstipation	Morphine therapy was started a week before admission, no laxatives prescribed. Admitted because of constipation diarrhea.
	LMWH	Pulmonary embolism	LMWH was prescribed after a big pulmonary embolism. Planned treatment time was 12 months. After 3 months, LMWH was discontinued for unclear reason. Three weeks later, the patient was admitted with a new pulmonary embolism.
	Enalapril, amlodipine	TIA	The patient had high blood pressure (176/114 mmHg) at admission. A TIA was diagnosed. All antihypertensive therapy was discontinued 1–2 months before hospitalization for unclear reason. Therapy with enalapril 10 mg and amlodipine 10 mg was restarted.
Noncompliance	Glipizide	Hyperglycemia	
	Insulin (4)	Hyperglycemia	
	Insulin	Hypoglycemia	
	Insulin	Ketoacidosis	
Unnecessary drug therapy	Metoprolol, amlodipine	Hypotension	Increased confusion after fall at home a week before admission. Blood pressure 90/57 mmHg. Amlodipine 5 mg discontinued, metoprolol 50 mg lowered to 25 mg.

TIA transient ischemic attack, *LMWH* low-molecular-weight heparin

the prescription of alternative devices, such as nebulizers or pressurized metered dose inhalers used with a spacer instead of handheld devices [23].

Other common compliance problems in this study occurred with insulin therapy. Many patients were living at home and were responsible for their own insulin administration despite severe

Table 5 Drug-related problems classified as a probably cause for or probably contributing factor to admission

Symptoms/diagnosis/causes at admission (n = 78)	Drugs involved	Type of drug-related problem
Acute renal failure (n = 1)	Ciprofloxacin	Dosage too high
Anemia (n = 8)	Warfarin	Dosage too high
	Sulfamethoxazole/trimethoprim + warfarin	Interaction
	Acetylsalicylic acid, prednisolone, donepezil without PPI	Needs additional drug therapy
	Citalopram + warfarin	Interaction
	Acetylsalicylic acid (2)	ADR
	Warfarin[a]	Ineffective/inappropriate drug
	Methotrexate + sulfamethoxazole/trimethoprim long term treatment	Interaction
Angina (n = 1)	Needs glyceryl trinitrate pro re nata	Needs additional drug therapy
Asthma (n = 3)	Fluticasone/salmeterol, tiotropium[b]	Noncompliance
	Fluticasone/salmeterol discontinued	Needs additional drug therapy
	Terbutaline, budesonide discontinued	Needs additional drug therapy
Atrial fibrillation/heart failure (n = 2)	Needs beta-blocker	Needs additional drug therapy
	Metoprolol	Noncompliance
Atrial fibrillation/hypokalemia (n = 1)	Bendroflumethiazide, potassium	ADR
Bradycardia (n = 2)	Metoprolol	ADR
	Metoprolol	Unnecessary drug therapy
Confusion (n = 10)	Tolterodine	Ineffective/inappropriate drug
	Propiomazine, zolpidem	Ineffective/inappropriate drug
	Ketobemidone	ADR
	Zolpidem	ADR
	Levodopa/carbidopa	Dosage too high
	Morphine	Dosage too high
	Levodopa/benserazide	Dosage too high
	Trihexyphenidyl	Dosage too high
	Morphine	Ineffective/inappropriate drug
	Acetaminophen/codeine	Ineffective/inappropriate drug
COPD exacerbation (n = 1)	Tiotropium, indacaterol, budesonide/formoterol[b]	Noncompliance
Dehydration (n = 1)	Furosemide	Dosage too high
Dizziness (n = 1)	Risperidone	Dosage too high
Fall (n = 12)	Alfuzosin	ADR
	Alprazolam	ADR
	Bisoprolol	ADR
	Nitrazepam	Ineffective/inappropriate drug
	Haloperidol	Dosage too high
	Zopiclone, mirtazapine	ADR
	Ramipril, furosemide	Unnecessary drug therapy
	Verapamil, melatonin, clomethiazole	ADR
	Alfuzosin	ADR
	Clomethiazole, risperidone, citalopram	ADR
	Propiomazine, zolpidem	Ineffective/inappropriate drug
	Oxazepam	ADR
Fatigue (n = 3)	Digoxin	Dosage too high
	Gabapentin	ADR
	Memantine	ADR
Hemorrhage (n = 1)	Citalopram + acetylsalicylic acid + galantamine	Interaction
Heart failure (n = 4)	Furosemide + cholestyramine	Interaction
	Furosemide, enalapril, metoprolol	Noncompliance

Table 5 (continued)

Symptoms/diagnosis/causes at admission (n = 78)	Drugs involved	Type of drug-related problem
	Enalapril discontinued	Needs additional drug therapy
	Furosemide	Dosage too low
Hyperkalemia (n = 2)	Spironolactone + ramipril	Interaction
	Enalapril + potassium	Interaction
Hypoglycemia (n = 1)	Insulin	Dosage too high
Hyponatremia (n = 4)	Escitalopram	ADR
	Citalopram	ADR
	Bendroflumethiazide	ADR
	Furosemide, venlafaxine, omeprazole	ADR
Liver disorder (n = 1)	Acetaminophen	Dosage too high
NSTEMI (n = 1)	Metoprolol discontinued	Needs additional drug therapy
Obstipation (n = 1)	Buprenorphine without laxantia	Needs additional drug therapy
Orthostatic hypotension (n = 5)	Alfuzosin	ADR
	Bendroflumethiazide, metoprolol, enalapril	ADR
	Bendroflumethiazide, enalapril	ADR
	Losartan, metoprolol	ADR
	Alfuzosin, bisoprolol	ADR
Pain (n = 1)	Prednisolone	Dosage too low
Sedation (n = 4)	Acetylsalicylic acid/ dextropropoxyphene	Dosage too high
	Oxazepam, morphine, amitriptyline	ADR
	Oxycodone, olanzapine	ADR
	Morphine	Ineffective/inappropriate drug
Seizure (n = 2)	Carbamazepine	Noncompliance
	Carbamazepine	Dosage too low
SIADH (n = 1)	Buspirone	ADR
Syncope (n = 2)	Enalapril comp	ADR
	Enalapril	Unnecessary drug therapy
Urinary infection (n = 1)	Ceftibuten	Noncompliance
Vomiting (n = 1)	Levetiracetam	ADR

ADR adverse drug reaction, *COPD* chronic obstructive pulmonary disease, *NSTEMI* non-ST-segment elevation myocardial infarction, *SIADH* syndrome of inappropriate antidiuretic hormone (ADH) secretion

[a] Contraindicated drug in that patient

[b] All in different inhalers not adapted for people with dementia

cognitive impairment in some cases. These problems are probably less likely to occur among individuals without cognitive impairment.

In the category *needs additional drug therapy*, some important drug-related problems were found. For example, problems with constipation among people receiving opioids without concomitant prescription of laxatives. Patients with dementia or cognitive impairment might have extra difficulties in recognizing and communicating adverse drug events. A side effect that may be relatively easy to handle normally may become a major problem in patients with dementia, leading possibly to hospitalization if recognition is delayed.

Other drug-related problems in this category were drug discontinuations despite ongoing indications, such as discontinuation of low-molecular-weight heparin and antihypertensive medications, leading to adverse events in the patients. Changes in medications always entail a certain risk because symptoms may reappear or withdrawal symptoms may occur, why it is important to carefully consider and monitor any change of medication.

Cardiovascular drugs was the most frequently observed drug class causing or contributing to hospital admissions in the present study. This finding is in line with previous studies reporting adverse drug events caused by this drug class, with hypotension and electrolyte disturbances being responsible

Table 6 Drug classes and drugs causing or contributing to hospital admissions due to DRP

Drug class involved	Frequency (%)	Drugs involved (number), *n* = 264
Cardiovascular drugs	78 (29.5)	
Diuretics (29)		Bendroflumethiazide (11)
		Furosemide (10)
		Spironolactone (6)
		Amiloride/hydrochlorothiazide (1)
		Hydrochlorothiazide (1)
Agents acting on the renin-angiotensin system (20)		Enalapril (11)
		Losartan (4)
		Candesartan (2)
		Ramipril (2)
		Enalapril/hydrochlorothiazide (1)
Beta blocking agents (17)		Metoprolol (12)
		Bisoprolol (5)
Calcium channel blockers (4)		Amlodipine (3)
		Verapamil (1)
Other cardiovascular drugs (8)		Digoxin (2)
		Isosorbide mononitrate (2)
		Glyceryl trinitrate (2)
		Amiodarone (1)
		Cholestyramine (1)
Psychotropic drugs	72 (27.3)	
Anxiolytics, hypnotics and sedatives (31)		Zopiclone (7)
		Propiomazine (6)
		Zolpidem (5)
		Oxazepam (3)
		Alprazolam (2)
		Clomethiazole (2)
		Diazepam (2)
		Nitrazepam (2)
		Buspirone (1)
		Melatonin (1)
Antidepressant drugs (29)		Citalopram (13)
		Sertraline (4)
		Mirtazapine (4)
		Venlafaxine (3)
		Escitalopram (2)
		Amitriptyline (2)
		Mianserin (1)
Antipsychotics (12)		Risperidone (4)
		Olanzapine (3)
		Haloperidol (2)
		Clozapine (1)
		Lithium (1)
		Perphenazine (1)
Analgesic drugs and NSAID	20 (7.6)	
Opioid analgesics (13)		Morphine (8)
		Oxycodone (3)
		Buprenorphine (1)
		Ketobemidone (1)

Table 6 (continued)

Drug class involved	Frequency (%)	Drugs involved (number), $n = 264$
Acetaminophen/codeine (4)		Acetaminophen (2)
		Acetaminophen/codeine (2)
NSAID/dextropropoxyphene (3)		Ibuprofen (2)
		Acetylsalicylic acid/dextropropoxyphene (1)
Drugs for obstructive airway diseases	19 (7.2)	Tiotropium (5)
		Fluticasone/salmeterol (4)
		Budesonide (3)
		Budesonide/formoterol (2)
		Indacaterol (2)
		Terbutaline (2)
		Formoterol (1)
Antithrombotic agents	18 (6.8)	Warfarin (9)
		Acetylsalicylic acid (7)
		LMWH (2)
Drugs used in diabetes	13 (4.9)	Insulin (11)
		Glipizide (1)
		Metformin (1)
Urological drugs	9 (3.4)	Alfuzosin (6)
		Solifenacin (2)
		Tolterodine (1)
Antibacterials for systemic use	6 (2.3)	Ciprofloxacin (2)
		Sulfamethoxazole/trimethoprim (2)
		Ceftibuten (1)
		Nitrofurantoin (1)
Antidementia drugs	5 (1.9)	Donepezil (2)
		Galantamine (2)
		Memantine (1)
Antiepileptic drugs	6 (2.3)	Carbamazepine (2)
		Gabapentin (2)
		Clonazepam (1)
		Levetiracetam (1)
Other	18 (6.8)	Prednisolone (5)
		Levothyroxine (2)
		Methotrexate (2)
		Potassium (2)
		Calcium (1)
		Clemastine (1)
		Glycopyrrolate (1)
		Levodopa/benserazide (1)
		Levodopa/carbidopa (1)
		Omeprazole (1)
		Trihexyphenidyl (1)

DRP drug-related problem, *ACE inhibitors* angiotensin-converting enzyme inhibitor, *ARBs* angiotensin receptor blockers, *NSAID* nonsteroidal anti-inflammatory drugs, *LMWH* low-molecular-weight heparin

for a large proportion of drug-related hospitalizations [7]. Also, psychotropic drugs were frequently observed causing or contributing to hospital admissions in the present study, which is also observed in previous research [7]. In the present study, falls were associated with the use of both cardiovascular drugs and psychotropic drugs.

Psychotropic drugs are prescribed commonly to people with dementia or cognitive impairment, and their use has been associated with adverse reactions such as falls [24–26]. Antihypertensive medications have also been associated with an increased risk of fall injuries among the elderly [27]. This finding indicates that monitoring of drug treatment is critical, particularly among this patient group.

Among incorrect dosages, *dosage too high* was observed more commonly than *dosage too low*. *Dosage too high* was responsible for 12.7 % of all drug-related hospitalizations. Typical manifestations were confusion and bradycardia. Meanwhile, *dosage too low* was associated with problems such as aggravation of heart failure. Too high doses leading to confusion and dehydration, and suboptimal prescribing leading to aggravation of heart failure have also been seen in previous research [28].

Patients with drug-related admissions had significantly more drugs prescribed to them than patients whose admission appeared to be unrelated to drugs. This result is consistent with earlier studies showing that polypharmacy is associated with a higher probability of ADRs [8], even though some authors have suggested that use of unnecessary or inappropriate medications is more important than the actual number of drugs [7].

Polypharmacy increases the risk of clinically significant drug-drug interactions [29], which accounted for 6.9 % of the drug-related admissions in the present study. Most of the observed interactions in the present study resulted in problems with bleeding or hyperkalemia. In addition to drug-drug interactions, polypharmacy may also be associated with drug-disease interactions giving rise to ADRs [7].

A significant age difference was observed between patients with versus without drug-related admissions. However, the absolute age difference between the groups was small, only 1.4 years. There were no other significant differences between patients with and without drug-related admissions nor were there differences related to sex or living arrangement. We might have expected a higher number of drug-related problems among the patients' living alone compared to those living with a relative or in a nursing home. However, no account was taken to if the patients' had compliance aids or carers, and this might have impacted the risk of hospitalizations due to for example problems with compliance. No associations were seen between drug-related admissions and any specific medical history factor. This finding could indicate that people with dementia may generally run a general higher risk of drug-related admissions without being able to identify any particular predisposing medical history factor.

As expected, in the present study, ADRs accounted for the largest proportion of the drug-related problems, 45.5 %. Interestingly though, if the study had focused on investigating ADRs only, the proportion of hospital admissions due to drug-related problems would have been only 18.8 %. This discrepancy may indicate that additional drug-related problems need to be taken into account when optimizing drug therapy for old patients, especially those with dementia or cognitive impairment.

Most of the drug-related admissions in this study may have been preventable, including the prevalent type-A ADRs (related to known pharmacological effects of the drug and dosage-related). Also, many of the other drug-related problems leading to hospitalization such as *needs additional drug therapy*, *ineffective*/*inappropriate drug*, *dosage too high or low*, and *interactions* may have been avoided by improved follow-up of drug therapy and education and advice to the prescribers.

We believe the results of this study are representative for people 65 years or older with dementia or cognitive impairment admitted to acute hospital wards, since no other inclusion or exclusion criteria were used. Also, out of 473 invited patients, only 13 declined participation.

Some limitations of this study have to be taken into account. The outcome, drug-related hospital admissions, is not a fully objective outcome measure because different assessors might judge a particular admission differently. Also, the expert group consisted exclusively of clinical pharmacists. Participation of a physician might have provided a more comprehensive perspective to the drug-related problems. However, the classification of admissions were noted individually at first and then, all admissions were discussed in the group of clinical pharmacists to come toward a consensus regarding classification of admissions.

In addition to age and cognitive function, degree of frailty, and severity of the underlying disease contribute to the risk of experiencing DRPs. Indisputably, the reasons for hospitalization are in many cases multifactorial, and DRPs are often only one of several factors leading to admission. As a result, many of the DRPs were classified as *possibly* contributing to admission. Sometimes more than one drug was suspected to be responsible in connection with fall incidents, for example. In these cases, all of the suspected drugs were regarded as contributing to admission because it was impossible to determine which drug was actually responsible.

Conclusion

Drug-related problems appear to be responsible for many hospitalizations among old people with dementia or cognitive impairment. This study indicates that targeted interventions such as education and medication reviews may be warranted to reduce drug-related problems in this exposed group of old people.

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Compliance with ethical standards

Author's contributions M. Gustafsson, B. Pfister, J. Jonsson, and H. Lövheim analyzed and interpreted the data and prepared the manuscript. M. Gustafsson, M. Sjölander, B. Pfister, J. Jonsson, J. Schneede, and H. Lövheim were responsible for the study concept and design. All authors carried out a critical revision of the manuscript, contributed with comments, and approved the final version.

Conflict of interest The authors declare that they have no conflicts of interest.

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