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RESEARCH ARTICLE

Clinical impact of potentially inappropriate medications during hospitalization of acutely ill older patients with multimorbidity

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ABSTRACT

Objective: To identify potentially inappropriate medications (PIMs), to compare drug changes between geriatric and other medical wards, and to investigate the clinical impact of PIMs in acutely hospitalized older adults.

Setting and subjects: Retrospective study of 232 home-dwelling, multimorbid older adults (aged $\geq$75 years) acutely admitted to Vestfold Hospital Trust, Norway.

Main outcome measures. PIMs were identified by Norwegian general practice (NORGEP) criteria and Beers' 2012 criteria. Clinical correlates were laboratory measures, functional and mental status, physical frailty, and length of stay.

Results: Mean (SD) age was 86 (5.7) years, and length of stay was 6.5 (4.8) days. During the stay, the mean number of drugs used regularly changed from 7.8 (3.6) to 7.9 (3.6) ($p = 0.22$), and drugs used *pro re nata* (prn) changed from 1.4 (1.6) to 2.0 (1.7) ($p < 0.001$). The prevalence of any PIM changed from 39.2% to 37.9% ($p = 0.076$), while anticholinergics and benzodiazepines were reduced significantly ($p \leq 0.02$). The geriatric ward reduced drug dosages ($p < 0.001$) and discontinued PIMs ($p < 0.001$) significantly more often than other medical wards. No relations between number of PIMS and clinical outcomes were identified, but the concomitant use of $\geq$3 psychotropic/opioid drugs was associated with reduced hand-grip strength ($p \leq 0.012$).

Conclusion: Hospitalization did not change polypharmacy or PIMs. Drug treatment was more appropriate on the geriatric than other medical wards. No clinical impact of PIMs was observed, but prescribers should be vigilant about concomitant prescription of $\geq$3 psychotropics/opioids.

KEY POINTS

- Acute hospitalization of older patients with multimorbidity did not increase polypharmacy or potentially inappropriate medications.
- Prescription of anticholinergics and benzodiazepines was significantly reduced.
- The geriatric ward reduced drug dosages and discontinued potentially inappropriate medications more frequently than the other medical wards.

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Aged, clinical pharmacists, general practice, general practitioners, geriatric assessment, inappropriate prescribing, Norway, polypharmacy, psychotropic drugs

Introduction

Medication prescription is a predominant aspect of geriatric health care, and the prescription rate of potentially inappropriate medications (PIMs) is the focus of national health care quality reports in many countries. Polypharmacy and PIMs are highly prevalent in nursing home residents, home-dwelling older adults, and among an increasing proportion of older adults emergency-admitted to hospitals [1,2].

Many consensus-based PIM lists have been developed for use in geriatric drug prescription, but the most widely cited is Beers' criteria. Several studies and the Norwegian patient safety programme have used the Norwegian General Practice (NORGEP) criteria, a drug-oriented list based on Beers' criteria and developed to assess PIM use among adults $\geq$70 years in general practice [3]. According to NORGEP, the proportion of PIMs used by home-dwelling older adults was 35%, of which 65% were psychoactive medications [1]. Among older adults acutely hospital-admitted, the number of PIMs increased from 24% to 35% during their hospital stay [4]. Although drug therapy is often necessary for treating acute illness, subsequent failure to revise prescriptions given during hospitalization might increase the polypharmacy and instigate new PIMs. However, a

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previous study reported that older adults treated in a specialized geriatric hospital ward were discharged with a more appropriate drug profile than older adults treated in general medical wards. [5]. These findings need to be replicated in other geriatric hospitals' wards.

Polypharmacy and PIMs among home-dwelling older adults have previously been associated with a significant decline in activities of daily living (ADL), increased risk of hospitalization, and mortality [6–8]. One study found an association between PIMs in older acute medical inpatients with low functional status and reduced health-related quality of life, although the clinical impact of PIMs in acutely ill older adults with multimorbidity has been poorly studied [9]. Excessive use of inappropriate prescription tools as indicators for quality of drug treatment in older adults also demands greater knowledge regarding the clinical consequences of PIMs. Hence, there is a need for studies that turn consensus-based plausibility into clinical evidence, and studies that translate PIMs into clinical outcomes relevant for geriatric patients have therefore been strongly encouraged [1,10].

The objective of this study was to identify PIMs upon acute hospital admission and discharge, to compare the patterns of drug prescriptions between a dedicated geriatric ward and other medical wards, and to investigate associations between PIMs and clinical outcomes among older acutely ill medical patients.

Materials and methods

Setting and study population

This retrospective study was part of a quality assurance and evaluation project assessing health outcomes and special health care service needs following acute illness and hospitalization among home-dwelling older patients with multimorbidity. Enrolled patients were admitted as medical emergencies to Vestfold Hospital Trust and observed during their hospitalization and for one year after discharge.

The Vestfold Hospital Trust is a central hospital serving 220 000 inhabitants of 12 municipalities in Vestfold County, which covers an area of 2216 km^2 in southern Norway. Vestfold Hospital Trust is part of the public health care system in Norway which is financed by the public sector, and all acute medical patients within this area are admitted to Vestfold Hospital Trust, regardless of economic or social status. The medical clinic, which is organized into seven departments, treated 19 364 medical inpatients during 2012.

The study patients were recruited from six of the Vestfold County municipalities. They were home-dwelling and received home health care services or had been in short-term institution stays prior to hospital admission. A collaborating network between the hospital and health care service in the target municipalities ensured collection of adequate patient medical information at admission and enabled patient observation for up to one year after their acute inpatient stay. All older adult patients admitted as medical emergencies during eight months in 2012 were screened for participation eligibility. Inclusion criteria were: $\geq$75 years of age, acute admission to the hospital, ability to give informed consent, and multimorbidity defined as three or more different morbidities for which they were under care. Patients with reduced capacity to consent because of critical illness such as multiple traumas or severe dementia were excluded. We also excluded patients admitted for mechanical ventilation, patients with short life expectancy and patients living in a long-term care facility before admission.Multimorbidity was first defined by one of the project nurses based on the patient's medical admission reports and information from the municipality health care service. Second, two geriatricians independently assessed the patient's multimorbidity using the Cumulative Illness Rating Scale for Geriatrics. Potentially eligible patients were approached concerning study participation within a few days after hospital admittance (usually the day after admission). Written informed consent was obtained from all participants. Patients were included consecutively, regardless of which of the seven medical wards they were admitted to. The seven wards were comparable in terms of staffing, but only the specialized geriatric ward had a multidisciplinary team of a physiotherapist, an occupational therapist, and a clinical pharmacist in addition to the geriatric medicine specialist nurses and physicians. Hence, the patients admitted to the geriatric ward received comprehensive geriatric assessment and care.

The study was conducted in accordance with Norwegian legal regulations.

Data collection

Medical history information was obtained from participants' medical records, referral letters from their general practitioners, and in some cases information was given by their municipality health care workers. We specifically used clinical examination and medical records during participants' hospitalizations. A clinical pharmacist reviewed the drug treatment regimens of approximately 70% of the patients admitted to the geriatric unit. Potential drug-related problems were communicated to the ward physicians.

Information on prescribed drugs was collected retrospectively from the patients' medical records by one clinical pharmacist. The drug records included daily

doses used regularly and prn at admittance, during the hospital stay, and at hospital discharge.

Potentially inappropriate medications

PIMs were identified using a modified and updated list of explicit criteria in older adults in the general practice setting (NORGEP). NORGEP was originally derived from Beers' 2003 criteria through a three-round Delphi consensus involving 48 specialists in geriatrics, clinical pharmacology, and family medicine [3]. The NORGEP consists of 36 criteria, including 21 single drugs and 15 drug combinations to be avoided in patients over 70 years. In the present study, we updated NORGEP according to Beers' 2012 criteria, resulting in 38 single drugs and the original 15 drug combinations to be avoided. These 53 criteria were categorized into nine subgroups based on the rationale for the drug's inappropriateness (Appendix 1). Inappropriate medication use in older adults because of drug–disease or drug–syndrome interactions (including first- and second-generation antipsychotics prescribed to people with dementia) are not included. Three drugs (chlorpromazine, carisoprodol, and dextropropoxyphene), were removed from the list because they have been withdrawn from the Norwegian market since the NORGEP was published. The list of anticholinergic drugs that should be avoided was updated according to Beers' 2012 criteria. Additionally, eight drugs have since been added to the original NORGEP (2009) in accordance with Beers' 2012 criteria.

Clinical outcome measures

Clinical assessments were performed by one of the four study nurses within three days after hospital admission. All four study nurses were trained in the study protocol and the assessment battery. Laboratory measures potentially associated with the rationale for the drugs' inappropriateness were included in this study (e.g. potassium levels). Cognitive status was assessed using the Norwegian version of the Mini Mental State Examination (MMSE-NR) [11] and the short version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [12–13], a 16-item instrument developed to acquire proxy information on the patient's performance on daily tasks that require memory. Activities of daily living were assessed using Barthel's Index [14]. The two measures of physical function and possible frailty were the Timed Up and Go (TUG) test and a Dynamometer. TUG is a test for identifying balance or gait problems by measuring the time that it takes a person to rise from a chair, walk three metres, turn round, walk back to the chair, and sit down [15]. The Dynamometer was used to weight the hand-grip strength (HGS), which is another indicator of overall strength and general health [16]. HGS was measured three times, and the mean value was used in analyses. Finally, the length of hospital stay was recorded.

Covariates

Biomedical factors that may interfere with drug response were recorded as covariates. Kidney function was measured using the glomerular filtration rate (GFR) estimated by the modification of diet in renal disease (MDRD) study equation [17]. Body mass index (BMI) was calculated from weight and height, and the stage of dementia was rated using the MMSE-NR in combination with IQCODE and according to the Cumulative Illness Rating Scale for Geriatrics (CIRSG). Illness severity and comorbidity were assessed by two geriatricians using the CIRSG [18]. The geriatricians also evaluated the presence of delirium on admission using clinical judgement: a validated delirium screening tool was not used; hence, this variable was analysed as a covariate rather than an outcome measure.

Statistical analyses

Drug use was assessed using a repeated measure design, and a paired samples Student's *t*-test was used to compare participants' means on admission to and discharge from the hospital. The change in frequency of PIMs from admission to discharge was compared using McNemar's test for each of the nine criteria and for the total number of PIMs. The geriatric ward was compared with the six other medical wards (combined as one group) using Mann–Whitney U tests. A *post hoc* power calculation showed that subgroups of 20 were sufficient to detect clinically relevant differences between PIM users and non-users, and clinical outcome measures were compared between patients with 0, 1, and $\geq$2 PIMs using analysis of variance (ANOVA). Pearson's correlation matrix for all variables was inspected before the effects of criteria 1, 2, and 9 on the outcome measures were analysed using unadjusted and adjusted linear regression models adjusting for covariates with significance level $p < 0.1$. Additionally, parametric comparisons were performed for graphic presentations of the results. To adjust for multiple comparisons, the level of significance was set to 1%. IBM SPSS version 19 was used for all statistical analyses.

Results

Approximately 10% (250) of the 2347 screened patients were enrolled. Reasons for ineligibility were: living in another municipality ($n = 791$), not receiving health care services prior to admission ($n = 776$), living in a long-term care institution ($n = 104$), unable to carry out the study protocol or reduced capacity to assent due to critical illness ($n = 192$), declined participation ($n = 87$), or administration difficulties (i.e. predominantly incorrect registration of patients transferred from surgery as medical emergencies) ($n = 147$). Consent was withdrawn by eight enrolled patients, and 10 were later excluded because of elective admission or transfer to a surgical ward. A final $n = 232$ patients were included in analyses.

The participants had ≥3 morbidities, 43.5% had mild to severe dementia, and almost all the patients received domiciliary care prior to admission. Approximately 55.0% of participants were referred as hospital emergencies by their general practitioner, where they were referred from the emergency room to one of seven medical wards; approximately 23% were admitted to the geriatric ward.

Characteristics of the study population are given in Table 1 and the various reasons for acute hospitalization are shown in Figure 1.

Table 1. Study sample ($n = 232$) characteristics (n = valid cases for each characteristic).

Characteristic	Mean (SD) or frequency (%)
Age	*86.1 (5.7)*
Female gender	137 (59.1)
Living conditions before admission	
Living alone	166 (71.6)
Living with others	66 (27.4)
Number of health care services used before admission*	
0	0 (0)
1	169 (73.0)
≥ 2	63 (27.0)
Number of drugs used regularly	*7.8 (3.6)*
Number of drugs used prn	*1.4 (1.6)*
Potentially inappropriate medications	*0.6 (1.0)*
BMI (kg/m^2)	*23.6 (4.5)*
CIRSG total score	*21.7 (6.2)*
CIRSG Severity Index	*2.4 (0.3)*
GFR	*47.2 (15.0)*
S-haemoglobin (g/dL)	*11.0 (1.9)*
S-potassium (mmol/L	*3.7 (0.5)*
Delirium**	74 (31.9)
Dementia rating scale	
No dementia	131 (56.0)
Mild dementia	55 (23.7)
Moderate dementia	36 (15.5)
Severe dementia	10 (4.3)
MMSE	*23.0 (5.2)*
IQCODE	*60.8 (12.6)*
TUG (sec)	*32.0 (19.7)*
Grip strength left hand (kg)	*13.3 (8.4)*
Grip strength right hand (kg)	*14.1 (8.6)*
Barthel's index	*13.0 (4.9)*

*Health care services include short-term institutional care, home care nursing, day care, and practical home care services.

**Delirium was based on the clinical judgement of two gerontologists. Abbreviations: BMI = body mass index, CIRSG = Cumulative Illness Rating Scale for Geriatrics, GFR = glomerular filtration rate (calculated by the Modification of Diet in Renal Disease (MDRD) formula), MMSE = Mini Mental State Examination, IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, TUG = Time Up and Go.

Drug changes during hospitalization

The mean number of drugs regularly used was approximately the same at hospital admission 7.8 (3.6) and discharge 7.9 (3.6); however, many drug changes were made during hospitalization. In addition to the 133 patients who had one to seven prescribed drugs removed from their medication records, 102 total daily doses were reduced. Cardiovascular drugs, predominantly diuretics, were most often withdrawn, reduced, or replaced. In addition, the dosage of psycholeptic drugs and analgesics was among the quantities most frequently reduced. Furthermore, 133 patients were discharged with one to seven new prescriptions, and 184 daily doses were increased at the hospital. Paracetamol was the drug most frequently changed, mainly because of initiated treatment or dose increment, but new prescriptions for laxatives and mineral supplements for regular use, and higher dosages of glucocorticoids and inhalation drugs used for obstructive lung disease were also relatively often initiated at the hospital. The mean number of drugs used prn increased significantly from hospital admission 1.4 (1.6) to discharge 2.0 (1.7), ($p < 0.001$). More than 70% of the as-needed drugs instigated at the hospital were laxatives, or a short course of antibiotics and glucocorticoids to be discontinued by the general practitioner after short-term use.

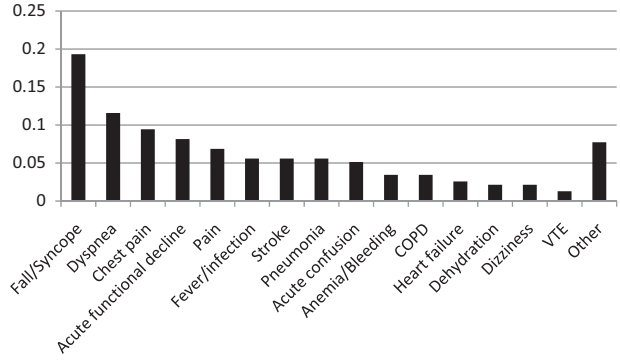

Figure 1. Reasons for acute admission to Vestfold Hospital Trust; $N = 232$, X-axis = n/N.
VTE = venous thromboembolism.

Potentially inappropriate medications

During hospitalization, 49 PIMs were withdrawn, while 30 new PIMs were prescribed and the patients had up to five PIMs at both time points. Almost 30% of the new

Table 4. Analyses of variance (ANOVA) comparing mean differences in clinical outcome measures between patients with 0, 1, and ≥ 2 PIMs at hospital admission.

	Number of PIMs present						
	0 ($n = 141$)		1 ($n = 54$)		≥2 ($n = 37$)		
Clinical outcomes	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	Between-groups variance, F (p-value)
MMSE	139	22.7 (5.3)	53	23.2 (5.4)	36	23.9 (4.6)	0.8 (0.5)
IQCODE	75	61.1 (12.8)	32	58.7 (12.5)	21	63.0 (12.5)	0.8 (0.5)
TUG (sec)	71	31.1 (18.3)	28	33.8 (22.4)	22	32.4 (21.3)	0.2 (0.8)
Grip strength left hand (kg)	108	14.3 (9.0)	45	12.1 (7.2)	31	11.2 (7.7)	2.2 (0.1)
Grip strength right hand (kg)	108	14.9 (8.9)	45	12.8 (7.6)	31	13.3 (8.7)	1.1 (0.3)
Barthel's index	140	13.2 (4.8)	53	12.9 (4.7)	35	12.2 (5.3)	0.6 (0.6)
Length (days) of hospital stay	141	6.4 (4.4)	54	6.7 (4.2)	37	6.8 (6.1)	0.1 (0.9)

Abbreviations: MMSE = Mini Mental State Examination, IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, TUG = Time Up and Go.

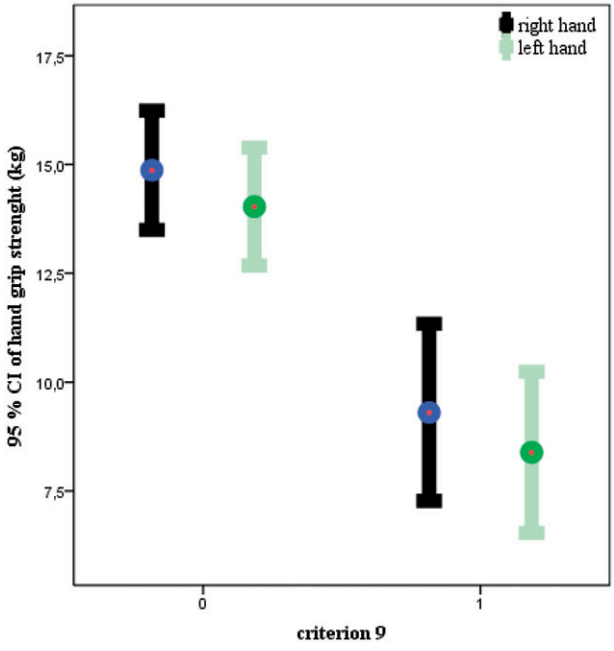

Figure 2. Hand-grip strength measured by dynamometer for non-users (0) and users (1) of ≥ 3 psychotropic drugs or opioids (criterion 9).

PIMs introduced were because of the combination of ACE inhibitor and potassium/potassium-sparing diuretics, but none of the patients using this PIM combination had hyperkalaemia; their potassium levels ranged from 3.50 mmol/L to 4.70 mmol/L. The prevalence of anticholinergic drugs and benzodiazepines was significantly reduced, ($p < 0.02$) (Table 2). Among the PIMs identified by the present criteria list, 53 were not captured by NORGEP.

Drug changes in the geriatric ward compared with other medical wards

There were more drug changes made on the geriatric ward than on other medical wards, i.e. there were significantly more discontinuations and dosage reductions, $p < 0.001$ (Table 3). Diuretics, benzodiazepines, and anticholinergics were more often discontinued or reduced in the geriatric ward. Despite more PIMs being reduced and fewer new PIMs being initiated on the geriatric ward compared with the other medical wards, the total reduction of PIMs did not differ significantly.

Table 3. Frequencies of drug changes in geriatric ward versus other medical wards.

Drug changes	Geriatric ward ($n = 54$) *n* (%)	Medical ward ($n = 178$) *n* (%)	Mann Whitney test *p*-value
Withdrawals	97 (79.6%)	208 (50.6%)	<0.00
Dosage reduced	41 (51.9%)	61 (25.3%)	<0.00
New regular drugs	66 (63%)	186 (55.6%)	0.25
New as-needed drugs	69 (68.5%)	170 (65.1%)	0.11
Dosage increased	30 (42.6%)	88 (34.8%)	0.381
Withdrawals of PIMs	20, 22.2% (1–3)	31, 12.4% (1–3)	0.115
New PIMs prescribed	3, 5.6% (1)	26, 11.8% (1–2)	0.287

The percentages in each subgroup do not ad up to 100% because subjects may have had several drug changes within categories.

Relation between PIMs and clinical health outcomes

The number of PIMS at admission was not significantly associated with any of the clinical outcomes measured during hospitalization or with the length of the hospital stay (Table 4). Furthermore, there were no significant differences between the users and non-users of drugs in criterion 1 (anticholinergics) and criterion 2 (benzodiazepines) on clinical outcomes for cognitive function, muscle strength, mobility, or functional level ($p > 0.30$). However, the 31 patients using three or more psychotropic drugs (criterion 9) at admission had significantly lower hand-grip strength (HGS) with > –5.5 kg (95% CI –8.0, –3.4) in both hands ($p < 0.01$) (Figure 2). The contribution of criterion 9 drugs remained significant after adjusting for the effect of comorbidity, gender, and age ($p < 0.01$).

Discussion

Despite changes to many patients' prescribed drugs from hospital admission to discharge, the number of drugs used regularly and the total number of PIMs did not differ. The multidisciplinary team in the geriatric ward made significantly more changes to patients' drug therapy compared with the other medical wards. The total number of PIMs at acute hospital admission of older adults aged $\geq$75 years with multimorbidity was not significantly associated with patients' cognitive measures, level of activities in daily living, or physical frailty. However, concomitant use of $\geq$3 psychotropic drugs was significantly associated with reduced HGS.

Strengths and limitations

Many previous studies of PIMs have been limited by their lack of clinical information regarding the patients, and studies designed to assess the impacts of PIMs on health outcomes have been encouraged [1]. Investigation of how PIMs affect the clinical condition of acutely ill older adult patients is a major strength of the present study. The value of this study is further increased by our having including a naturalistic patient group that represents an increasing proportion of hospital admissions – and a group expected to continue increasing because of the ageing population with multimorbidity and polypharmacy use.

Although this study was not designed to investigate the clinical impact of PIMs on the study population, many of the clinical data recorded are relevant geriatric outcomes for the overall effect of complex medication therapy. The criteria list used to identify PIMs has not been previously validated but was based strictly on NORGEP and Beers' criteria, both of which have been thoroughly validated [3,19].

The study was limited by the relatively small and unequally sized subgroups, which might have caused type II errors. Hence, we cannot rule out the possibility that this study may have lacked statistical power to detect small differences between PIM users and non-users. However, a *post hoc* power calculation showed that the statistical power was sufficient to detect a clinically meaningful cognitive and functional difference between subgroups with $n \geq 20$. On the other hand, there is also a risk of type I error due to multiple significance tests. This was adjusted for by using a significance level of 1% in the multiple comparisons and by performing both parametric and non-parametric sensitivity tests. Hence, we believe that the observed differences in this study are noteworthy.

Drug changes during hospitalization

According to previous findings, hospitalization is related to an increase in the number of drugs and PIMs [4]. Interestingly, no such increase was found in this study. An average number of drugs for this population was used at admission, but the prevalence of PIMs was relatively high compared with a similar study [4]. It is possible that the high number of PIMs at admission contributed to the numbers not increasing further during hospitalization [4]. Nevertheless, many drug changes were made during the hospital stays, and significantly more drug changes were made on the geriatric ward compared with the other medical wards. Previous studies have shown positive effects of comprehensive geriatric assessment and care for older acute medical patients on critical outcomes [20], while other studies have shown that clinical pharmacists are able to identify and prevent drug-related problems through active participation in the geriatric multidisciplinary health care team [21]. Accordingly, it is likely that the comprehensive geriatric assessment and care given by a specialized interdisciplinary team resulted in a more dynamic approach to the drug therapy compared with the other medical wards. Significantly more dosages were reduced, and significantly more drugs were discontinued. In particular, drugs considered to be inappropriate for older adults (e.g. diuretics were reduced, and anticholinergics were withdrawn) were more often adjusted in the geriatric ward. Hence, drug therapy was more tailored to vulnerable geriatric patients. A previous study consistently concluded that more appropriate drug treatment patterns were developed for older patients in the geriatric ward compared with other medical wards [5].

Clinical impact of potentially inappropriate medications

The number of PIMs has previously been associated with negative health outcomes (e.g. low functional status, reduced health-related quality of life) for older adults [9]. However, in this study, the total number of PIMs was not associated with any of the clinical outcomes measured. This lack of effect might denote the general limitations of all drug-oriented geriatric prescription tools. Older adults are a heterogeneous group with regard to drug response because of divergent ageing processes, functional status, organ function, and morbidity. Therefore, so-called inappropriate drugs might be needed and well tolerated in some, while others might experience harmful side effects. Accordingly, general lists of drugs to be avoided might classify appropriate drugs as inappropriate [10].

Our criteria list included anticholinergic drugs and benzodiazepines, which are considered to be

inappropriate because use of such drugs is related to cognitive and physical impairments in older adults [22–26]. Higher anticholinergic and sedative drug burden has also been shown to predict the length of hospital stay independently [23].

In contrast, we did not find any significant differences between the users and non-users of anticholinergics and benzodiazepines concerning the clinical outcomes for cognitive function, muscle strength, mobility, functional level, or length of stay. This lack of effect might be because of the relatively small number of patients using anticholinergics and benzodiazepines despite the statistical power being sufficient to detect a clinically meaningful cognitive and functional difference between the groups. Another explanation may be the focus on safe drug therapies for older adults for several years in Norwegian municipalities. Consequently, the general practitioners included in this study might have performed drug reviews and evaluated the appropriateness of the pharmacotherapy on a regular basis. However, our findings are consistent with others that have not shown cognitive effects of high anticholinergic drug burden and benzodiazepine use in older patients [27–29].

We found that concomitant use of $\geq$3 psychotropic drugs was significantly related to lower HGS. This is in accordance with a previous study, and the result is important because HGS could be used as an indicator of overall strength and general health [9,16]. This association should be studied further in larger study populations.

Conclusion

Although hospitalization did not change the degree of polypharmacy or the number of PIMs, the present study shows that a collaborative approach to drug prescription within the context of geriatric evaluation and management units improves drug therapy appropriateness.

No association was found between the prescription rate of PIMs on admission, the length of hospital stay, and several measures related to the rationale for the drug's inappropriateness. However, concomitant prescription of $\geq$3 psychotropic drugs was significantly associated with reduced HGS, and prescribers should be attentive to this prescription criterion.

Ethics

The study was conducted according to the agreement by the Regional Committee for Medical Research Ethics and approved by the Norwegian Social Science Data Services.

Quality assurances that do not require approval from the REC are available in Norwegian.

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Declaration of interest

The authors report no conflict of interest. The authors take all responsibility for the content and the writing of this paper.

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References

1. Nyborg G, Straand J, Brekke M. Inappropriate prescribing for the elderly: a modern epidemic? Eur J Clin Pharmacol 2012;68:1085–94.
2. Bergman A, Olsson J, Carlsten A, Waern M, Fastbom J. Evaluation of the quality of drug therapy among elderly patients in nursing homes. Scand J Prim Health Care 2007;25:9–14.
3. Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients: A modified Delphi study. Scand J Prim Health Care 2009;27:153–9.
4. Bakken MS, Ranhoff AH, Engeland A, Ruths S. Inappropriate prescribing for older people admitted to an intermediate-care nursing home unit and hospital wards. Scand J Prim Health Care 2012;30:169–75.
5. Saltvedt I, Spigset O, Ruths S, Fayers P, Kaasa S, Sletvold O. Patterns of drug prescription in a geriatric evaluation and management unit as compared with the general medical wards: A randomised study. Eur J Clin Pharmacol 2005;61:921–8.
6. Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging 2009;26:1039–48.
7. Hilmer SN, Gnjidic D, Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther 2009;85:86–8.
8. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: A population-based study of the very old. Drugs Aging 2005;22:69–82.
9. Jensen LD, Andersen O, Hallin M, Petersen J. Potentially inappropriate medication related to weakness in older acute medical patients. Int J Clin Pharm 2014;36:570–80.
10. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, Hanlon JT. Appropriate prescribing in elderly people: How well can it be measured and optimised? Lancet 2007;370:173–84.
11. Braekhus A, Laake K, Engedal K, Braekhus A, Laake K, Engedal K. The Mini-Mental State Examination: Identifying the most efficient variables for detecting cognitive impairment in the elderly. J Am Geriatr Soc 1992;40:1139–45.
12. Jorm AF. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): A review. Int Psychogeriatr 2004;16:275–93.

13. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Development and cross-validation. Psychol Med 1994;24:145–53.
14. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. MD State Med J 1965;14:61–5.
15. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther 2000;80:896–903.
16. Shiratori AP, Iop RD, Borges Junior NG, Domenech SC, Gevaerd MD. Evaluation protocols of hand grip strength in individuals with rheumatoid arthritis: A systematic review. Rev Bras Reumatol 2014;54:140–7.
17. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.
18. Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, Spazzafumo L, Mancinelli L, Espinosa E, Rappelli A, Dessi-Fulgheri P. A manual of guidelines to score the Modified Cumulative Illness Rating Scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926–31.
19. American Geriatrics Society. Updated Beers Criteria for Potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616–31.
20. Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: Meta-analysis of randomised controlled trials. BMJ 2011;343:d6553.
21. Viktil KK, Blix HS. The impact of clinical pharmacists on drug-related problems and clinical outcomes. Basic Clin Pharmacol Toxicol 2008;102:275–80.
22. Landi F, Russo A, Liperoti R, Cesari M, Barillaro C, Pahor M, Bernabei R, Onder G. Anticholinergic drugs and physical function among frail elderly population. Clin Pharmacol Ther 2007;81:235–41.
23. Lowry E, Woodman RJ, Soiza RL, Hilmer SN, Mangoni AA. Drug burden index, physical function, and adverse outcomes in older hospitalized patients. J Clin Pharmacol 2012;52:1584–91.
24. Cao YJ, Mager DE, Simonsick EM, Hilmer SN, Ling SM, Windham BG, Crentsil V, Yasar S, Fried LP, Abernethy DR, Cao YJ, Mager DE, Simonsick EM, Hilmer SN, Ling SM, Windham BG, Crentsil V, Yasar S, Fried LP, Abernethy DR. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. Clin Pharmacol Ther 2008;83:422–9.
25. Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, Smithard D, Coulton S, Katona C, Boustani MA, Brayne C. Anticholinergic medication use and cognitive impairment in the older population: The Medical Research Council cognitive function and ageing study. J Am Geriatr Soc 2011;59:1477–83.
26. Lampela P, Lavikainen P, Garcia-Horsman JA, Bell JS, Huupponen R, Hartikainen S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: A population-based study. Drugs Aging 2013;30:321–30.
27. Kersten H, Molden E, Tolo IK, Skovlund E, Engedal K, Wyller TB. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: A randomized controlled trial. J Gerontol A Biol Sci Med Sci 2013;68:271–8.
28. Tollefson GD, Montague-Clouse J, Lancaster SP. The relationship of serum anticholinergic activity to mental status performance in an elderly nursing home population. J Neuropsychiatry Clin Neurosci 1991;3:314–19.
29. Hoiseth G, Tanum L, Tveito M, Kristiansen KM, Kvande K, Lorentzen B, Refsum H, Bramness J. A clinical study of the cognitive effects of benzodiazepines in psychogeriatric patients. Pharmacopsychiatry 2013;46:209–13.

Appendix 1

Appendix 1. Fifty-three criteria for potentially inappropriate medications in older adults based on NORGEP and Beers' 2012, and categorized into nine subgroups.

Criteria	Rationale
1. Anticholinergic drugs Antidepressants (amitriptyline, clomipramine, doxepin, nortriptyline*, paroxetine*, trimipramin) Antipsychotics (chlorprothixene, clozapine*, levomepromazine, olanzapine*, prochlorperazine, perphenazine*) Antihistamines (alimemazine, dexchlorfeniramine, hydroxyzine, loratidine*, meclizine*, promethazine) Urinary spasmolytics (darifenacin* fesoterodine* oxybutynin* solifenacin* tolterodine*)	Anticholinergic adverse effects including increased risk of impaired cognitive function
2. Long acting benzodiazepines and high doses of benzodiazepines and benzodiazepine-related drugs (alprazolam > 4.5 mg/24 h*, clonazepam*, diazepam, flunitrazepam, nitraxepam, oxazepam > 30 mg/24 h, zolpidem > 5 mg/24 h*, zopiclone > 7.5 mg/24 h)	Prolonged elimination half-life, risk of accumulation, muscular weakness, falls and fractures
3. Theophylline	Increased risk of arrhythmias and no documented effect in chronic obstructive pulmonary disease
4. Antiarrhythmic drugs, Class 1a, 1c, III (amidarone*, disopyramide*, dronedarone*, flecainide*, sotalol)	Increased risk of arrhythmias and poor safety record
5. Metoclopramide*	Increased risk of extrapyramidal adverse effects
6. Combinations with warfarin:	Increased risk of intestinal bleeding
warfar*in* + NSAID, warfar*in* + ofloxacin/	Increased risk of bleeding due to inhibition of warfarin metabolism
ciprofloxacin warfari *n* + erythromycin/ clarithromycin warfarin + SSRI	Increased risk of bleeding due to a direct platelet-inhibiting effect
7. Combinations with NSAIDs:	Increased risk of renal failure
NSAIDs (or coxib) + ACE inhibitor/ARB	Reduced effect of diuretics
NSAID + diuretic	Increased risk of intestinal bleeding. Risk of fluid retention
NSAIDs + glucocorticoid	Increased risk of gastrointestinal bleeding
NSAIDs + SSRI	
8. Other combinations	(i)–(iv): Potentially harmful pharmacokinetic CYP interactions
(i) Erythromycin/claritromycin + statin	(i) and (ii): Increased risk of adverse effects of statins, including rhabdomyolysis, due to inhibition of statin metabolism
(ii) Diltiazem + lovastatin/simvastatin	
(iii) Floxetine/fluvoxamine + TCA	Increased risk of adverse effects of TCAs due to inhibition of TCA metabolism
(iv) Erythromycin/claritromycin + carbamazepine	Increased risk of adverse effects of carbamazepine due to inhibition of its metabolism
(v) ACE inhibitor + potassium/potassium-sparing diuretic	(v) and) vi): Potentially harmful pharmacodynamic interactions
vi) Beta blocker + cardioselective calcium antagonist	Increased risk of hyperkalaemia Increased risk of atrioventricular block and myocardial depression
9. Concomitant prescription of three or more drugs from the groups centrally acting analgesics, antipsychotics, antidepressants, and/or benzodiazepines	Increased risk of muscle weakness, fall, fractures, and cognitive impairments

Drugs from Beers' 2012 that are not included in the NORGEP criteria.