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Need for Deprescribing in Hospital Elderly Patients Discharged with a Limited Life Expectancy: The REPOSI Study

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Significance of the Study

- Pharmacotherapy in older patients with a limited life expectancy should avoid unnecessary polypharmacy and focus on symptom control. This study showed a small reduction in the use of commonly prescribed preventive medications. Medications could be reviewed to optimize polypharmacy.

Keywords
Elderly · End of life · Limited life expectancy · Polypharmacy · Symptomatic medications

Abstract

Objective: Older people approaching the end of life are at a high risk for adverse drug reactions. Approaching the end of life should change the therapeutic aims, triggering a reduction in the number of drugs. The main aim of this study is to describe the preventive and symptomatic drug treatments prescribed to patients discharged with a limited life expectancy from internal medicine and geriatric wards. The secondary aim was to describe the potentially severe drug-drug interactions (DDI). ***Materials and Methods:*** We analyzed Registry of Polytherapies Societa Italiana di Medicina Interna (REPOSI), a network of internal medicine and geriatric wards, to describe the drug therapy of patients discharged with a limited life expectancy. ***Results:*** The study sample comprised 55 patients discharged with a limited life expectancy. Patients with at least 1 preventive medication that could be considered for deprescription at the end of life were significantly fewer from admission to discharge ($n = 30$; 54.5% vs. $n = 21$; 38.2%; $p = 0.02$). Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, lipid-lowering drugs, and clonidine were the most frequent potentially avoidable medications prescribed at discharge, followed by xanthine oxidase inhibitors and drugs to prevent fractures. Thirty-seven (67.3%) patients were also exposed to at least 1 potentially severe DDI at discharge. ***Conclusion:*** Hospital discharge is associated with a small reduction in the use of commonly prescribed preventive medications in patients discharged with a limited life expectancy. Cardiovascular drugs are the most frequent po-

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tentially avoidable preventive medications. A consensus framework or shared criteria for potentially inappropriate medication in elderly patients with limited life expectancy could be useful to further improve drug prescription.

Introduction

The end of life is the preterminal phase of a person's decline towards death and normally involves accumulating health problems over a period of weeks to months, with failing homeostasis that is irreversible and inexorably leads to death [1]. Older people approaching the end of life are at a high risk for adverse drug reactions resulting from polypharmacy, declining organ function, comorbidity, malnutrition, cachexia, and changes in body composition [2]. As a consequence, approaching the end of life should shift the therapeutic aims, triggering a reduction in the number of drugs, but this is not the usual practice [3–5].

The aim of pharmacotherapy in the rising numbers of end-of-life older people should be to avoid polypharmacy and focus on controlling symptoms rather than prolonging life [1, 2]. Although polypharmacy is very common among older end-of-life patients, with their need to relieve symptoms, disease-related problems, and quality of life [6–8], it may also be a major risk factor for inappropriate prescribing and potentially severe drug-drug interactions (DDI) [2, 9, 10]. In this circumstance, drugs for the prevention of secondary diseases are of no value if the time to therapeutic benefit exceeds the probable life expectancy and should be discouraged. However, the few studies that have examined drug therapy in patients at the end of life have found that about half of them continued to take ineffective and unnecessary medication for the prevention or treatment of chronic diseases [11], although the potential for harm can be expected to outweigh any benefit in view of the limited life expectancy [6, 12]. Statins, antihypertensives and bisphosphonates are frequently used in patients with a terminal disease and advanced disability, although the real benefits are unknown because their safety and efficacy have been demonstrated for a young general population but evidence supporting their utility at the end of life is limited [12–14].

No study has examined the prescription of internal and geriatric hospital specialists to patients with a limited life expectancy. The main aim of this study was to describe the preventive and symptomatic drug treatments prescribed to patients discharged with a limited life expectancy from internal medicine and geriatric wards. The secondary aim was to describe the potentially severe DDI.

Materials and Methods

Data Collection

The Registry of Polytherapies Societa Italiana di Medicina Interna (REPOSI) is a collaborative, independent initiative of the Italian Society of Internal Medicine (SIMI), the Istituto di Ricerche Farmacologiche Mario Negri IRCCS, and the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation. The registry was set up in 2008 by a network of internal medicine and geriatric wards in order to collect information on elderly hospital in-patients with multimorbidities receiving multiple drugs. The first run of data collection was between January and December 2008, and the second, third, and fourth runs as well as ongoing runs took place between January and December 2010, 2012, 2014, and 2016, respectively. To ensure an unselected population of elderly patients admitted to internal medicine and geriatric wards, the first 5 patients admitted to the wards participating in this study during 4-week periods 3 months apart were consecutively recruited if they were 65 years old or older. Participation was voluntary and all patients gave signed informed consent. Data collection complied fully with Italian law on personal data protection and this study was approved by the ethics committees of each ward participating in REPOSI.

The attending physicians completed a standardized web-based case report form, recording sociodemographic details and the diagnosis and drug treatment at admission, during the hospital stay, and at discharge. From the second REPOSI runs we collected the following additional information for a short-term follow-up in order to improve the quality of the data: main laboratory parameters, comorbidity according to the Cumulative Illness Rating Scale (CIRS), basic activities of daily living, cognitive impairment, depression, and clinical events during the hospital stay. Patients were followed for 3 months after discharge via a telephone interview in order to collect information on new diagnoses, hospital readmissions, drug regimens, adverse events, basic activities of daily living, and mortality.

To describe the drug therapy of patients discharged with a limited life expectancy, we considered eligible for analysis all patients discharged in "critical condition," defined as a high risk of short-term mortality (at 3 months) on the basis of the clinical evaluation. Analysis of each patient's drug therapy at admission reflects drugs prescribed by general practitioners for patients who lived at home, or physicians in nursing homes for those in an institution; drug therapy at discharge referred to prescriptions by hospital internists or geriatricians. Patients transferred to palliative care wards, though potentially terminally ill, were excluded because the drug therapy at discharge was not collected.

Classification of Drug Therapies

The drugs prescribed at admission and discharge were divided into the following 3 main classes according to their preventive or symptomatic effects: (1) potentially avoidable preventive medications, i.e., drugs that usually have no place in the end-of-life patient because the time to benefit is clearly shorter than the life expec-

Table 1. Main characteristics and diagnosis of the 55 patients discharged in critical condition

Characteristic	Value
Age, years	80.8± 83
Female sex, %	43.6
Caregiver	38 (71.7)
Hospital admission in the previous 6 months	27 (49.1)
BMI	23.6±3.7
Underweight	4 (9.7)
Normal	25 (61.0)
Overweight	12 (29.3)
Bedridden	20 (40.8)
Pressure sores	24 (66.7)
Systolic blood pressure	116.2±22.1
Diastolic blood pressure	67.1±12.4
Short Blessed Test	15.6±8.6
Barthel index	54.7±34.4
Geriatric depression scale	1.8±1.1
Cumulative illness rating scale	
Severity index	1.9±0.4
Comorbidity index	3.9±2.1
Main diagnosis	
Hypertension	41 (74.6)
Heart failure	15 (27.3)
Chronic renal failure	13 (23.6)
Atrial fibrillation	14 (25.4)
Cancer	23 (41.8)
Diabetes	13 (23.6)
Ischemic heart disease	14 (25.4)
Chronic bronchitis	13 (23.6)
Anemia	11 (20.0)
Dementia	13 (23.6)
Cachexia	1 (0.2)

Values are presented as means ± SD or numbers (%) unless otherwise stated.

tancy; (b) medications of uncertain appropriateness, i.e., drugs that need a case-by-case evaluation because they could have a role in end-of-life patients but their real effectiveness is questionable on account of the short life expectancy; and (c) potentially appropriate treatments, i.e., drugs that provide symptomatic relief or that should be tapered slowly over several weeks or months in order to avoid withdrawal symptoms, such as psychotropic drugs or proton pump inhibitors [15]. A geriatrician and a clinical pharmacologist separately analyzed drug prescriptions and resolved any discordances with a final round.

Statistical Analysis

The patients' sociodemographic characteristics were compared using univariate analysis by χ^2 tests for categorical variables and *t* tests or matched pair *t* tests for continuous variables. The McNemar test was used to compare drug treatments at admission and discharge. $p < 0.05$ were considered statistically significant. Analyses were done using JMP Pro 12 (SAS Institute Inc., Cary, USA).

Results

The sample comprised 55 end-of-life patients recruited among the patients discharged by the internal medicine and geriatric wards of REPOSI. Follow-up data were available for 30 of those discharged in critical conditions; 27 (90%) died between discharge and the 3-month follow-up, confirming their limited life expectancy. The main sociodemographic characteristics and diagnoses are reported in Table 1. Patients had high rates of comorbidity and most of them suffered from cardiovascular diseases. About 72% had a caregiver and most had cognitive impairment consistent with a diagnosis of dementia. Half of the patients had been admitted in the previous 6 months and were bedridden at discharge with pressure sores.

The mean number of drugs remained the same from admission to discharge (mean ± SD: 5.5 ± 3.6 and 5.5 ± 3.4; $p = 0.97$). Table 2 lists the drugs that we considered as potentially avoidable preventive medications in end-of-life patients, those of uncertain appropriateness, and those that were potentially appropriate. There were significantly fewer patients with at least 1 preventive medication that could be considered for deprescription at the end of life from admission to discharge ($p = 0.02$). Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, lipid-lowering drugs, and clonidine were the most frequent potentially avoidable cardiovascular medications prescribed at discharge, followed by xanthine oxidase inhibitors and drugs to prevent fractures. Drugs for peptic ulcer and gastroesophageal reflux disease, analgesics, psychotropic drugs, and systemic corticosteroids were the potentially appropriate symptomatic medications maintained at discharge.

Patients exposed to at least 1 potentially severe DDI slightly increased between admission (31; 56.4%) and discharge (37; 67.3%; $p = 0.18$); drugs that concomitantly increased the risk of QT prolongation and torsades de pointes, followed by those that increased the risk of bleeding, were the most frequent potentially severe DDI (Table 3).

Discussion

Identification of the end of life should bring about a significant reduction in the number of daily drugs, but this was not observed in the present study. Hospital discharge was associated with only a small, though significant, reduction in the use of preventive medications that are commonly prescribed. However, these results could be further

Table 2. Main pharmacological treatment of patients discharged in critical condition

	Patients	
	admission	discharge
Potentially avoidable preventive medications		
At least 1	30 (54.5)	21 (38.2)
Cardiovascular drugs		
Omega-3	1	1
Statins	5	3
Clonidine	3	3
ACE inhibitors or ARB	15	9
Calcium channel blockers	10	4
Hematological agents		
Iron	–	1
Folic acid	–	2
Antidiabetic agents		
Oral antidiabetic	4	0
Other		
Xanthine oxidase inhibitors	11	5
Calcium carbonate	1	1
Cholecalciferol	–	1
Preventive medications of uncertain appropriateness		
At least 1	34 (61.8)	30 (54.5)
Hematological agents		
Low-molecular-weight heparin	12	20
Erythropoietin-stimulating agents	2	4
Antiplatelets	18	7
Oral anticoagulants	4	4
Other		
Antineoplastic agents	1	0
Immunosuppressants	2	0
Doxophylline	–	1
Albumin	1	2
Cholestyramine[a]	–	1
Potentially appropriate drugs		
At least 1	50 (90.9)	47 (85.5)
Cardiovascular drugs		
High-ceiling diuretic	21	19
β-Blockers	15	10
Diltiazem	1	1
Potassium-sparing diuretics	9	5
Long-acting nitrates[b]	7	7
Cardiac therapy	9	8
Analgesics	11	17
Gastrointestinal drugs		
Drug for peptic ulcer and GERD	35	36
Laxatives	3	4
Prokinetics	2	3
Psychotropic drugs		
Antidepressants[c]	7	5
Hypnotic sedatives	5	3
Antipsychotics	4	5
Antidiabetic agents		
Insulin	10	11
Other		
Systemic corticosteroids	10	20
Antiasthmatics	11	8
Antibiotics	8	16
Alpha antagonists for BPH	5	4
Testosterone 5α-reductase inhibitors	2	2
Antiepileptics	9	7
Antifungals	1	4
Antiparkinson	3	1
Thyroid therapy	6	5

Values are presented as numbers (%) or numbers. ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor antagonist; BPH, benign prostatic hypertrophy; GERD, gastroesophageal reflux disease. [a] To relieve itching caused by partial biliary obstruction. [b] Including nitroglycerin and isosorbide. [c] Including trazodone, venlafaxine, and duloxetine; $p = 0.02$.

improved since in fact about 40% of patients were discharged with avoidable medications. Cardiovascular drugs were the potentially avoidable preventive medications most frequently prescribed at admission that were partially reduced at discharge. Most cardiovascular drugs usually have no place in end-of-life patients because the time to benefit is clearly shorter than the life expectancy [2]; when prescribed to prevent diabetic nephropathy or reduce mortality from heart failure angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers (excluding diltiazem or verapamil) are of little value when a patient's life expectancy is severely curtailed as a result of other irreversible disorders. Similarly, lipid-lowering drugs are almost always inappropriate at the end of life. There were definite reductions in the prescription of oral antidiabetics and xanthine oxidase inhibitors at discharge. Stopping these drugs is generally appropriate because the goals for managing diabetes change at the end of life since it is no longer important to prevent the long-term effects of hyperglycemia. Similarly, treating asymptomatic hyperuricemia to prevent gout is clearly inappropriate [16] in the end-of-life patient.

Among the preventive medications of uncertain appropriateness, the use of low-molecular-weight heparin increased at discharge while the proportion of patients treated with antiplatelet drugs decreased; these drugs could be useful in preventing thrombotic events, although they increase the risk of bleeding in older and frailer pa-

Table 3. Most frequent potentially severe DDI

Drug class combination	Potential adverse events	Patients	
		admission	discharge
Drugs associated with QT prolongation [22]	Increased risk of QT prolongation and torsades de pointes	26 (47.3)	32 (58.2)
Anticoagulants or antiplatelets + antiplatelets or SSRI	Increased risk of bleeding	10 (18.2)	11 (20.0)
Digoxin + high-ceiling diuretic	Increased risk of digoxin toxicity	4 (7.3)	5 (9.1)
SSRI + opioid analgesic	Increased risk of serotonin syndrome	3 (5.5)	1 (1.8)
Potassium-sparing diuretics + ACE inhibitors or potassium supplements or enoxaparine	Increased risk of hyperkalemia	2 (3.6)	4 (7.3)
Statin + inhibitor of hepatic metabolism[a]	Increased risk of myopathy including rhabdomyolysis	2 (3.6)	2 (3.6)
Fluoroquinolones + systemic corticosteroid	Increased risk of tendon rupture	2 (3.6)	1 (1.8)

Values are presented as numbers (%). SSRI, selective serotonin reuptake inhibitors; ACE, angiotensin converting enzyme.
[a] Ticagrelor.

tients who often fall. It is hard to assess the appropriateness of these medications and a case-by-case evaluation is needed, although anticoagulants and antiplatelets were frequently involved in potentially severe DDI at discharge, increasing the risk of adverse drug events. Because deprescribing must consider not only the risks of individual drugs but also the cumulative risk of DDI [17], the higher percentage of patients exposed to potentially severe DDI emphasizes the need for closer evaluation of drugs prescribed to end-of-life patients.

Our findings suggest that the review of drug medications, optimizing polypharmacy and deprescribing could be further improved in older adults discharged with a very limited life expectancy (e.g., less than 3 months). A consensus framework, or shared criteria with deprescribing guidelines for potentially inappropriate medication, could be useful in rationalizing drug therapy. Careful consideration of a patient's life expectancy, the time to benefit of treatments, goals of care, and treatment targets for each drug (including those used for a long time before the end-of-life period) is important for recommending any rational framework for decision making [2, 5, 18].

There may be several reasons for physicians not considering the discontinuation of futile medications in patients with a limited life expectancy. Scant awareness, as well the reactions of patients or their relatives, seems to be an important factor [19]. Unexpectedly, patients may be more willing to stop unnecessary medications than their physicians believe, as observed in a study of older patients with multiple chronic morbidities who were favorable to discontinue medication in 90% of cases [20]. Emphasizing the positive aspects of stopping medicines, such as reducing the burden of taking pills, rather than insisting on the uselessness of continuation, may be a helpful approach [21] that physicians could emphasize in conversations with patients and relatives.

The strength of this study is that this it analyzes how the hospital transition can be associated with changes in preventive and symptomatic medications by internal medicine and geriatric specialists for patients with a limited life expectancy.

This study has some limitations. First, REPOSI was not specifically designed to collect information about patients with a limited life expectancy and only those able to give written informed consent were enrolled, thus excluding those who were too frail to give consent. The sample of patients is very small, because we focused on patients in 'critical conditions', so we could assess the use of preventive or symptomatic drugs in patients with a limited life expectancy according to the clinical evaluation.

Conclusion

Hospital discharge is associated with a small reduction in the use of commonly prescribed preventive medications in patients discharged with a limited life expectancy. Cardiovascular drugs are the most frequent potentially avoidable preventive medications. A consensus framework or shared criteria for potentially inappropriate medication in elderly patients with a limited life expectancy could help improve drug prescription.

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Disclosure Statement

The authors declare no conflict of interests.

Appendix

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