ORIGINAL RESEARCH

Potentially Inappropriate Prescriptions in Ambulatory Elderly Patients Living in Rural Areas of Romania Using STOPP/START (Version 2) Criteria

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Background: Rational use of medications and monitoring of prescriptions in elderly patients is important to decrease the number and duration of hospitalizations, emergency medical consultations, mortality, as well as medical costs.

Purpose: To identify potentially inappropriate medications (PIMs) and potential prescription omissions (PPOs), and determine their prevalence based on the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) v2 criteria and Screening Tool to Alert doctors to Right Treatment (START) v2 criteria for patients aged >65 years.

Methods: This cross-sectional study was conducted in two rural counties in Romania based on electronic prescriptions for chronic conditions (EPCCs) issued from 30 days to 90 days by a specialist or general practitioner. Collected EPCCs were evaluated by an interdisciplinary team of specialists based on 26 STOPP v2 criteria and 10 START v2 criteria.

Results: PIM prevalence was 25.80% and PPO prevalence was 41.72% for 646 EPCCs. The mean age of patients was 75 years and the mean number of drugs per EPCC was four. The most frequently identified PIMs were treatment duration (6.65%), theophylline administration (5.72%), drug indication (4.64%), cyclo-oxygenase-2 non-steroidal anti-inflammatory drugs (1.39%), and zopiclone prescription (0.77%). Statins (24.76%), beta-blockers (8.04%), and beta-2 agonist/antimuscarinic bronchodilators (5.88%) were the most frequently identified PPOs.

Conclusion: PPOs were more prevalent than PIMs for elderly populations living in the two rural counties in Romania we studied. Health practitioners (family physicians, specialists, and pharmacists) should focus on prophylactic and curative considerations when prescribing agents to decrease the morbidity and mortality of elderly rural Romanian patients.

Keywords: Romanian elderly, rural zones, chronic prescriptions, STOPP, START

Introduction

In 2019, the number of Romanians aged >65 years represented ~18.2% of the country's total population.[1]

The Eurostat (Brussels, Belgium) predictions for 2100 estimate a significant increase in the number, but also in the complexity of the pharmacotherapeutic approaches for the elderly (secondary to increased life expectancy and migration). Therefore, aged people will represent ~31.3% of the total population in the European Union, compared with 19.8% in 2018.[1] Moreover, life expectancy will increase by ~7.8 years for men (from 78.3 in 2016 to 86.1 in 2070) and 6.6 years for women (from 83.7 in 2016 to 90.3 in 2070).[2]

Comorbidities and polymedication, together with the pharmacokinetic and pharmacodynamic particularities of drugs administered to the elderly, increase the risk of adverse reactions and potentially dangerous drug interactions by up to ~30%.[3–5] This scenario leads to an increase in the number and duration of hospitalizations, emergency medical consultations, mortality, as well as medical costs in the elderly population.[6–8] Therefore, it is very important to monitor prescriptions and to pursue rational utilization of drugs in this population. Appropriate prescribing of drugs will require special attention (age-centered and age-integrated new challenges) of health professionals: guidelines for appropriate prescription and higher-education programs for patients, as well as for medical practitioners.[9,10]

Primejdie et al assessed inappropriate prescribing in Romania. They showed disparities between community-dwelling and institutionalized patients regarding the prevalence of inappropriate prescribing in urban settings.[11] Differences in the prevalence of inappropriate prescribing are also expected between urban and rural settings.[12] Indeed, patients from rural areas have little access to specialist physicians for several reasons: high costs, infrastructure problems, patients' level of education and awareness of the importance of being evaluated by a specialist.[13] Also, some general practitioners (GPs) from rural areas (mostly over 50–60 years of age) prefer to prescribe their own treatment, without insisting that the patient should also be evaluated by a specialist. In addition, many patients from the countryside are treated by a GP for a lifetime, and reach a specialist or the hospital only if their chronic conditions worsen or decompensate.[14] Therefore, a problem which will have to be solved in the future, due to the increasing number of elderly people,[1] is to ease their access to specialized medical services to keep their diseases under control. Romania is currently confronted with an acute lack of specialist physicians in rural areas.[14]

In recent years, the concerns of medical specialists have been geared towards finding and applying appropriate criteria for prescribing drugs for each patient. Therefore, Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) were designed to detect risk or inadequate prescriptions for elderly patients to optimize their pharmacotherapy.[15] STOPP detects potentially inappropriate prescribing whereas START identifies necessary (but omitted) drugs that increase the efficiency of pharmacotherapy and

prevent complications. STOPP/START criteria are suitable for hospitalized and community-dwelling patients.[16,17]

The main objective of our study was to identify and determine the prevalence of potentially inappropriate medications (PIMs) and potential prescription omissions (PPOs) based on STOPP/START v2 criteria for patients aged >65 years. The secondary objectives (not detected by STOPP/START v2 and not involved in PIMs or PPOs) of our study were identification of: (i) the most common chronic drug indications and prescribed drugs; (ii) prescribing errors (drugs prescribed at too low/too high a dose, diagnostic codes, number of erroneous day administrations); (iii) differences in prescription habits between the rural areas of two counties in Romania: Arad and Timis.

Patients and Methods

This cross-sectional study was conducted in Arad and Timis. The study included the analysis of the chronic treatment of patients based on electronic prescriptions for chronic conditions (EPCCs) issued over a period of 30, 60, or 90 days by specialist physicians or GPs. We included only EPCCs to have an overview of the main and predominant treatments taken by the elderly which could induce (due to the long administration period) major adverse events.

EPCC collection was done from eight rural community pharmacies. The analyzed prescriptions were reimbursed by the County Health Insurance Agency of Arad and Timis.

Data of the EPCCs were collected in the pharmacies within a 5-month period (November 2017 to March 2018). Duplicate EPCCs of the same patient, but at different times, were excluded.

EPCCs were gathered based on the following criteria: age of patient ≥65 years; living at home; chronic drug treatment (already taken for >3 months).

In Romania, the electronic prescription form can contain a maximum of seven drugs prescribed on the basis of the international drug name (IDN) or trade name; in the present study, most prescriptions were written in the IDN.[18] They included only approved medications to be settled by health-insurance agencies, with over-the-counter (OTC) drugs and dietary supplements not being part of the reimbursement system.

The drugs included in the psychotropic list (eg, barbiturates, benzodiazepines, zolpidem – Table III) and narcotic list (eg, opioids – Table II) are released on the basis of a secured non-electronic prescription form, which is imposed by Romanian legislation.[19] Hence, these types of prescriptions

were not included in our study. Importantly, in Romania, zopiclone is not included in the psychotropic list and, therefore, can be prescribed on an electronic prescription.

All the collected EPCCs were evaluated (face-to-face meetings) by an interdisciplinary team of specialists (cardiologist, psychiatrist, neurologist, pulmonologist, rheumatologist, and gastroenterologist) as well as one family physician, three clinical pharmacists, one pharmacist, and two students of clinical pharmacy, based on a selection of STOPP/STARTv2 criteria.

Twenty-six STOPP criteria and 10 START criteria (Addendum Table A) could be applied to the database of this study based on the medication classes and medical conditions for which data were available (though the STOPP/START v2 criteria contain 80 STOPP criteria and 34 START criteria).[15] The collected EPCCs did not contain all the required clinical data of patients (eg, glomerular filtration rate, potential hydroelectrolyte imbalances, cardiac frequency). Another impediment was that, based on the prescribing form, the diagnostic codes used did not provide additional data regarding the characteristics of the disease (eg, heart failure with maintained systolic ventricular function, type of arrhythmia) or its severity (eg, moderate, severe hypertension). Moreover, some of the comorbidities of the patients were identified based on diagnostic codes found in the EPCCs.

The secondary outcomes were identified based on the prevalence of the diagnostic codes from EPCCs (drug indications) and drug leaflets (prescribing errors). Another objective was to identify possible prescribing differences between the two counties because the municipality of Timis, Timisoara, is a prestigious university center going back more than 50 years.

Moreover, we verified if the age and sex of patients, number of drugs, and days of treatment were associated with the prevalence of PIMs and PPOs based on STOPP/ START v2 criteria.

The present study was approved by the Ethics Committee of the "Victor Babes" University of Medicine and Pharmacy of Timisoara, Romania.

Statistical Analyses

Quantitative data are the mean ± standard deviation. Qualitative data are described using percentages. SPSS v17 (IBM, Armonk, NY, USA) was used to process data. Differences between the study groups represented by numerical independent data were obtained using the Mann–Whitney test. Differences between categorical data were obtained using the chi-squared test; $p < 0.05$ was considered significant. Logistic regression was applied to see if age, number of drugs, days of treatment, and sex of patients were associated with the prevalence of PIMs and PPOs based on STOPP and START criteria. In this way, STOPP/START were considered dependent variables and the remainder of the variables were considered independent variables).

Results

A total of 982 EPCCs were included initially, from which 336 were excluded because they were duplicate EPCCs for the same patient at different periods of time. As a result, 646 EPCCs of 646 patients were gathered and analyzed. Of these, 221 EPCCs (34.21%) were from Arad and 425 EPCCs (65.79%) were from Timis.

Of the total number of EPCCs evaluated, 65% of them were written for female patients. The mean age of patients was 75–76 years.

We compared the collected data from the two study regions to ascertain if there were major differences in prescription habits between the counties.

Table 1 shows the demographic data for the EPCCs. There was no significant difference with regard to age between the two counties. Life expectancy is significantly higher for females than for males in both counties.[20] Indeed, there were more EPCCs for females' prescriptions (>50% of the total number of EPCCs evaluated) compared with those for males.

From the EPCCs collected, 97.21% were released by a GP (in Arad all the collected EPCCs were released by

Table 1 Demographic Data of Prescriptions

Demographic Data of Prescriptions		Total (n=646)	AR Rural (n=221)	TM Rural (n=425)	p[sig] Using Mann–Whitney, or Chi[2] Tests
Sex of patients	Female Male	420 (65.01%) 226 (34.98%)	132 (59.73%) 89 (40.27%)	288 (67.76%) 137 (32.23%)	0.042[s]
Age (years)		75.38 ± 7.59	74.84 ± 7.43	75.92 ±7.76	0.089[ns]

Notes: [sig]Statistical significance; [s]Significant differences; [ns]Non-significant differences.

Table 2 Characteristics of Prescriptions

Characteristics of Prescriptions		Total (n=646)	AR Rural (n=221)	TM Rural (n=425)	p^{sig} Using Mann–Whitney, or Chi^2 Tests
Physician	General	628 (97.21%)	221 (100%)	407 (95.76%)	0.002^s
	Specialist	18 (4.23%)	0	18 (4.23%)	
Mean number of prescribed drugs on a prescription		4.01 ± 1.73	3.55 ± 1.71	4.47 ±1.75	$<0.001^s$
Days of treatment	30	512 (79.25%)	158 (71.49%)	354 (83.29%)	$<0.001^s$
	60	41 (6.34%)	36 (16.29%)	5 (1.18%)	
	90	93 (14.39%)	27 (12.22%)	66 (15.53%)	

Notes: [sig]Statistical significance; [s]Significant differences.

a GP). The mean number of medications contained on an EPCC was four, with the drugs usually being prescribed for 30 days (Table 2).

Table 3 lists the most common diagnostic codes for the analyzed EPCCs. Cardiovascular diseases were the most common: essential hypertension (>70% of all EPCCs in both counties), chronic ischemic heart disease (24% in Arad versus 46% in Timis), dyslipidemia (23% versus 16%), and peripheral circulatory disorders (varicose veins of lower limbs, 8% versus 3%). Also, digestive disorders, such as gastritis and duodenitis (12% in Arad versus 20% in Timis), as well as chronic obstructive pulmonary disease (COPD, 4% versus 10%), and diseases of the prostate gland (~7% of all EPCCs in both counties) had important roles in the pyramid of diseases in these two counties.

The most frequently prescribed drugs were beta-blockers (48% in Timis versus 38.46% in Arad), angiotensin-converting enzyme inhibitors (ACEIs) (47.76% versus 30.32%), statins (42.82% versus 28.96%), thiazide-like diuretics and calcium-channel blockers (Addendum Table B). Given that in Romania the prevalence of cardiovascular diseases is the highest, these data are not surprising.[22]

Compared with Arad, in Timis central-acting antihypertensive drugs were prescribed significantly more often (p=0.004), which was also seen for statins (p<0.001), antiepileptic drugs (p=0.039), theophylline (p=0.022), and allopurinol (p=0.003) (Addendum Table B).

Forty-three EPCCs revealed a problem regarding treatment duration. We identified 18 EPCCs (8.14%) in Arad versus 25 EPCCs (5.88%) in Timis in which drugs were prescribed for a long time (>2 weeks for non-steroidal anti-inflammatory drugs (NSAIDs) and >8 weeks for proton pump inhibitors (PPIs)). There was a tendency to prescribe PPIs and NSAIDs for long-term management of diseases, with NSAIDs ranked first in both counties (17% in Arad versus 20% in Timis) (Table 4).

Theophylline was prescribed as monotherapy in a high proportion of patients with COPD, most of whom were in Timis (6.62% versus 3.62%). Cyclooxygenase (COX)-2-selective NSAIDs were also prescribed in patients with cardiovascular problems (Table 4).

Altogether, 30 EPCCs had no valid drug indication. In Arad, the main problems related to the indication of drugs were dextromethorphan prescribed for bronchitis; trazodone for dementia; theophylline/gabapentin/desloratadine for chronic ischemic heart disease; furosemide for angina pectoris; first-generation antipsychotics for depressive episodes; trimetazidine for hypertension. In Timis, the PIMs identified were PPIs prescribed for bronchitis; beta-blockers for spondylosis; tramadol for lipidemia; propafenone/nitrate derivatives/trimetazidine for hypertension; tamsulosin for gastritis and duodenitis; alphacalcidol for arterial disease. Some of these problems could be the consequence of an error in typing the diagnostic code for the prescribed drug (Table 4).

Drug duplications were approximately identical in both counties (2.71% in Arad versus 2.82% in Timis). The main frequently duplicated pharmacologic classes/drugs were diuretics, beta-blockers, timolol (ophthalmic use), and NSAIDs (prescribed in two pharmacologic products for the same patients) (Table 4).

Three EPCCs contained a molecule from the central-antihypertensive class of drugs as first-line treatment. In 17 (4.00%) EPCCs, the patient was at risk of hyperkalemia due to the associations of drugs.

Overall, 25.80% of the analyzed EPCCs had at least one PIM. Timis had the most prescribing problems according to STOPP criteria (Table 5).

Table 3 The Most Used Diagnostic Codes as Indications for Prescriptions

Diagnostic Code	Diagnostic Code Description	Total (n=646)	AR Rural (n=221)	TM Rural (n=425)	p[sig] Using Chi^2 Test
	Cardiovascular and cerebrovascular disorders				
453	Essential hypertension	532 (82.35%)	157 (71.04%)	375 (88.24%)	<0.001[s]
458	Angina pectoris	19 (2.94%)	17 (7.69%)	2 (0.47%)	<0.001[s]
462	Chronic ischemic heart disease	247 (38.23%)	53 (23.92%)	194 (45.65%)	<0.001[s]
476	Cardiomyopathy	30 (4.64%)	17 (7.69%)	13 (3.06%)	0.008[s]
480	Unspecified stoke	14 (2.17%)	10 (4.52%)	4 (0.94%)	0.003[s]
481	Other cerebrovascular diseases	86 (13.31%)	20 (9.05%)	66 (15.52%)	0.022[s]
485	Other peripheral vascular diseases	40 (6.19%)	17 (7.69%)	23 (5.41%)	0.254[ns]
491	Varicose veins of lower limbs	30 (4.64%)	18 (8.14%)	12 (2.82%)	0.002s
	Nervous system disorders				
300	Dementia without specification (presenile, senile)	3 (0.46%)	2 (0.90%)	1 (0.23%)	0.233[ns]
303	Other mental disorders due to brain injury	8 (1.88%)	–	8 (1.88%)	–
312	Schizophrenia	2 (0.30%)	1 (0.45%)	1 (0.23%)	0.631[ns]
321	Depressive episode	7 (1.08%)	3 (1.35%)	4 (0.94%)	0.633[ns]
325	Anxiety disorders	21 (4.94%)	–	21 (4.94%)	–
350	Hyperkinetic disorders	24 (3.71%)	7 (3.16%)	17 (4%)	0.592[ns]
364	Parkinson's disease	8 (1.88%)	5 (2.26%)	3 (0.71%)	0.092[ns]
368	Alzheimer's disease	15 (2.32%)	1 (0.45%)	14 (3.29%)	0.023[s]
373	Epilepsy	10 (1.54%)	1 (0.45%)	9 (2.11%)	0.105[ns]
	Metabolic and endocrine disorders				
203	Iron deficiency anemia	1 (0.15%)	1 (0.45%)	–	–
236	Hypothyroidism due to subclinical iodine deficiency	7 (1.08%)	2 (0.90%)	5 (1.17%)	0.753[ns]
289	Metabolism disorders of lipoproteins and other lipidemia	230 (35.60%)	50 (22.62%)	180 (42.35%)	<0.001[s]
290	Metabolism disorders of purine and pyrimidine	14 (2.16%)	1 (0.45%)	13 (3.06%)	0.031[s]
630	Gout	7 (1.08%)	–	7 (1.65%)	–
	Respiratory system disorders				
526	Other chronic obstructive pulmonary diseases	52 (8.04%)	9 (4.07%)	43 (10.12%)	0.007[s]
527	Asthma	34 (5.26%)	7 (3.17%)	27 (6.35%)	0.086[ns]
	Gastrointestinal tract disorders				
559	Gastritis and duodenitis	110 (17.02%)	27 (12.21%)	83 (19.52%)	0.019[s]
	Musculoskeletal system disorders				
632	Polyarthrosis	39 (6.03%)	17 (7.69%)	22 (5.17%)	0.202[ns]
648	Spondylosis	24 (3.71%)	15 (6.78%)	9 (2.12%)	0.003[s]
661	Osteoporosis	13 (2.01%)	5 (2.26%)	8 (1.88%)	0.744[ns]
	Genitourinary system disorders				
701	Benign prostatic hyperplasia	45 (6.96%)	16 (7.24%)	29 (6.82%)	0.842[ns]

Notes: [sig]Statistical significance; [s]Significant differences; [ns]Non-significant differences. Data from CASDJ.[21]

The prevalence of PPOs in our study population was 41.72%, with no significant difference between the two counties (though it was higher in Arad: 23.53%) (Table 6).

Table 7 presents the START criteria that were applied to the EPCCs included in our study. In the two rural areas studied, statins were poorly prescribed as prophylactic or curative drugs. The Romanian population presents a high

Table 4 STOPP Criteria Detected in Study Population

STOPP Criteria (n=26)	Total (n=646)		AR Rural (n=221)		TM Rural (n=425)		p^{sig} Using Chi^2 Test
	PIM (n)	%	PIM (n)	%	PIM (n)	%	
Treatment duration	**43**	**6.65%**	18	8.14%	25	5.88%	0.275[ns]
Theophylline as monotherapy for COPD – risk of adverse effects	**37**	**5.72%**	8	3.62%	29	6.82%	0.097[ns]
Drug indication	**30**	**4.64%**	17	7.69%	13	3.05%	0.008[s]
ACEIs or ARBs – in patients with hyperkalemia	**21**	**3.25%**	4	1.81%	17	4.00%	0.137[ns]
Drug duplication	**18**	**2.78%**	6	2.71%	12	2.82%	0.936[ns]
COX-2 selective NSAIDs with concurrent cardiovascular disease – increased risk of stroke and myocardial infarction	**9**	**1.39%**	3	1.35%	6	1.41%	0.951[ns]
Hypnotic Z-drugs (zopiclone) – increase the risk of falls due to daytime sedation	**5**	**0.77%**	–	–	5	1.17%	–
Central-acting antihypertensive (eg methyldopa, clonidine, rilmenidine)	**4**	**0.61%**	1	0.45%	3	0.70%	0.700[ns]
Neuroleptic drugs – increase the risk of falls	**4**	**0.62%**	2	0.90%	2	0.47%	0.508[ns]
Loop diuretic – as a first-line treatment for hypertension	**2**	**0.30%**	1	0.45%	1	0.23%	0.631[ns]
Neuroleptics (with moderate-marked anticholinergic effects) with a history of prostatism or previous urinary retention – high risk of urinary retention	**2**	**0.30%**	2	0.90%	–	–	–
Pump-proton inhibitor (full therapeutic dosage for > 2 months) for uncomplicated peptic ulcer disease or erosive peptic oesophagitis	**2**	**0.30%**	–	–	2	0.47%	–
Two or more drugs with anticholinergic properties (eg intestinal antispasmodics, first generation antihistaminic drugs) – risk of increased antimuscarinic toxicity)	**2**	**0.30%**		–	–	2	0.47%
Beta-blocker associated with verapamil/diltiazem	**1**	**0.15%**	1	0.45%	–	–	–
Aldosterone antagonists associated with potassium-sparing drugs	**1**	**0.15%**	–	–	1	0.23%	–
Associated antithrombotic drugs in patients with stable peripheral arterial, cerebrovascular or coronary disease	**1**	**0.15%**	–	–	1	0.23%	–
NSAID associated with oral anticoagulants	**1**	**0.15%**	1	0.45%	–	–	–
Tricyclic antidepressants administered in patients with cardiac conduction abnormalities, prostatism, dementia, narrow angle glaucoma, or history of urinary retention – risk of worsening the conditions	**1**	**0.15%**	1	0.45%	–	–	–
Tricyclic antidepressants as first-line antidepressant treatment – higher risk of ADRs	**1**	**0.15%**	1	0.45%	–	–	–

Notes: [sig]statistical significance; [s]significant differences; [ns]non-significant differences. Bold font indicates the main findings. Adapted from O'Mahony et al.[15]
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARBs, angiotensin II receptor blockers; NSAID, non-steroidal anti-inflammatory drug; ADRs, adverse drug reactions; Z-drugs, non-benzodiazepines drugs.

cardiovascular risk[22] and, in both counties, approximately 23–25% of EPCCs required co-administration of a statin. In addition, beta-blockers should be prescribed more often (especially in Arad), as well as beta-2 adrenergic or anticholinergic bronchodilators (especially in Timis). A first-line antihypertensive drug with proven efficacy over time (as recommended in international guidelines) should be prescribed more frequently, especially in Arad.

Only age and the number of drugs were significant predictors associated with the prevalence of PIMs and

Table 5 STOPP Prevalence (PIM – Potentially Inappropriate Medication)

Total PIM	AR Rural	TM Rural	p^{sig} Using Chi^2 Test
25.80%	10.00%	15.80%	0.042[s]

Notes: [sig]Statistical significance; [s]Significant differences.

Table 6 START Prevalence (PPO – Potentially Prescription Omissions)

Total PPO	AR Rural	TM Rural	p^{sig} Using Chi^2 Test
41.72%	23.53%	18.19%	0.132[ns]

Notes: [sig]Statistical significance; [ns]Non-significant differences.

Table 7 The Applied START Criteria

START Criteria (10)	Total (n=646)		AR Rural (n=221)		TM Rural (n=425)		p[sig] Using Chi[2] Test
	PPO	%	PPO	%	PPO	%	
Statins in patients with documented history of coronary, cerebral, or peripheral vascular disease	160	24.76%	51	23.08%	109	25.65%	0.473[ns]
Beta-blockers in patients with ischemic heart disease	52	8.04%	25	11.31%	27	6.35%	0.028[s]
Regular inhaled beta2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or COPD	38	5.88%	6	2.71%	32	7.53%	0.014[s]
Antihypertensive therapy if systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg	32	4.95%	18	8.14%	14	3.29%	0.007[s]
Bone anti-resorptive or anabolic therapy in patients with documented osteoporosis	8	1.23%	2	0.90%	6	1.41%	0.578[ns]
Vitamin D and calcium supplement in patients with known osteoporosis	5	0.77%	5	2.26%	–	–	–
Bisphosphonates, vitamin D, and calcium with long-term systemic corticosteroid therapy	3	0.46%	1	0.45%	2	0.47%	0,972[ns]
Disease-modifying anti-rheumatic drug with active, disabling rheumatoid disease	1	0.15%	–	–	1	0.24%	–

Notes: [Sig]statistical significance; [s]Significant differences; [ns]Non-significant differences. Bold font indicates the main findings. Adapted from O'Mahony et al.[1515]
Abbreviation: COPD, chronic obstructive pulmonary disease.

PPOs using STOPP and START v2 criteria (p<0.001 for both using logistic regression) (Tables 8 and 9).

With regard to prescription errors (Table 10), the main problems were medications prescribed at too high a dose, and the number of administrations within 24 h.

In Arad, 5.43% of EPCCs were prescribed at too low a dose based on the drug leaflet. For example, dextromethorphan (20 mg), pentoxifylline (400 mg), trimebutine (200 mg), nitrate derivatives, betahistine, and vincamine were prescribed only once a day. In Timis, the number of EPCCs containing drugs prescribed at too low a dose was lower (3.52%). For example, diosmin, nitrate derivatives, trimebutine, fenspiride, vincamine, nicergoline, and pramiracetam were prescribed only once a day. They were not considered PIMs.

The medications prescribed at too high a dose most often were beta-blockers, ACEIs, and dihydropyridines, which, in general, were prescribed at a maximum dose twice daily (a problem observed particularly in Arad).

Discussion

We evaluated EPCCs issued in two rural areas in Romania to people over 65 years of age. We found that 25.80% of patients had PIMs and 41.72% had PPOs according to STOPP and START v2 criteria. The most common PIMs were related to treatment duration (6.65%), theophylline administration (5.72%), drug indication (4.64%), COX-2-selective NSAIDs (1.39%), and zopiclone prescription (0.77%). The most frequent PPOs were statins (24.76%), beta-blockers (8.04%), and beta-2 agonist/antimuscarinic bronchodilators (5.88%).

Moreover, we conducted a separate analysis in the two counties to ascertain if there were major differences in prescribing habits. We found minor differences between the two counties with regard to potentially inappropriate prescribing.

Compared with the study undertaken by Primejdie et al in 2016, we found a lower prevalence of PIMs in these two

Table 8 Variables Associated with STOPP Prevalence

Variables in the Equation	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Gender	0.196	0.204	0.919	1	0.338	1.216	0.815	1.815
Age	0.055	0.012	19.827	1	<0.001	1.057	1.031	1.083
No. of drugs	0.258	0.054	22.575	1	<0.001	1.295	1.164	1.440
Days of treatment	−0.005	0.005	1.144	1	0.285	0.995	0.986	1.004
Constant	−6.402	1.012	40.056	1	<0.001	0.002		

Table 9 Variables Associated with START Prevalence

Variables in the Equation	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
							Lower	Upper
Gender	0.206	0.179	1.336	1	0.248	1.229	0.866	1.744
Age	0.051	0.011	20.707	1	<0.001	1.053	1.030	1.076
No. of drugs	0.328	0.049	44.089	1	<0.001	1.388	1.260	1.529
Days of treatment	−0.004	0.004	0.962	1	0.327	0.996	0.989	1.004
Constant	−4.925	0.899	30.033	1	<0.001	0.007		

Table 10 The Prescription Errors Observed

Prescription Errors	Total (n=646)		AR Rural (n=221)		TM Rural (n=425)		p^{sig} Using Chi^2 Test
	N	%	N	%	N	%	
Medication underdosed	**27**	**4.17%**	12	5.43%	15	3.52%	0.250[ns]
Medication overdosed	**16**	**2.47%**	9	4.07%	7	1.64%	0.060[ns]
Wrong diagnostic code	**20**	**3.09%**	9	4.07%	11	2.58%	0.299[ns]

Notes: [sig]Statistical significance; [ns]Non-significant differences. Bold font indicates the main findings.

rural areas compared with 34.49% reported for urban areas.[11]

In 2018, O'Riordan et al looked at PIMs in elderly people living in urban and rural settings in Ireland, Switzerland, and the Netherlands. They found that the highest percentage of PIMs was in elderly patients in Switzerland (16.7%), the Netherlands (12.5%), and Ireland (8.7%). With respect to START criteria, the prevalence of PPOs was lower for the elderly in Ireland (14%) compared with those in the Netherlands (24%) and Switzerland (25.3%).[23] Our results show that for elderly people living in two rural counties of Romania, the prevalence of PIMs and PPOs was higher.

Other studies conducted in the ambulatory setting showed the prevalence of PIMs to vary from 27.3% (Serbia) to 57% (Ireland) and for the prevalence of PPOs to vary from 40.5% (Spain) to 73.3% (Turkey). In those studies, the most frequent PIMs were represented by PPIs, drugs without an indication, NSAIDs, and benzodiazepines, whereas PPOs were represented by statins, antiplatelet agents, calcium, and vitamin D.[24–27]

The most prevalent PIMs observed in our study are in accordance with those from other studies.[28–32] A study in Romania by Primejdie et al in 2016 using the STOPP/START criteria of 2008 showed that the drug class with the highest percentage of use was NSAIDs (56.66% of outpatients and 35.63% of hospitalized patients), followed by benzodiazepines. That study did not assess PPOs.[11] In our study, NSAIDs were the most prevalent drugs

prescribed for >2 weeks. NSAIDs are recommended for use with caution in elderly patients for a short period of time and at a minimal therapeutic dose due to: (i) their side effects; (ii) an increased risk of falls and stroke.[33]

Regarding PPOs, we observed poor management for the prophylaxis of cerebrovascular or cardiovascular complications (acute myocardial infarction (AMI) or stroke) in elderly patients diagnosed with hypertension and/or coronary artery disease. Indeed, under-prescription of statins attested to this phenomenon. This poor management translates to a high prevalence of AMI or stroke, as reported by Eurostat as well as in Romania.[22] Kovačeic et al also reported the under-prescription of cardiovascular drugs in Serbian patients with coronary, cerebral, or peripheral vascular disease.[26] Moreover, for a country with a high prevalence of cardiovascular disease and cardiovascular events, apart from statins, beta-blockers should be prescribed for ischemic heart disease. Theophylline should be avoided in patients with cardiovascular complications, and beta-2 agonists/antimuscarinic bronchodilators should be first-line treatment.

We found a mean number of four drugs per EPCC to be consistent with the average reported in other studies of elderly patients living in Europe.[23,27] Moreover, a study conducted in Serbia concluded that utilization of >4 medications prescribed to the elderly could be linked to a higher probability of having a PIM.[26] A study conducted in 2016 by a Romanian research team stated that the median number of prescribed medications in elderly patients was three.[11]

Psychotropic medications were prescribed mostly in Timis. These were represented by new, well-chosen drugs according to international recommendations (most probably as a consequence of being prescribed by specialists).[34,35] Conversely, the EPCCs collected in Arad had a lower percentage of psychotropic drugs (probably because most were penned by a GP).

The predominant diseases in Romania are cardiovascular diseases according to Eurostat. These are followed by metabolic and endocrine disorders, diseases of the gastrointestinal tract, respiratory system, and nervous system.[22] Use of STOPP and START criteria in rural regions could help rationalize curative and preventive medications for these conditions, along with non-pharmacologic measures (ie, good diet, exercise, smoking cessation, as well as periodic monitoring of body weight, blood pressure, heart rate, lipid/carbohydrate profile, and laboratory investigations[36]) addressed in concert with a GP and pharmacist.[37]

Despite limited access to physicians in rural areas, we observed that EPCCs from GPs were, in general for 30 days. Hence, the GP could monitor outcomes and adjust (as appropriate) the treatment regimen and drug dose.

With regard to prescription errors not detected using STOPP and START v2 criteria, the highest share was represented by the prescription of some drugs under the therapeutic dose (which could lead to therapeutic failure), dosing regimen, and an unadjusted dose in accordance with disease stage or based on patients' characteristics. Calcium-channel blockers were among the medications at which too high a dose was prescribed (the maximum dose used was twice daily).

Our study had three main limitations. First, the frailty of patients was not recorded. Second, we could apply only a subset of STOPP and START v2 criteria because the database available did not cover all the required elements to assess all criteria. The prevalence of PIMs and PPO should, therefore, be interpreted with caution.[38] Due to lack of data, we could not identify certain omissions of anticoagulants in chronic atrial fibrillation; Getachew et al noted their absence in 41.2% of elderly patients.[39] Third, we did not include data regarding vaccination or OTC medications (eg, aspirin or laxatives). Physicians and pharmacists should monitor the adherence of patients to OTC drugs and cardiovascular aspirin therapy to avoid under-prescribing of such agents.

We also noticed positive aspects that reflect adequate prescription of medications in the elderly. For instance: allopurinol was prescribed for hyperuricemia; topical antiglaucoma drugs were chosen for glaucomatous disease; second-generation antipsychotics were recommended for psychomotor agitation; second-generation anti-allergic drugs were recommended appropriately.

Access to medical care in rural regions is challenging. More than in other settings, the network of healthcare professionals is important, and the pharmacist can play a key part in detection of inappropriate prescribing. The importance of the pharmacist in identifying potentially inadequate prescriptions based on STOPP/START criteria has been documented.[40,41] In 2016, Tommelein et al developed an explicit screening tool which could PIMs in community pharmacies.[42] Optimization of drug therapy by a clinical pharmacist can improve the quality of care and lower the costs of polymedication.[43]

Conclusions

PPOs were more prevalent than PIMs for elderly populations living in the two rural counties in Romania we studied. Health practitioners (family physicians, specialists, and pharmacists) should focus on prophylactic and curative considerations when prescribing agents to decrease the morbidity and mortality of elderly rural Romanian patients.

Disclosure

Dr Liana Dehelean reports personal fees from Johnson and Johnson, Lundbeck, Eli Lilly and Angelini, outside of the submitted work. The authors report no other conflicts of interest in this work.

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