Potentially Inappropriate Medication Use Among Elderly Home Care Patients in Europe

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Context Criteria for potentially inappropriate medication use among elderly patients have been used in the past decade in large US epidemiological surveys to identify populations at risk and specifically target risk-management strategies. In contrast, in Europe little information is available about potentially inappropriate medication use and is based on small studies with uncertain generalizability.

Objective To estimate the prevalence and associated factors of potentially inappropriate medication use among elderly home care patients in European countries.

Design, Setting, and Participants Retrospective cross-sectional study of 2707 elderly patients receiving home care (mean [SD] age, 82.2 [7.2] years) representatively enrolled in metropolitan areas of the Czech Republic, Denmark, Finland, Iceland, Italy, the Netherlands, Norway, and the United Kingdom. Patients were prospectively assessed between September 2001 and January 2002 using the Minimum Data Set in Home Care instrument.

Main Outcome Measures Prevalence of potentially inappropriate medication use was documented using all expert panels criteria for community-living elderly persons (Beers and McLeod). Patient-related characteristics independently associated with inappropriate medication use were identified with a multiple logistic regression model.

Results Combining all 3 sets of criteria, we found that 19.8% of patients in the total sample used at least 1 inappropriate medication; using older 1997 criteria it was 9.8% to 10.9%. Substantial differences were documented between Eastern Europe (41.1% in the Czech Republic) and Western Europe (mean 15.8%, ranging from 5.8% in Denmark to 26.5% in Italy). Potentially inappropriate medication use was associated with patient's poor economic situation (adjusted relative risk [RR], 1.96; 95% confidence interval [CI], 1.58-2.36), polypharmacy (RR, 1.91; 95% CI, 1.62- 2.22), anxiolytic drug use (RR, 1.82; 95% CI, 1.51-2.15), and depression (RR, 1.29; 95% CI, 1.06-1.55). Negatively associated factors were age 85 years and older (RR, 0.78; 95% CI, 0.65-0.92) and living alone (RR, 0.76; 95% CI, 0.64-0.89). The odds of potentially inappropriate medication use significantly increased with the number of associated factors ($P<.001$).

Conclusions Substantial differences in potentially inappropriate medication use exist between European countries and might be a consequence of different regulatory measures, clinical practices, or inequalities in socioeconomic background. Since financial resources and selected patient-related characteristics are associated with such prescribing, specific educational strategies and regulations should reflect these factors to improve prescribing quality in elderly individuals in Europe.

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Use of potentially inappropriate medications in elderly patients is a major health care concern. It is likely to increase the risk of adverse drug events, which are estimated to be the fifth most common cause of death among hospitalized patients[1] and which account for a large number of hospital admissions and a substantial increase in health care costs.[2]

In the United States and Canada, epidemiological studies have documented widespread use of potentially inappropriate medications among nursing home residents (up to 40%) and community-dwelling elderly persons (14%-37%).[3-13] In general, these studies have adopted explicit criteria developed by panels of experts, which recommend avoiding medications with a high potential for adverse events and prefer alternatives with lower risk. Most medications are deemed inappropriate independently of clinical indica-

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tions and concomitant diagnoses, dosing, or concurrent medications.[14-17]

In the United States, explicit criteria were initially developed for nursing home residents (Beers et al 1991),[14] and later for community-dwelling elderly individuals (Beers 1997).[15] Although another set of criteria was created for Canada (McLeod et al 1997),[16] Beers 1997 criteria in their original or revised version (Zhan et al 2001)[4] have been used most commonly in epidemiological research. These criteria were recently updated (Beers 2003)[17] to reflect newly attained evidence on efficacy and safety of various medications.

In Europe, no similar criteria have been developed, owing to substantial differences in national drug formularies and prescribing attitudes, as well as the criticism that explicit criteria cannot fully capture all factors defining drug appropriateness. As a result, few studies describing potentially inappropriate medication use have been conducted, mainly in the Nordic countries (Sweden, Finland)[18,19] and in Italy.[20] These studies usually adopted Beers 1997 criteria and documented a somewhat lower prevalence of inappropriate medication use than in the United States, ranging from 12.1% (Finland) to 14.6% (Italy). Performed in specific populations, diverse settings, and at a different time, these studies have little comparability. Until European-specific criteria for potentially inappropriate medication use that consider country-specific formularies are created, the Beers and McLeod criteria represent available standards of currently identified inappropriate medications in elderly patients and the best method for cross-sectional assessment of potentially inappropriate medication use in Europe.

Thus, the aims of our study were to determine in a large sample of European home care elderly patients the prevalence of potentially inappropriate medication use, applying all available sets of criteria, and to identify independent correlates of potentially inappropriate medication use.

METHODS

This is an ancillary study of the AdHOC (Aged in Home Care) project, a multicenter project funded by the European Union Commission under the Vth Framework Programme (2000-2003). The AdHOC project was designed to compare the case-mix of elderly patients receiving home care services across 11 European countries along with a series of structural and organizational characteristics of the services themselves. The project has been approved by the ethics committees of participating countries and written consent was obtained from all participants. The AdHOC project has been described in detail elsewhere[21] and its principal features are briefly outlined herein.

AdHOC Project

In each participating country, the project coordinator identified municipalities providing formal home care services and selected a population considered representative of the country's urban area. Patients were selected at random by computer-driven randomization from all patients aged at least 65 years who were identified in home care provider records. Where specific services (eg, health and social care) were provided by different agencies, stratified samples were obtained to reflect the proportion of the services provided. In total, 3877 patients were assessed in Prague, Czech Republic (n=428), Copenhagen, Denmark (n=400), Helsinki, Finland (n=187), Amiens, France (n=312), Nürnberg and Bayreuth, Germany (n=612), Reykjavik, Iceland (n=405), Milan-Monza district, Italy (n=412), Rotterdam, the Netherlands (n=198), Oslo, Norway (n=388), Maidstone and Ashford, United Kingdom (n=289), and Stockholm, Sweden (n=246). In the AdHOC data set, comprehensive baseline data on medication use were available for the entire samples of 8 participating countries (Denmark, Finland, Iceland, Italy, the Netherlands, Norway, United Kingdom, and Czech Republic; 2707 patients) and used in our study.

Based on power calculations (NCSS Pass 6.0 statistical software; NCSS Statistical Software, Kaysville, Utah), a sample size of 350 patients for each area allowed 80% power to detect significant variations in indices of functional ability (the outcome variables for the main study) within each catchment area with a probability error of .05. We assumed a corresponding dropout rate of 15% or less and thus 405 patients were randomly selected in each country. Among the 8 countries participating in our study, 4 (Denmark, Iceland, Italy, and Norway) achieved planned participation rates and were representative of the national home care elderly populations. Three countries (Finland, United Kingdom, the Netherlands) exceeded estimated refusal rates mostly due to patients' unwillingness to be troubled or fear of what was involved. The Czech Republic was only marginally above the 15% refusal rate.[21] All samples significantly differed from the national statistics on the elderly population by age, sex, and the prevalence of major comorbidities ($P<.001$). Considering that inappropriate medication use should be independent of the population structure and comorbidities, all samples finally entered the statistical analysis.

Comprehensive Geriatric Assessment

All patients were assessed at home by specifically trained staff, either home care nurses or research assistants. Detailed information was recorded using the interRAI Minimum Data Set for Home Care instrument (MDS-HC),[22,23] which was translated, back-translated, and examined for face validity in the language of each participating country. Assessments were completed at baseline and after a 1-year study period, with a 6-month briefer reassessment using only selected items. For our cross-sectional analysis, baseline data were used.

The MDS-HC instrument consists of more than 350 items, including sociodemographic, physical, cognitive, and psychological characteristics of the patient, as well as relevant clinical information. The MDS-HC has excellent interrater reliability and has been used for epidemiological research in both the

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Table 1. Inappropriate Medications and Classes to Avoid in Elderly Patients, as Defined by Expert Panel Criteria

Inappropriate Medication by Class	Expert Panel Criteria: Beers 1997[15]	McLeod 1997[16]	Beers 2003[17]
Analgesic/anti-inflammatory			
Indomethacin	✓	✓	✓
Ketorolac		✓	✓
Mefenamic acid		✓	✓
Meperidine	✓	✓	✓
Naproxen, oxaprozin, piroxicam		✓	
Naproxen, oxaprozin, piroxicam in full-dose, long-term use			✓
Pentazocin	✓	✓	✓
Phenylbutazone	✓	✓	✓
Propoxyphene and combinations	✓		✓
Antianemic			
Ferrous sulfate >325 mg/d			✓
Antiarrhythmic			
Amiodarone			✓
Digoxin >0.125 mg/d (except in atrial arrhythmias)			✓
Disopyramide	✓	✓	✓
Antibacterial			
Nitrofurantoin			✓
Anticholinergic			
Anticholinergic and antihistamines: chlorpheniramine, diphenhydramine, hydroxyzine, cyproheptadine, promethazine, tripelennamine, dexchlorpheniramine	✓		✓
Gastrointestinal antispasmodics: dicyclomine, hyoscyamine, propantheline, belladonna alkaloids, clidinium, clidinium-chlordiazepoxide			✓
Oxybutynin	✓		
Oxybutynin short-release form			✓
Anticlotting			
Dipyridamole	✓	✓	
Dipyridamole, short-acting			✓
Ticlopidine	✓		✓
Antidepressant			
Amitriptyline	✓	✓	✓
Doxepin	✓		✓
Fluoxetine (daily)			✓
Imipramine		✓	
Antidiarrheal			
Diphenoxylate		✓	
Antiemetic			
Trimethobenzamide	✓		✓
Antihypertensive			
Clonidine			✓
Doxazosin			✓
Guanadrel			✓
Guanethidine			✓
Methyldopa	✓		✓
Nifedipine, short-acting			✓
Reserpine >0.25 mg/d	✓	✓	✓
Antipsychotic			
Mesoridazine			✓
Perphenazine-amitriptyline	✓		✓
Thioridazine			✓

(continued)

United States and Europe.[21-23] Information about psychosocial and medical conditions and medication use was recorded based on interviews with patients and caregivers as well as medical record review. Information on current and past services utilization was also gathered, including hospitalization in the prior 30 days, nursing home stay in the prior 5 years, and emergency home or emergency department visits 3 months prior to the assessment.

Drug Information

In addition to MDS-HC data, assessors collected information on all the medications patients had been taking in the prior 7 days—both prescribed and over-the-counter medications—used regularly or on an as-needed basis. Drug information included nonproprietary and proprietary name, Anatomical Therapeutic and Chemical code, formulation, dosage, frequency, and route of administration.

Investigators documented whether patients or caregivers reported that any physician had provided a medication review in the previous 6 months and whether patients were adherent with the prescription within a week preceding the assessment. Assessors also reviewed physicians' medical records or patients' discharge sheets, if available, to assess medication use and adherence. To further assess adherence, patients' pillboxes were also checked if available.

Nonadherence was coded when the patient was less than 80% adherent to all medications used in the prior 7 days. Patients were also asked if they had experienced economic difficulties in the prior 30 days that precluded them from being able to pay for prescribed medications, heating, medical care, adequate nutrition, and home help or home care. Patients reporting any difficulties were classified as having poor economic status.

Criteria for Potentially Inappropriate Medication Use

To determine the use of potentially inappropriate medications, we adopted all

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explicit criteria previously published by panels of experts for community-living elderly individuals (TABLE 1), using them separately and all combined. We adopted only parts of criteria related to "medications that should be avoided in the elderly" excluding sections related to drug-drug and drug-disease interactions. Thus, our study describes only errors of commission (medications that generally should not be prescribed) but not other types of prescribing errors (eg, errors of omission). Although the Beers 2003 criteria had not been published at the time the data were collected, information regarding adverse events associated with these drugs in elderly patients was available at that time and these criteria were included to improve comparability with other studies.

When several definitions of inappropriateness for a substance were present on the combined criteria list, the latest published definition was accepted to determine the whole prevalence (eg, short-acting oxybutynin [Beers 2003 criteria] instead of all formulations of oxybutynin [Beers 1997 criteria]). Expert panel criteria were used as a screening tool with regard to specific comorbidities that might affect prescribing appropriateness. We considered all potentially inappropriate medications (with the exception of stimulant laxatives) where definition of inappropriateness was limited to long-term use that we could not ascertain. For the same reason, the definition of inappropriateness for nonsteroidal anti-inflammatory drugs was limited to the use of a maximum daily dose irrespective of the length of the exposure. Only systemically acting drug formulations were analyzed.

Table 1. Inappropriate Medications and Classes to Avoid in Elderly Patients, as Defined by Expert Panel Criteria (cont)

Inappropriate Medication by Class	Expert Panel Criteria		
	Beers 1997[15]	McLeod 1997[16]	Beers 2003[17]
All barbiturates except phenobarbital	✓	✓	
All barbiturates except phenobarbital and except seizure control			✓
Diuretic			
Ethacrynic acid			✓
Ergot mesyloid	✓		✓
H_2 antagonist			
Cimetidine			✓
Hormonal			
Dessicated thyroid			✓
Estrogens only (oral)			✓
Methyltestosterone			✓
Hypoglycemic			
Chlorpropamide	✓		
Laxative			
Long-term use of stimulant laxative: bisacodyl, cascara sagrada			✓
Mineral oil			✓
Muscle relaxants and antispasmodics: methocarbamol, carisoprodol, chlorzoxazone, metaxalone, cyclobenzaprine, orphenadrine	✓	✓	✓
Niacin		✓	
Sedative			
Chlordiazepoxide	✓	✓	✓
Chlordiazepoxide-amitriptyline			✓
Diazepam	✓	✓	✓
Flurazepam	✓	✓	✓
Meprobamate	✓		✓
Quazepam, halazepam, chlorazepat			✓
Triazolam		✓	
Triazolam >0.25 mg/d			✓
Short-acting benzodiazepines: lorazepam >3 mg/d, oxazepam >60 mg/d, alprazolam >2 mg/d, temazepam >15 mg/d			✓
Stimulant			
Amphetamines (excluding methylphenidate) and anorexics			✓
Methylphenidate		✓	
Vasodilator			
Cyclandelate	✓		✓
Isoxsuprine			✓
Nylidrin		✓	
Pentoxifylline		✓	

Analytical Approach

Descriptive MDS-HC data from the baseline assessment, including sociodemographic characteristics (eg, age, sex, living alone, lack of informal helper, economic status) as well as functional, cognitive, and mood status characteristics, were computed for each country and for the total sample. Activities of daily living (ADLs) disability was defined as a score of at least 2 on the MDS-HC ADL Scale that was computed using items on patients' performance in personal hygiene, toilet use, locomotion, and eating.[24] Instrumental activities of daily living (IADLs) disability was classified as dependency in at least 2 of the following: meal preparation, ordinary housework, managing finances, managing medications, telephone use, shopping, and transportation.[22] Cognitive impairment was determined as a score of at least 2 on the Cognitive Performance Scale (CPS),[25] a validated instrument (range, 0-6; a score of 2 corresponds to 22 on the Mini-Mental State Examination). Clinically significant depression was defined as a score of at least 3 on the Depression Rating Scale (DRS; range, 0

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[intact] through 14 [severely depressed]).[26]

Statistical Analysis

Data were analyzed using SPSS software version 12 (SPSS Inc, Chicago, Ill) and Egret software version 2.03 (Cytel Software Corporation, Cambridge, Mass). Differences in distributions of categorical variables among countries and between users and nonusers of inappropriate medications were compared using the χ^2 test.

A multiple logistic regression model was created to determine patient-related characteristics associated with inappropriate medication use. Only dichotomous variables were entered into the logistic regression model. Multicollinearity was tested using the χ^2 test and the coefficient of contingence, which determines the strength of the association between 2 dichotomous variables (value range from 0 to 1, where 0 equals complete independence).

A stepwise logistic regression was applied in the exploratory phase of the statistical modeling. Due to the great number of potential predictive variables and interactions among them, variables were tested gradually simultaneously. The Wald test and the likelihood ratio test were used to test the significance of a single predictive variable. The variable was included in the model only if both tests were statistically significant. To test the overall significance of the model, the model χ^2 statistic was applied. We also computed the goodness-of-fit χ^2 statistic ($-2 \times$ the log likelihood) to measure the model fitness and Nagelkerke R^2 statistic to determine the strength of associations between inappropriate medication use and predictive variables. The degree of excess heterogeneity due to overdispersion was explored.

Because inappropriate medication use was common in the whole sample (>10%), the adjusted odds ratios could not be used to approximate the relative risks (RRs). The method of Zhang and Yu was applied to estimate the RRs.[27] The trend of the unadjusted odds for the use of an inappropriate medi-

Table 2. Study Population Characteristics by Country

	% (No.)								
	Overall (n = 2707)	Czech Republic (n = 428)	Denmark (n = 400)	Finland (n = 187)	Iceland (n = 405)	Italy (n = 412)	The Netherlands (n = 198)	Norway (n = 388)	United Kingdom (n = 289)
Sociodemographic characteristics									
Age, y									
65-74	17.5 (474)	17.1 (73)	11.5 (46)	22.5 (42)	17.8 (72)	27.9 (115)	22.2 (44)	7.5 (29)	18.3 (53)
75-84	44.8 (1212)	47.7 (204)	40.5 (162)	41.2 (77)	48.1 (195)	40.5 (167)	49.0 (97)	48.7 (189)	41.9 (121)
≥85	37.7 (1021)	35.3 (151)	48.0 (192)	36.4 (68)	34.1 (138)	31.6 (130)	28.8 (57)	43.8 (170)	39.8 (115)
Female sex	74.4 (2013)	79.0 (338)	79.3 (317)	81.3 (152)	74.3 (301)	62.9 (259)	77.3 (153)	71.6 (278)	74.4 (215)
Live alone	61.2 (1657)	64.7 (277)	75.3 (301)	83.4 (156)	68.1 (276)	12.9 (53)	61.6 (122)	73.5 (285)	64.7 (187)
No informal helper	13.3 (360)	13.8 (59)	14.8 (59)	36.9 (69)	13.3 (54)	2.7 (11)	25.3 (50)	5.2 (20)	13.1 (38)
Poor economic situation*	7.6 (207)	32.7 (140)	0.8 (3)	11.8 (22)	2.0 (8)	1.7 (7)	4.0 (8)	2.3 (9)	3.5 (10)
Clinical and functional status characteristics									
Multiple comorbidity (≥4 diseases)†	37.9 (1026)	79.9 (342)	10.8 (43)	57.8 (108)	38.8 (157)	25.0 (103)	22.7 (45)	24.5 (95)	46.0 (133)
Dependency in IADL (score ≥2)	69.8 (1890)	80.4 (344)	49.0 (196)	59.4 (111)	46.9 (190)	93.7 (386)	75.3 (149)	67.8 (263)	86.9 (251)
Dependency in ADL (score ≥2)	39.3 (1063)	38.6 (165)	25.8 (103)	26.2 (49)	19.5 (79)	84.2 (347)	18.2 (36)	24.2 (94)	65.7 (190)
Cognitive impairment (CPS score ≥2)	28.6 (773)	33.6 (144)	20.8 (83)	22.5 (42)	17.5 (71)	52.2 (215)	27.8 (55)	20.6 (80)	28.7 (83)
Depression (DRS score ≥3)	16.6 (450)	29.2 (125)	8.8 (35)	6.4 (12)	9.4 (38)	26.2 (108)	21.7 (43)	5.9 (23)	22.8 (66)
Drug-related characteristics									
7-Day drug use									
≥1 Drugs	95.1 (2574)	97.7 (418)	93.3 (373)	95.2 (178)	97.8 (396)	93.7 (386)	94.9 (188)	91.8 (356)	96.5 (279)
≥6 Drugs	51.0 (1380)	68.5 (293)	50.5 (202)	73.3 (137)	63.7 (258)	36.2 (149)	35.4 (70)	33.8 (131)	48.4 (140)
≥9 Drugs	22.2 (600)	39.0 (167)	18.0 (72)	41.2 (77)	31.6 (128)	7.0 (29)	13.1 (26)	11.1 (43)	20.1 (58)
Psychotropic drug use	43.4 (1176)	46.7 (200)	40.3 (161)	62.6 (117)	61.6 (249)	36.4 (150)	29.8 (59)	41.8 (162)	27.0 (78)
Lack of medication review‡	17.9 (484)	11.7 (50)	29.3 (117)	21.9 (41)	9.6 (39)	3.9 (16)	20.7 (41)	4.4 (17)	56.4 (163)
Nonadherence§	12.4 (335)	32.9 (141)	12.0 (48)	9.1 (17)	4.9 (20)	2.7 (11)	11.6 (23)	7.0 (27)	16.6 (48)

Abbreviations: ADL, activities of daily living[24]; CPS, Cognitive Performance Scale[25]; DRS, Depression Rating Scale[26]; IADL, instrumental activities of daily living.[22]
*Patients' poor economic situation, as defined in the "Methods" section.
†Polymorbidity defined as presence of 4 or more Minimum Data Set for Home Care comorbidities.[22]
‡The lack of comprehensive medication review by the physician in the prior 180 days.
§Subjective nonadherence (adherence <80% of the treatment time in prior 7 days).

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cation with increasing number of associated factors was tested using the Mantel-Haenszel statistic. A 2-tailed $P<.05$ was selected as the level of statistical significance.

RESULTS

Principal characteristics of the population studied are shown in TABLE 2. Mean (SD) age of the patients was 82.2 (7.2) years; most were women (74.4%) and lived alone (61.2%), but rarely reported a poor economic situation (7.6%). Most of the patients were dependent in IADLs (69.8%), but fewer were dependent in ADLs (39.3%). A minority had cognitive impairment (28.6%) or clinical depression (16.6%). Differences among countries were statistically significant for all variables presented in Table 2.

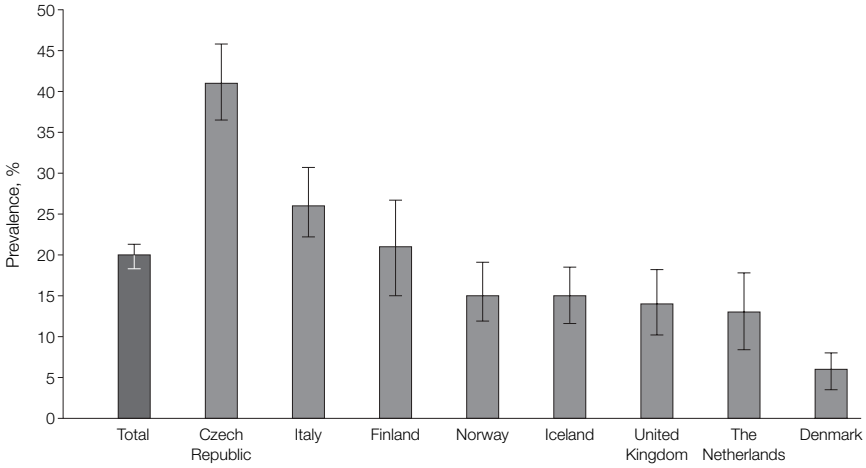
When 7-day prevalence of medication use was evaluated, more than 95% of patients received at least 1 medication and polypharmacy (defined as the use of ≥6 medications) was documented in 51.0% of patients. Medication adherence was high except in the Czech Republic; reported lack of regular medication review ranged from 3.9% in Italy to 56.4% in the United Kingdom.

Considering all explicit criteria combined, 19.8% used at least 1 potentially inappropriate medication. The highest prevalence (41.1%) was documented in the Czech Republic compared with a mean of 15.8% for all the other countries, ranging from 5.8% in Denmark to 26.5% in Italy (FIGURE 1). Results using only Beers 2003 criteria were similar to those obtained with combined criteria except in the Czech Republic. The application of Beers 1997 or McLeod criteria yielded half the prevalence of the total sample and 1.2- to 3.9-fold lower prevalence in individual countries (FIGURE 2).

TABLE 3 presents the 10 most commonly used inappropriate medications considering all explicit criteria combined. While some medications, namely diazepam and amitriptyline, were frequently used in all countries, others were prescribed to a higher extent only in certain countries, eg, pentoxifylline, high-dose digoxin, and chlordiazepoxide in the Czech Republic; ticlopidine and amiodarone in Italy; and unopposed estrogens in older women in Iceland.

Based on several types of patient characteristics (TABLE 4), 6 variables were identified as independent predictors of inappropriate medication use

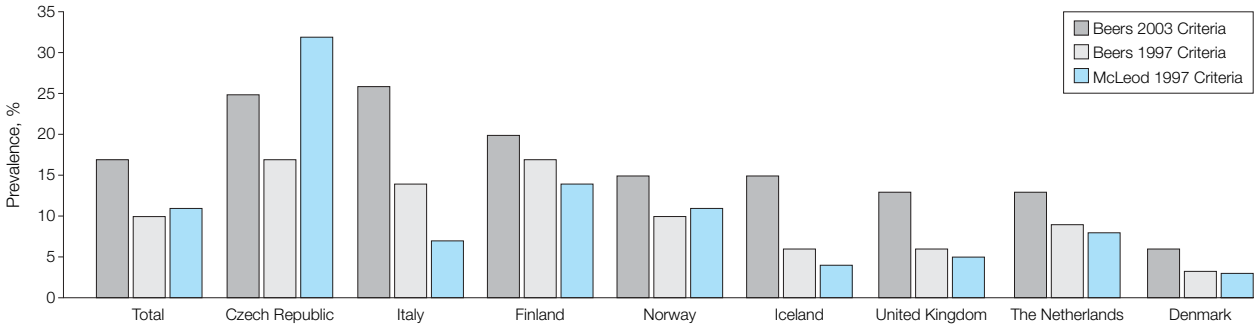
Figure 1. Prevalence of Potentially Inappropriate Medication Use Considering All Explicit Criteria Combined (Beers 1997,[15] Beers 2003,[17] and McLeod 1997[16])



No./Total	535/2707	176/428	109/412	39/187	60/388	61/405	41/289	26/198	23/400

Error bars indicate 95% confidence intervals.

Figure 2. Prevalence of Potentially Inappropriate Medication Use by Individual Criteria (Beers 1997,[15] Beers 2003,[17] and McLeod 1997[16])



No./Total									
Beers 2003 Criteria	458/2707	108/428	106/412	38/187	57/388	61/405	39/289	26/198	23/400
Beers 1997 Criteria	265/2707	67/428	56/412	32/187	38/388	24/405	17/289	18/198	13/400
McLeod 1997 Criteria	295/2707	136/428	28/412	27/187	44/388	18/405	15/289	15/198	12/400

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Table 3. Prevalence of the 10 Most Common Inappropriate Medications in the Entire Sample and by Country*

	% (No.)								
	Overall (n = 2707)	Czech Republic (n = 428)	Denmark (n = 400)	Finland (n = 187)	Iceland (n = 405)	Italy (n = 412)	The Netherlands (n = 198)	Norway (n = 388)	United Kingdom (n = 289)
Pentoxifylline	3.5 (94)†	20.3 (87)†	NA	1.1 (2)	NA	1.2 (5)	NA	NA	NA
Diazepam	3.1 (84)†	5.6 (24)†	2.0 (8)	5.3 (10)†	0.7 (3)	2.7 (11)	4.0 (8)†	4.9 (19)†	0.3 (1)
Amiodarone	2.0 (53)	4.0 (17)†	0	0	1.7 (7)	5.1 (21)†	1.0 (2)	0	2.1 (6)
Amitriptyline	1.4 (39)	0.5 (2)	0	4.8 (9)†	1.7 (7)	0.5 (2)	1.0 (2)	2.1 (8)	3.1 (9)†
Ticlopidine	1.3 (35)	0.2 (1)	0	NA	0	8.3 (34)†	NA	0	0
Digoxin >0.125 mg/d	1.0 (26)	3.5 (15)†	0	0	0.5 (2)	1.7 (7)	1.0 (2)	0	0
Unopposed estrogens in older (≥75 y) women	1.0 (17)	0	0.3 (1)	1.6 (2)	5.5 (14)†	0	0	0	0
Doxazosine	0.8 (22)	1.2 (5)	0	NA	0	1.5 (6)	2.0 (4)	0.3 (1)	2.1 (6)
Fluoxetine daily	0.8 (21)	2.1 (9)	0.3 (1)	0.5 (1)	0.7 (3)	0.5 (2)	0	0.3 (1)	1.4 (4)
Piroxicam	0.7 (20)	1.9 (8)	0.3 (1)	0	0	1.0 (4)	0	1.8 (7)	0
Dipyridamole, short-acting	0.7 (19)	0.2 (1)	0.5 (2)	1.6 (3)	0.7 (3)	0.2 (1)	1.5 (3)	0.8 (3)	1.0 (3)
Nifedipine, short-acting	0.7 (19)	0.2 (1)	0	2.1 (4)	0.5 (2)	1.0 (4)	0	1.0 (4)	1.4 (4)
Oxybutynin, short-acting	0.7 (18)	0.9 (4)	0	1.1 (2)	0.5 (2)	0.7 (3)	1.5 (3)	NA	1.4 (4)
Chlordiazepoxide	0.6 (15)	3.3 (14)†	0	0.5 (1)	0	0	0	NA	0

Abbreviation: NA, not available (not approved for clinical use).
*Only drugs with prevalence exceeding 0.5% in the total sample are listed. No other potentially inappropriate medications were prescribed in individual countries with a proportion higher than 1.7%. All percentages by country were computed in country-specific total frequencies.
†Drug extensively prescribed (prevalence ≥3%).

(TABLE 5). Individuals reporting a poor economic situation had a 1.96-fold higher relative risk of receiving an inappropriate medication than the reference group. This factor was significantly associated with living in the Czech Republic (contingency coefficient, 0.38; $P<.001$), where 32.7% of patients reported a poor economic situation compared with an average of 2.9% in all the other countries. The relative risk of inappropriate medication use was 1.8-fold higher among users of anxiolytic drugs and 1.9-fold higher among patients receiving 6 or more medications. Polypharmacy covaried with having 4 or more medical conditions (contingency coefficient, 0.36; $P<.001$). Depression appeared to be a weaker predictive variable (RR, 1.29; 95% CI, 1.06-1.55). On the other hand, individuals aged 85 years or older and those living alone were less likely to receive inappropriate medications. We found a significant colinearity between not living alone and dependency in self-care (contingency coefficient, 0.31; $P<.001$). Relative risks derived from the corresponding odds ratios were all statistically significant (Table 5). All associated factors were significant in individual countries except poor economic situation, which was a country-specific factor (Czech Republic). Collinearity between associated factors and other variables than tested was excluded.

Although the logistic regression model was statistically significant ($P<.001$), a large amount of variability remained unexplained (Nagelkerke R^2 coefficient, 11.0%). However, the likelihood of being prescribed an inappropriate medication increased exponentially ($P<.001$) with the number of predictive variables and reached an odds ratio of 10.96 in patients with at least 4 predictive factors (FIGURE 3).

COMMENT

While US national surveys have documented that among community-dwelling elderly persons more than 7 million use potentially inappropriate medications,[4] no such evidence has been available for Europe. In fact, small-scale national studies have been conducted only in a few European countries using different methods and with little comparability.[18-20] To our knowledge, the findings of this study represent the first comparative estimates of potentially inappropriate medication use in a large sample of community-dwelling elderly persons in major metropolitan areas of 8 European countries. In addition, this study compared all available explicit criteria of inappropriate medication use to generate the most comprehensive evaluation of this issue in Europe, where specific criteria are not available.

Differences Between Europe and North America

Differences exist between panels of medications available in the United States and in countries in Europe, as well as across countries in Europe. Several potentially inappropriate medications listed in the criteria were not approved in all AdHOC countries (eg, chlorzoxazone, halazepam, quanadrel, metaxalon, methocarbamol, nylidrin, oxaprozin, phenylbutazone, quazepam, trimethobenzamide). While in some national formularies selected inappropriate medications are not available, eg, belladonna alkaloids (Italy), hyosciamine (Iceland), and pentoxifylline (Norway), other countries use these drugs rarely in elderly patients (hyosciamine in Finland and Italy, pen-

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toxifylline in Finland) or frequently (eg, long-acting benzodiazepines and pentoxifylline in Czech Republic). Overall, nearly half the medications from the combined list were not approved in most of the European countries.[28-35] The percentage of approved drugs in individual countries was 31.6% in Norway, 48.1% in the Netherlands, 50.6% in Iceland, 51.9% in Denmark, and Czech Republic, 55.7% in Finland and United Kingdom, and 70.9% in Italy.

Moreover, some medications not available in the United States (eg, flunitrazepam and etofylline) are available in Europe and have potentially harmful properties similar to medications on the list. These specific substances should be identified in the future by expert panel groups in Europe. It is also likely that economic constraints contribute substantially to inappropriate medication use. For example, ticlopidine was recommended for use in elderly patients consistently in all countries except in Norway. Clopidrogel, believed to be a safer alternative,[15,17] was more expensive and therefore economically unavailable.

As discussed previously, no criteria for potentially inappropriate medications have been developed for European countries. Until such criteria are available, existing standards permit comparisons of inappropriate medication use across countries and our study provides the most comprehensive cross-sectional estimate of this issue in Europe to date. Considering all explicit criteria combined, we found a 20% prevalence of inappropriate medication use. This estimate is similar to those documented by epidemiological surveys in the United States. These surveys found that applying only Beers 1997 criteria, a prevalence of inappropriate medication use yielded 21% in community-dwelling elderly individuals[4] and 23% in Medicare-managed care elderly patients.[13] When we considered the same approach (Beers 1997 criteria), the prevalence of inappropriate medication use appeared to be lower (<11% in the majority), in agreement with results of previous small-scale

Table 4. Univariate Analysis of Variables Associated With Inappropriate Medication Use

Characteristics	Inappropriate Medication Use, % (No.) No (n = 2172)	Yes (n = 535)	*P* Value
Sociodemographic characteristics			
Age ≥85 y	39.9 (866)	29.0 (155)	<.001
Female sex	74.6 (1620)	73.5 (393)	.59
Live alone	62.7 (1362)	55.1 (295)	.001
No informal helper	13.5 (294)	12.3 (66)	.46
Poor economic situation	5.8 (125)	15.3 (82)	<.001
Loneliness*	20.8 (452)	26.9 (144)	.002
Clinical and functional status characteristics			
Multiple comorbidity (≥4 diseases)	34.5 (750)	51.6 (276)	<.001
Dependency in IADL (score ≥2)	68.2 (1482)	76.3 (408)	<.001
Dependency in ADL (score ≥2)	37.8 (821)	45.2 (242)	.002
Cognitive impairment (CPS score ≥2)	28.2 (613)	29.9 (160)	.44
Depression (DRS score ≥3)	14.7 (319)	24.5 (131)	<.001
Self-reported poor health	29.5 (640)	30.8 (165)	.53
Unstable disease status†	24.3 (528)	29.9 (160)	.008
Service use characteristics			
Hospitalization in prior 30 d	11.5 (249)	11.4 (61)	.97
Emergency home or hospital visit in prior 3 mo	14.6 (317)	16.4 (88)	.28
Nursing home stay in prior 5 y	8.4 (182)	11.4 (61)	.03
Lack of medication review	18.6 (404)	15.0 (80)	.047
More care needed‡	16.6 (360)	23.0 (123)	.001
Drug-related characteristics			
Polypharmacy (≥6 drugs)	46.6 (1012)	68.8 (368)	<.001
Psychotropic drug use (≥1 drugs)	40.2 (874)	56.4 (302)	<.001
Antipsychotic drug use	6.4 (140)	7.9 (42)	.25
Anxiolytic drug use	10.1 (220)	23.6 (126)	<.001
Antidepressant drug use	14.9 (324)	20.0 (107)	.004
Hypnotic drug use	22.7 (492)	26.7 (143)	.046
Nonadherence (<80%)	11.4 (248)	16.3 (87)	.002

Abbreviations: ADL, activities of daily living[24]; CPS, Cognitive Performance Scale[25]; DRS, Depression Rating Scale[26]; IADL, instrumental activities of daily living.[22]
*Defined as patient reported being and/or feeling lonely.
†Defined as worsening of the functional status (cognition, mood, or self-care performance) in the prior 30 days; recurrence of a chronic disorder in the prior 3 months; or medication change due to a new clinical problem in the prior 30 days.
‡Defined as the decrease in patient's self-performance 3 months prior to the assessment and patient's need for more care provision (based on opinion of home care nurse).

Table 5. Multivariate Analysis of Variables Independently Associated With Inappropriate Medication Use*

Factor Associated With Inappropriate Medication Use	OR (95% CI)	*P* Value	RR (95% CI)
Poor economic situation†	2.48 (1.82-3.39)	<.001	1.96 (1.58-2.36)
Polypharmacy (≥6 drugs)‡	2.19 (1.78-2.70)	<.001	1.91 (1.62-2.22)
Anxiolytic drug use§	2.19 (1.70-2.82)	<.001	1.82 (1.51-2.15)
Depression (DRS score ≥3)§	1.37 (1.07-1.75)	.01	1.29 (1.06-1.55)
Age (≥85 y)	0.73 (0.59-0.90)	.004	0.78 (0.65-0.92)
Live alone‖	0.71 (0.58-0.86)	<.001	0.76 (0.64-0.89)

Abbreviations: CI, confidence interval; DRS, Depression Rating Scale; OR, odds ratio; RR, relative risk.
*Odds ratios were adjusted for other factors in the table. The RRs were calculated from the ORs using the method of Zhang and Yu.[27]
†Factor significantly colinear with living in Czech Republic (*P*<.001).
‡Factor significantly colinear with multiple comorbidity (≥4 diseases) (*P*<.001).
§The significant association with inappropriate medication use not influenced by only use of benzodiazepines (*P*<.001).
‖Factor not living alone significantly colinear with dependency in self-care. The higher proportion of dependency in self-care the lower proportion of living alone (*P*<.001). Dependency in self-care classified as activities of daily living score of 2 or more.

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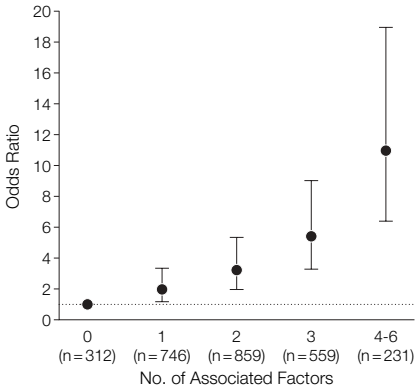
Figure 3. Odds of Potentially Inappropriate Medication Use According to the Number of Patient-Related Predictive Factors



Factors are listed in Table 5. No associated factor is the referent group. Error bars indicate 95% confidence intervals.

studies from Finland, Sweden, and Italy.[18-20] However, longer assessment periods tend to find higher prevalence rates, suggesting that an assessment longer than our 7 days might find different results. It is also likely that the absence of many inappropriate medications in the European national formularies accounted in part for the "relatively better prescribing practice" in Europe.

Differences Among European Countries

The prevalence of inappropriate medication use varied substantially among countries. The most striking was the difference between the Czech Republic and countries in Western Europe. In Prague, 41% of home care elderly patients were prescribed at least 1 inappropriate medication compared with only 16% in Western European countries. It is likely that prescribing habits along with socioeconomic factors, including prescribing limits and patients' inability or unwillingness to copay for safer alternatives, were responsible for the high proportion of potentially inappropriate medication use in the Czech Republic. Indeed, other studies have documented reduced access to safer treatments[36] and higher frequency of potentially inappropriate prescriptions in low-income elderly.[37] Noticeably, the findings for the Czech Republic were greatly influenced by the very frequent use of pentoxifylline (>20%), which is considered potentially inappropriate based solely on the McLeod 1997 criteria. While a detailed evaluation of this finding is beyond the scope of this study, our results confirm recent data that pentoxifylline belongs to the top 10 most commonly prescribed medications in the Czech Republic.[38]

Substantial differences were also found among Western European countries, with a higher prevalence of potentially inappropriate medication use in Italy and Finland. However, it should be noted that nearly 50% of this prevalence represented potentially inappropriate medications that particularly in low-dose regimens "might have some indications in the old age" based on recommendations of national drug formularies (eg, diazepam and amitriptyline in Finland, amiodarone and ticlopidine in Italy).[28-35] We could not evaluate appropriateness at the individual patient level and as such our findings should be corroborated by further studies.

These limitations notwithstanding, the extensive use of some inappropriate medications in particular countries is concerning and merits further study. In agreement with our findings, a recent study in Italy confirmed ticlopidine and amiodarone to be the most commonly prescribed potentially inappropriate medications.[39] In Finland, a national study has documented that psychotropic drugs are often inappropriately prescribed in community-dwelling elderly patients, particularly diazepam for the treatment of depression.[40]

The differences in inappropriate medication use might also be influenced by country-specific regulatory measures. The strikingly low prevalence in Denmark despite high rates of polypharmacy is likely related to drug utilization review provided by the National Institute of Health with feedback to individual physicians.[41] Similarly, in the United Kingdom, implementation of guidelines and clinical pharmacists' auditing has probably contributed to lower prevalence of inappropriate medication use.[42] In the United States, computerized alert systems with personal feedback to physicians effectively reduced the amount of newly prescribed inappropriate medications.[43]

Our findings document that the addition of several substances into the Beers 2003 list nearly doubled the prevalence obtained with Beers 1997 criteria. This might indicate physicians' better knowledge of older Beers criteria and less confidence with newly attained pharmacoepidemiological and pharmacological evidence confirming harmful properties of several other medications later included in the Beers 2003 list (eg, short-acting nifedipine, short-acting oxybutynin, daily fluoxetine) (Table 1).[42,44]

Factors Associated With Inappropriate Medication Use

In agreement with previous US studies, similar independent predictors of inappropriate medication use were identified in Europe: patient's poor economic situation, polypharmacy, anxiolytic drug use, and depression.[1,10,18] On the other hand, individuals aged 85 years or older or living alone were significantly less likely to receive inappropriate medications.[4,9,10]

Many studies have highlighted polypharmacy as a significant risk for inappropriate medication use, adverse drug events, for the increase in health care utilization, and costs.[45] In addition, patients with depression and elderly patients treated with psychotropic medications are at risk for inappropriate prescription.[10,18,43] Studies from the United States and Canada have confirmed that auditing drug regimens in these populations might reduce the prevalence of inappropriate medication use.[1,6,9]

Individuals living alone might be less likely to receive a potentially inappropriate medication as a consequence of less frequent contact with primary care

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physicians.[4] Similar reduced risk in patients 85 years or older could be explained by greater physician awareness of this issue in the oldest old[9] or by a higher mortality rate in this age group.

No other characteristics (eg, recent medication review, cognitive impairment, hospitalization in the past 30 days) were associated with inappropriate medication use. Despite a number of patient-related characteristics being tested, a large amount of variance in the model remained unexplained. It is likely that physician-related factors might account for a significant part of this variance (eg, knowledge of the expert panels' criteria, adherence to guidelines, amenability to pharmaceutical marketing). Due to strong societal or individual influences on prescribing practice,[1,17] these factors should be considered in future sociobehavioral studies.

Limitations

Our results need to be interpreted with caution due to several limitations. Results of our study cannot be generalized to the whole community-dwelling elderly population because of the higher frailty of home care elderly patients. Additionally, because inappropriate medication use is sensitive to regional marketing strategies and prescribing practices, our findings are not generalizable to other European countries. We were unable to determine country-specific factors associated with inappropriate medication use due to small samples; future large studies should explore this issue. Also, residual confounding is always a possibility.

An important concern is the very definition of "inappropriateness," which is rather relative than absolute. Under specific circumstances, some "inappropriate" medications might be appropriately indicated. However, the design of our study did not allow evaluating the medication appropriateness at an individual level and our results only screen populations at risk. We cannot dismiss conclusively the possibility that some individuals had tried safer alternatives in the past. Finally, we cannot imply that inappropriate medication use is necessarily linked to negative outcomes because this analysis was cross-sectional. However, current reports confirm these associations.[13,46]

CONCLUSIONS

In Europe, use of potentially inappropriate medications among frail community-dwelling elderly persons appears to be common, with substantial regional variations. The differences likely reflect country-specific drug policies, care provision differences, inequalities in socioeconomic background, differences in overall health conditions, and specific regulatory measures. While regional preferences for some inappropriate medications need a more in-depth evaluation, these variations indicate amenability to intervention, particularly in Eastern Europe. Future efforts should be targeted to modifiable correlates of inappropriate medication use and research should focus on outcomes and intervention strategies.

Despite previous criticism of the expert panels' criteria for their simplicity,[17] these tools increase clinicians' awareness about potentially inappropriate medications for older patients. Thoughtful adoption of these criteria by regulatory institutions, national guidelines, and computerized alert systems might improve prescribing. Because one of the current principal aims of the European Union is to improve practice, rules, and regulations throughout Europe, harmonizing drug policy and regulatory measures with respect to potentially inappropriate medication use should be a major focus (eg, withdraw ineffective and/or harmful medications, establish prescribing limits for the elderly, approve safer alternatives, harmonize prescribing guidelines). These strategies could help ensure that prescribing for older patients in Europe is improved and consistent across countries.

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Our character . . . is an omen of our destiny, and the more integrity we have and keep, the simpler and nobler that destiny is likely to be.
—George Santayana (1863-1952)

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