

Applicability of EU(7)-PIM criteria in cross-national studies in European countries

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Abstract

Background: The European Union (EU)(7)-PIM (potentially inappropriate medication) list presents the most comprehensive and up-to-date tool for evaluation of PIM prescribing in Europe; however, several country-specific studies have documented lower specificity of this list on pharmaceutical markets of some countries. The aim of our study was to describe approval rates and marketing of PIMs stated by EU(7)-PIM criteria in six EU countries [in comparison with the American Geriatric Society (AGS) Beers 2015 criteria].

Methods: Research teams of six EU countries (Czech Republic, Spain, Portugal, Serbia, Hungary and Turkey) participated in this study conducted by WG1b EU COST Action IS1402 group in the period October 2015–November 2018. Data on approval rates of PIMs and their availability on pharmaceutical markets have been obtained from databases of national drug-regulatory institutes and up-to-date drug compendia. The EU(7)-PIM list and AGS Beers 2015 Criteria (Section 1) were applied.

Results: PIMs from EU(7)-PIM list were approved for clinical use more often than those from the AGS Beers 2015 criteria (Section 1). Approval rates for EU(7)-PIMs ranged from 42.8% in Serbia to 71.4% in Spain (for AGS criteria only from 36.4% to 65.1%, respectively). Higher percentages of approved PIMs were documented in Spain (71.4%), Portugal (67.1%) and Turkey (67.5%), lower in Hungary (55.5%), Czech Republic (50.2%) and Serbia (42.8%). The majority of approved PIMs were also currently marketed in all countries except in Turkey (19.8–21.7% not marketed PIMs) and less than 20% of PIMs were available as over-the-counter medications (except in Turkey, 46.4–48.1%).

Conclusions: The EU(7)-PIM list was created for utilization in European studies; however, applicability of this list is still limited in some countries, particularly in Eastern and Central Europe. The EU project EUROAGEISM H2020 (2017–2021) that focuses on PIM prescribing and regulatory measures in Central and Eastern European countries must consider these limits.

Keywords: aged, geriatrics, PIMs, potentially inappropriate medications, regulatory measures

Received: 10 December 2018; revised manuscript accepted: 24 April 2019.

Introduction

Polypharmacy and high-risk prescribing are highly prevalent in the older population. One of the core strategies how to reduce these negative phenomena are pharmacist- or physician-led medication reviews, and the process of deprescribing. Deprescribing has been defined as ‘...withdrawal of inappropriate medication, supervised by a

healthcare professional with the goal of managing polypharmacy and improving older patient safety and health outcomes.¹ Many different tools have been developed for deprescribing [e.g. different geriatric risk scores, geriatric tools enabling identification of anticholinergic and sedative drug burden, implicit prescribing algorithms or explicit criteria of potentially inappropriate medications

Ther Adv Drug Saf

2019, Vol. 10: 1–22

DOI: 10.1177/
2042098619854014

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(so called PIMs)].² The latter are older and simpler tools, now more used in clinical practice and research.

The first explicit criteria of PIMs have been published already 20 years ago (Beers 1991 criteria)³ and the newest, extensive lists of PIMs applied in international research are (a) the American Geriatrics Society Beers criteria (AGS Beers criteria, with the previous version published in 2015,⁴ now newly updated in January 2019),⁵ (b) the STOPP/START 2015 criteria (version 2),⁶ and (c) the European Union (EU)(7)-PIM list from 2015.⁷ While the EU (7)-PIM list and Section 1 of the AGS Beers criteria state PIMs mostly disregard clinical conditions of inappropriateness and may be applied in regulatory studies, the application of STOPP/START criteria require clinical information on results of patients' clinical assessments and lab tests and these criteria are specifically designed for identification of PIMs in clinical practice.⁴⁻⁷ Of the three above-stated criteria, the EU(7)-PIM list is the first multicentric European tool developed by experts from seven EU countries, namely from Estonia, Netherlands, Finland, Spain, France, Sweden and Denmark.⁷ However, in national research and clinical practice, mostly higher specificity of national tools have been confirmed, for example, of Laroche's criteria in France,⁸ NORGEP⁹ and NORGEP-NH criteria in Norway,¹⁰ the PRISCUS list in Germany,¹¹ and McLeod's¹² and Rancourt's criteria in Canada,¹³ etc. These tools have been developed for specific national studies by excluding PIMs not approved on country-specific pharmaceutical markets and by inserting 'new PIMs' available only in a specific country. For these reasons, applicability of national criteria in the international context is limited.

Sufficient numbers of studies confirmed serious negative outcomes of PIMs, for example, increase in the prevalence of geriatric symptoms and syndromes (drug-related bradycardias, renal insufficiency, cognitive impairment, deliria, drug-related malnutrition, falls, etc.), increase in number and length of hospitalizations, worsening of geriatric frailty, higher utilization of healthcare services and costs, and also increase in mortality in several studies.¹⁴⁻¹⁹ However, despite much evidence on negative outcomes, prescribing of PIMs is still high in the older population and varies significantly across different settings of care, facilities, regions, and countries. As confirmed by two systematic reviews,

the weighted point prevalence of PIM use in European studies was 49.0% in institutional care and 22.6% in community-residing older adults.^{20,21} The US study by Jiron *et al.* described the decrease in PIM prevalence from 64.9% to 56.6% between 1997 and 2012, respectively.²² However, the Irish study found the increase in the prevalence from 32.6% to 37.3% in the same period.²³ It is well known that PIM prescribing is also strongly influenced by prescribing habits, different perceptions of physicians on inappropriateness of PIMs, different country-specific recommendations, guidelines and regulations.

Already, the multicentric European project ADHOC, the AgeD in HOme Care (7th Framework Program of the European Commission, 2001–2005) in one of its ancillary studies confirmed that the percentage of approved PIMs stated by combined lists of Beers 1997 and 2003 criteria and McLeod's 1997 criteria ranged from 31.6% in Norway to 70.9% in Italy. In the majority of European countries, approval rates of PIMs were around 50% (e.g. 48.1% in the Netherlands, 50.6% in Iceland, 51.9% in Denmark and Czech Republic (CZ), and 55.7% in Finland and United Kingdom), but these PIM lists and the prevalence of prescribing of individual PIMs widely differed. For example, pentoxifylline was overprescribed to 20% of older adults in the CZ (and broadly advertised) while in other EU countries, this PIM was not approved for clinical use (e.g. in Denmark, Iceland, Netherlands, Norway and the United Kingdom) or was used rarely (prevalence of 1.1% in Finland and 1.2% in Italy).²⁴ Similar discrepancies have also been found for many other PIMs. These findings raised attention to regulatory issues related to PIM use in our research.

In the European Union, protection of public health and the high quality, effective and safe medicinal products should be guaranteed by the European regulatory system for medicines within the EU. This system is represented by the network of medicines' regulatory authorities from 31 European Economic Area member states, the European Commission and the European Medicines Agency (EMA).²⁵ All medicines in the EU must be authorized before being available for patients and there are different routes for authorizing medicinal products. The centralized authorization procedure is laid down by the regulation (EC) no. 726/20042 of the European Parliament and of the Council. For this type of authorization

there is a single application, a single evaluation by the EMA's Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) and consecutively, the authorization is granted by the European Commission.²⁶ Such marketing authorization is valid for entire EU market and all member states.²⁷ Some specific medicines (e.g. most innovative medicines) fall into the scope of mandatory centralized authorization procedure.²⁵ However, there are also other types of authorization procedures, mainly the decentralized procedure, mutual-recognition and national authorization procedure. The decentralized procedure can be used in situation when a medicinal product is not authorized in any of the EU countries yet and the company applies for the authorization in more than one EU member state at the same time. The mutual-recognition procedure is represented by the situation when a medicinal product is authorized in only one EU member state and the company applies for authorization in other EU countries (this type of procedure allows EU member states to rely on each other's scientific assessments) and the national procedure represents the authorization procedure unique to every EU member state.^{25–27}

Most of the medicines available in the EU (and particularly, older medicines like PIMs mostly are) were authorized for clinical use at the national level. They were mostly authorized before EMA's creation and were not in the scope of the centralized authorization procedure. For this reason, approval rates, recommendations and preferences for the use of PIMs highly differ in different EU countries. Different approval rates of PIMs and regulations [e.g. prescribing limits for individual PIMs, over-the-counter (OTC) availability, etc.] also significantly influence the applicability of different PIM criteria in research and clinical practice.^{24,28}

Because the EU(7)-PIM list becomes one of the preferred tools for clinical practice and research in European studies, the aim of our study was to describe (using quantitative and qualitative analyses) the approval rates and selected regulatory aspects (e.g. EMA's authorization, actual availability on the pharmaceutical market, and availability only on prescription or as an OTC medication) for PIMs stated on the EU(7)-PIM list in comparison with PIMs stated by the AGS Beers criteria in several EU countries [Czech Republic (CZ),

Hungary (HU), Republic of Serbia (RS), Spain (ES), Portugal (PT), and Turkey (TR)], participating in the EU COST Action IS1402 WG1b research initiative.²⁹ The aim of our analyses was to obtain first evidence for the newly starting FIP7 EUROAGEISM Horizont 2020 project that will focus on documenting clinical conditions of PIM use, country-specific prescribing habits and regulatory measures related to PIM prescribing in different EU countries, including mainly Central and Eastern European countries.³⁰

Methodology

Research team

Research teams of six European countries (CZ, ES, PT, RS, HU, and TR) involved in the WG1b working subgroup 'Healthy clinical strategies for healthy aging' of the EU COST Action IS1402 initiative (2015–2018)²⁹ participated in this research study. Selection of countries was not intentional; all countries participating in the WG1b EU COST Action IS1402 group were invited, and finally the six above-stated EU countries joined this research held in the period 2015–2018.

Design and methodology of our research was set up at two initial EU COST Action IS1402 face-to-face meetings in Dublin, Ireland (October 2015) and Prague, CZ (April 2016). Discussions on data collection and corrections, as well as on analyses and results interpretation were conducted during other face-to-face scientific meetings, organized twice a year by the EU COST Action WG1b group in the period between December 2015 and October 2018, under financial support of the EU COST Action IS1402.

Explicit criteria of PIMs

The list of PIMs used in our research was created from two explicit criteria of PIMs in the older population published in the USA and Europe in 2015. These were the AGS 2015 Beers criteria (Section 1),⁴ which represented the latest Beers criteria update at the time of our study (in January 2019, a new update of AGS Beers 2019 was released).⁵ These criteria were developed by experts of the AGS. Also, the EU(7)-PIM list published by Renom-Guiteras and colleagues⁷ was used in our analyses as the first international European tool developed for international studies. Both of these criteria [EU(7)-PIM and AGS

Beers criteria] represent the most known and most comprehensive tools in the US and Europe today, applicable in regulatory studies. Because the STOPP/START criteria require for identification of PIMs the data on clinical conditions of medication use in an individual patient (lab values and results of other clinical assessments), they were not applicable in our research.⁶ The AGS 2015 Beers criteria (Section 1) and EU(7)-PIM list were mostly used because potential inappropriateness of PIMs according to these criteria was defined mostly by medication-related characteristics (e.g. limits of a single dose, retard and nonretard drug forms, route of application, etc.). The 2015 AGS Beers criteria consisted of four sections and of those only Section 1 (PIMs mostly independent on clinical conditions) was selected for our research.⁴ The EU(7)-PIM criteria stated mostly PIMs independent of diagnoses and other clinical conditions (with a few exceptions)⁶ and all items were included in analyses [e.g. disregarding the length of the treatment and several disease-related conditions for a few PIMs (on both lists) to use as extensive methodology as possible].

Focus of our analyses was mainly on approval rates of PIMs (with regard to or not including specific medication-related conditions of inappropriateness; and on actually marketed PIMs (see Figure 1 in the Results section), and their availability on prescription or also as OTC drugs (see Figure 3 in Results section). With regard to medication-related conditions of inappropriateness, we conducted evaluation of all approved brand names, drug forms and doses in individual countries. However, our intention was not to focus on comparisons of all relative contraindications, specific warnings for the geriatric population, and clinical conditions defining appropriate/inappropriate use of PIMs in the summary product characteristics (SPCs) because such study would require a huge effort of international expert teams and merits more extensive and specifically developed methodology. Considering the huge number of brand names of PIMs approved by national authorization procedures in different countries (different drug forms, doses, etc.), even our analyses comparing approval rates of PIMs, their marketing, and availability only on prescription or as OTC drugs required substantial effort and is exceptional in the scientific literature. We also studied qualitative differences in approval rates of PIMs,

means differences in PIMs withdrawn from the pharmaceutical markets by regulatory agencies between 2016 and 2018, and newly approved for clinical use in this period. We also searched which PIMs from the total list were approved by the central authorization procedure of the EMA.

Primary data for our study were collected between September and December 2016 and checked and corrected during spring 2017. Problematic areas were discussed during face-to-face meetings in the period 2016–2018, and last check and corrections of data were conducted in autumn 2018 (before first submission of our research paper) and during the first revisions in February–March 2019. Information was obtained from official websites of national drug-regulatory institutes^{31–43} and verified by national research teams using national drug compendia, national drug formularies, reimbursement compendia, or using opinions of experts from national regulatory institutes. Country-specific research teams recorded all necessary information (see Table 1) and this was checked twice by two independent researchers.^{31–51}

Data summary and statistical analyses

We used descriptive statistical methods to express quantitative differences in approval rates of PIMs in participating countries for 2018 year. Results of quantitative analyses were summarized in graphs presenting differences in approval rates of PIMs in participating EU countries using EU(7)-PIM list and 2015 AGS Beers criteria (comparing approved and currently marketed PIMs, as well as results obtained regarding or not including conditions of inappropriateness of PIMs; see Figure 1). Also another graph has been created to document absolute numbers of PIMs approved for clinical use in individual countries using EU(7)-PIM list and AGS 2015 Beers criteria based on the Anatomic Therapeutic Chemical (ATC) Classification System (again, both regarding and not including conditions of PIM inappropriateness, see Figure 2). We also documented percentages of marketed PIMs available only on prescription or as OTC medications (see Figure 3).

In the summary tables, we described changes in PIMs approved for clinical use on different pharmaceutical markets between 2016 and 2018 (see Table 3, newly approved PIMs and PIMs

Table 1. Example of the general table (part) used for recording of primary data about PIMs approved for clinical use in one participating country.

Potentially inappropriate medication (PIM)	Approved for clinical use 1 = yes, 0 = no	Most frequently used brand names	Doses in mg available on the market per one unit (e.g. tablet)	Combined drugs	Solid p.o. drug forms 1 = approved (at least 1), 0 = not approved	Oral liquids for systemic use (solutions, suspensions, syrups) 1 = approved (at least 1), 0 = not approved	Injections 1 = approved (at least 1), 0 = not approved	Suppositories 1 = approved (at least 1), 0 = not approved	Patches (for systemic treatment) 1 = approved (at least 1), 0 = not approved	Dispersible powder (systemic treatment) 1 = approved (at least 1), 0 = not approved	Available on prescription 1 = yes, 0 = no	Available as OTC meds 1 = yes, 0 = no	Prescription limits (1=yes/0=no)	Prescription limits (specialists) (example: Card, Neur, Psych, etc...)
Acarbose	1	Glucobay 50 mg, 100 mg tablet	50 mg, 100 mg	No	1	0	0	0	0	0	1	0	0	0
Acetofenac	0													
Acemetacin	1	Rantidil Forte 60 mg capsule	60 mg	No	1	0	0	0	0	0	1	0	0	0
Acemetacin (long-term use)	0													
Acenocoumarol	0													
Acepromazine	0													
Acetyldigoxin	0													
Acetylsalicylic acid	1	Andol PRO 75; 100 mg tablet, Aspirin protect 100 mg tablet, Aggrenox 200+25 mg capsule, DuoPlavin 75+75 (100) mg tablet, Concorasa 5(10)+100 mg capsule	75 mg, 100 mg	Dipyridamole/ acetylsalicylic acid, 200+25 mg tablet, Clopidogrel/ acetylsalicylic acid 75+(75) 100 mg tablet, Bisoprolol 5(10)+ acetylsalicylic acid 100 mg capsule	1	0	0	0	0	0	1	1	1	Card

withdrawn from the pharmaceutical market in individual countries) and characteristics of PIMs approved for clinical use in only one of six analyzed countries (see Table 4). Also, percentages of PIMs approved by the central authorization procedure of the EMA have been expressed and stated in the text in the Discussion section.

All charts were made using R software (version 3.5.1). The differences in the proportion of PIMs approved for clinical use on pharmaceutical markets according to the EU(7)-PIM list and 2015 AGS Beers criteria were stated using percentages. Differences in results over 5% were considered substantial.

In order to describe and appropriately comment on main differences between regulatory systems in different countries, we created Table 2 that describes the total number of inhabitants, proportion and absolute number of seniors in the population in individual countries, number of approved medicinal products, brand names and active substances, types of medicine authorization procedures and responsible national institutions, as well as selected information on specific educational programs or guidelines helping to increase

knowledge about PIMs and regulate PIM use at a national level (see references^{31–51}).

Results

Table 2 shows the differences in main characteristics among participating countries: the size of total and senior population, medicines marketing authorization procedures, national responsible institutions, and availability of medication safety and educational strategies or guidelines related to PIMs in individual countries. In relation to the areas described in Table 2, major differences were found in the size of total population (the largest country was TR with over 74 million inhabitants, and the second largest, ES, with more than 46 million inhabitants), in the proportion of older adults in the population (7.3% in TR compared with 15.8–19.0% in other countries), and in lower numbers of registered active substances in TR and RS (see Table 2). Comparing the medication authorization procedures, the EU countries (ES, PT, CZ and HU) respected the central authorization procedures of the EMA; however, in EU-candidate countries (TR and RS) only national medication authorization procedures were applied. No substantial

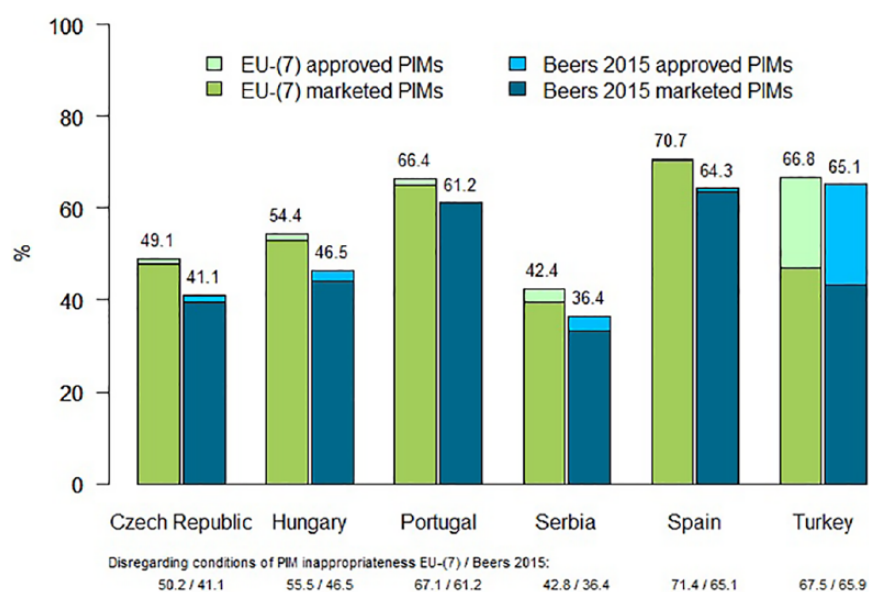


Figure 1. Percentages of approved and marketed PIMs by EU(7)-PIM list and AGS Beers 2015 criteria in six EU countries [regarding the conditions of inappropriateness of PIMs]. AGS, American Geriatric Society; ATC, Anatomic Therapeutic Chemical Classification System; PIM, potentially inappropriate medication.

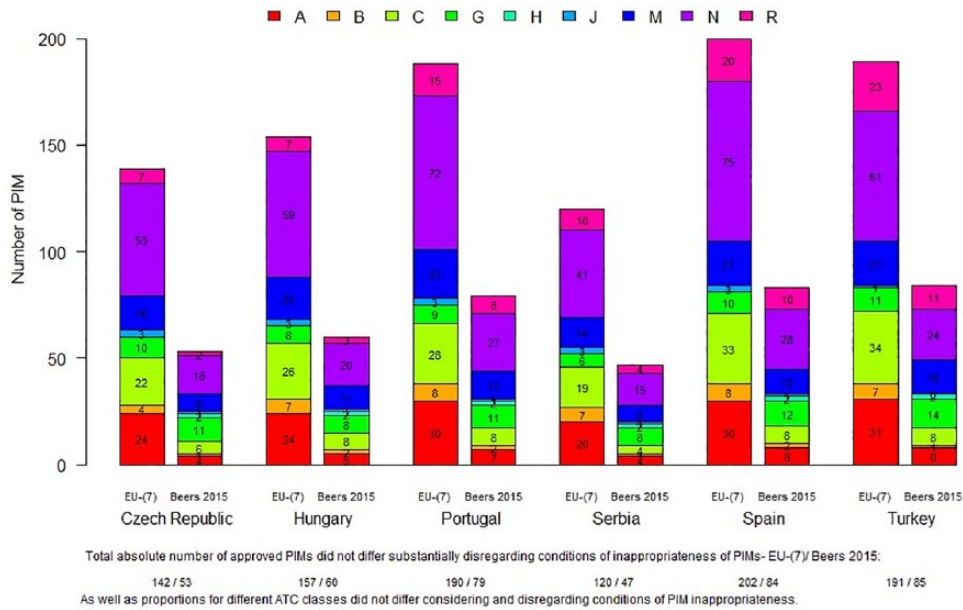


Figure 2. Absolute numbers of PIMs approved for clinical use according to EU(7)-PIM list and AGS Beers 2015 criteria (regarding medication-related conditions of PIMs' inappropriateness, by ATC classification). A (red)- PIMs used for the treatment of "ALIMENTARY TRACT AND METABOLISM", B (orange)- PIMs used for the treatment of "BLOOD AND BLOOD FORMING ORGANS", C (yellow)- "CARDIOVASCULAR SYSTEM" PIMs, G (green)- "GENITO URINARY SYSTEM AND SEX HORMONES" PIMs, H (light blue)- PIMs from "SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS", J (middle blue)- PIMs from "ANTIINFECTIVES FOR SYSTEMIC USE", M (dark blue)- "MUSCULO-SKELETAL SYSTEM" PIMs, N (purple)- "NERVOUS SYSTEM" PIMs and R (pink)- "RESPIRATORY SYSTEM" PIMs, AGS American Geriatric Society; ATC, Anatomical Therapeutic Chemical Classification System; PIM, potentially inappropriate medication.

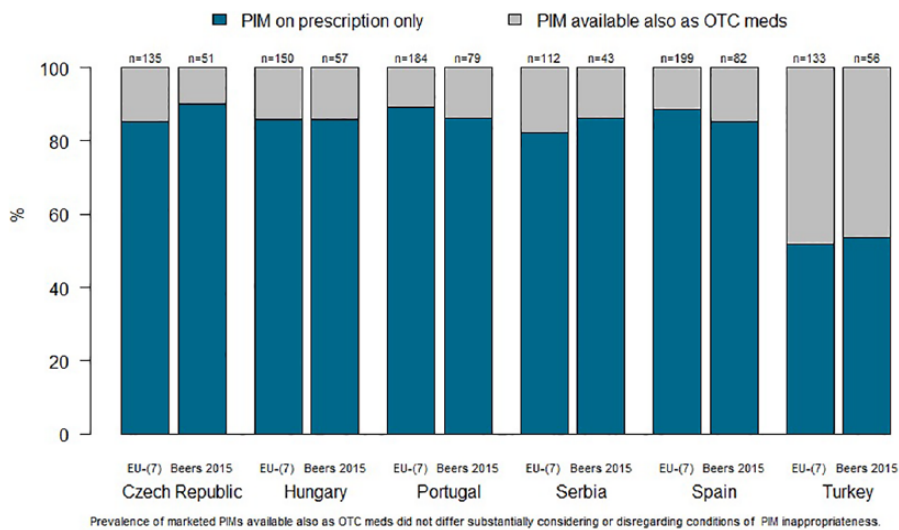


Figure 3. Percentages of marketed PIMs available on prescription only or as OTC medicines in six EU countries (with regard to the conditions of PIM inappropriateness). Prevalence of marketed PIMs also available as OTC medications did not differ substantially with regard to or not including conditions of PIM inappropriateness. EU, European Union; OTC, over the counter; PIM, potentially inappropriate medication.

Table 2. Main characteristics of analyzed countries regarding authorization of medicinal products and selected regulatory measures related to PIMs.³¹⁻⁵¹

	Czech Republic	Hungary	Portugal	Spain	Serbia	Turkey
Total population^a	10436560	9937628	10562178	46815910	7186862	74526000
Seniors (65+) in the whole population (n)^a	1644836	1677120	2010064	8115815	1250316	5445000
Seniors (65+) in the whole population (%)^a	15.8	16.9	19.0	17.3	17.4	7.3
65-74.9 (%)^a	9.1	9.5	9.9	8.3	9.7	4.4
75-84.9 (%)^a	5.2	5.7	6.9	6.7	6.6	2.4
85-94.9 (%)^a	1.4	1.6	2.1	2.2	NA	NA
95+ (%)^a	0.1	0.1	0.2	0.2	NA	NA
No registered active substances^{b,d}	1624	1631	2455	2470	1145	1459
No registered brand names^{b,d}	5787	3527	9002	14177	2526	5361
No registered medicinal products^{b,d}	56371	28850	16976	31482	5243	18981
National regulatory agency^b	State Institute for Drug Control	National Institute of Pharmacy and Nutrition	INFARMED: National Authority of Medicines and Health Products	Spanish Agency of Medicines and Sanitary Products	Medicines and Medical Devices Agency of Serbia	Turkish Medicines and Medicinal Devices Agency
EU centralized procedure	Yes	Yes	Yes	Yes	No	No
EU mutual-recognition procedure	Yes	Yes	Yes	Yes	No	No
EU decentralized procedure	Yes	Yes	Yes	Yes	No	No
National procedures	Yes	Yes	Yes	Yes	Yes	Yes
Any specific measures regulating PIM use in seniors are available on national level?	No	No	No	No	No	No

Table 2. (Continued)

	Czech Republic	Hungary	Portugal	Spain	Serbia	Turkey
Any specific measures regarding medication safety in seniors are available on national level (except regular (and mostly general) warnings in medication Summary product characteristics and patient leaflets)?	No	No	No	No	No	No
If there is any country-specific clinical guideline/recommendation regarding PIM use in older patients available?^c	Yes	No	No	Yes	No	Yes
Education course/courses on PIMs included regularly in pregraduate education of pharmacists	No*	No*	No*	No*	No*	No*
Education course/courses on PIMs included regularly in pregraduate education of physicians	No*	No*	No*	No*	No*	No*
Education course/courses on PIMs (efficacy, safety in older patients) included in postgraduate education of pharmacists/clinical pharmacists	No**	No**	No**	No**	No**	No**
Education course/courses on PIMs (efficacy, safety in older patients) regularly included in postgraduate education of general practitioners or other physicians	No, regular courses are organized only for geriatricians (twice a year)	No**	No**	No**	No**	No**

*Some faculties may have a separate lecture on this topics, but there are no obligatory subjects, courses, or modules taught as part of regular curricula.
**No specific courses; only general separate lectures in postgraduate continuing education courses are organized.
^a2011 census data sources: (a) for EU countries (Czech Republic, Hungary, Portugal and Spain); European Statistical System;⁴⁴ (b) for Serbia: Statistical Office of the Republic of Serbia;⁴⁵ (c) for Turkey: the Turkish Statistical Institute.⁴⁶
^bFor the majority of countries, excluding homeopathic products and radiopharmaceuticals, except Serbia, where all approved medicinal products are stated for all rows. Sources: (a) for the Czech Republic;⁴² (b) for Hungary;⁴⁰ (c) for Portugal;³⁵ (d) for Spain;⁴¹ (e) for Serbia;³⁶ (f) for Turkey.⁴³
^cSources: (a) for the Czech Republic;⁴⁷ (b) for Spain;^{48,49} (c) for Turkey.^{50,51}
^dLatest data for the majority of countries were available for 2017, except Portugal (2018) and Spain (2019). Radiopharmaceuticals, herbal, and homeopathic medicinal products were excluded from calculations (except Serbia where all medicinal products were included).
EU, European Union; NA, not available; PIM, potentially inappropriate medication.

Table 3. PIMs withdrawn or newly approved on pharmaceutical markets of participating countries between years 2016 and 2018.

PIMs withdrawn from pharmaceutical markets			PIMs newly approved		
PIMs	ATC code	Country	PIM	ATC code	Country
Acenocoumarol	B01AA07	Turkey	Acepromazine	N05CX	Turkey
Acetyldigoxin	C01AA02	Turkey	Acetylsalicylic acid (>325 mg)	N02BA01	Turkey
Amoxapine	N06AA17	Turkey	Atropine (excludes ophthalmic)	A03BA01	Serbia
Belladonna alkaloids	A03BA04, A03DB, A03CB, A06AB30	Czech Republic	Chlorzoxazone	M03BB03	Turkey
Benztropine (oral)	N04AC01	Turkey	Cyproheptadine	R06AX02	Turkey
Bethanechol	N07AB02	Turkey	Diclofenac	M01AB05	Turkey
Bromocriptine	N04BC01	Hungary	Diphenhydramine	R06AA02	Turkey
Clobazam (clobazepam)	N05BA09	Turkey	Diphenoxylate-atropine	Not available	Czech Republic
Dipyridamole	B01AC07	Serbia	Dronedarone	C01BD07	Turkey
Dronedarone	C01BD07	Serbia	Droperidol	N05AD08	Turkey
Droperidol	N05AD08	Serbia	Estrogen (oral)	G03C	Turkey
Flurbiprofen	M01AE09	Czech republic	Ethylmorphine	R05DA01	Turkey
Glipizide	A10BB07	Hungary	Ferrous sulfate/iron supplements (>325 mg)	B03AA	Turkey
Meprobamate	N05BC01	Hungary	Flupentixol	N05AF01	Czech Republic
Niacin (nicotinic acid)	C04AC01	Czech Republic	Guanfacine	C02AC02	Czech Republic
Piracetam	N06BX03	Serbia	Ketoprofen	M01AE03	Hungary
Prucalopride	A06AX05	Turkey	Ketorolac	M01AB15	Turkey
Racecadotril	A07XA04	Serbia	Labetalol	C07AG01	Czech Republic

Table 3. (Continued)

PIMs withdrawn from pharmaceutical markets			PIMs newly approved		
PIMs	ATC code	Country	PIM	ATC code	Country
Selegiline	N04BD01	Turkey	Methylropa	C02AB02	Turkey
Strontium ranelate	M05BX03	Serbia	Nifedipine (sustained release)	C08CA05	Turkey
Tolterodine	G04BD07	Hungary	Nitrofurantoin	J01XE01	Serbia, Turkey
Tolterodine (nonsustained release)	G04BD07	Hungary	Ofloxacin	J01MA01	Turkey
Tolterodine (sustained release)	G04BD07	Portugal	Oxaprozin (oral)	M01AE12	Turkey
Tranylcypromine	N06AF04	Spain	Oxazepam	N05BA04	Serbia
Vincamine	C04AX07	Portugal	Oxybutynine (nonsustained release)	G04BD04	Turkey
Zaleplon	N05CF03	Serbia	Oxybutynine (sustained release)	G04BD04	Czech Republic
Zaleplon (>5 mg)	N05CF03	Serbia	Prasugrel	B01AC22	Serbia
Zopiclone (>3.75 mg)	N05CF01	Serbia	Quinine and derivatives	M09AA	Turkey
Zuclopenthixol	N05AF05	Serbia	Tolterodine (sustained release)	G04BD07	Czech Republic
			Trihexyphenidyl	N04AA01	Turkey
			Zopiclone (>3.75 mg)	N05CF01	Portugal
			Zopiclone (>3.75 mg)	N05CF01	Turkey
ATC, Anatomic Therapeutic Chemical Classification System; PIM, potentially inappropriate medication.					

differences have been found in availability of specific regulatory measures related to PIM use or in educational strategies in this area. There were mostly unavailable specific guidelines, educational courses and regulatory measures related to PIMs as a specific group of risky medications in older patients in the majority of countries (the exceptional positive cases were only a few educational strategies, not regularly and systematically promoted or implemented at the national level in individual countries).

In quantitative analyses of approval rates of PIMs in individual countries (with regard to medication-related conditions of inappropriateness), three countries reached higher prevalence by EU(7)-PIM/AGS Beers 2015 criteria. These were ES (70.7%/64.3%), TR (66.8%/65.1%), and PT (66.4%/61.2%). In the other three countries, percentages of PIMs approved on pharmaceutical markets fluctuated at around 50% or less, namely in HU 54.4%/46.5%, CZ 49.1%/41.1%, and RS 42.4%/36.4%. There were substantial differences (>5%) in the proportion of PIMs approved on pharmaceutical markets in all countries according to the EU(7)-PIM list compared with AGS Beers 2015 criteria except in TR, where this difference did not exceed 1.7% (see Figure 1). Apart from conditions of PIM inappropriateness, results yielded nearly the same prevalence (difference was maximally 1.1% for all outputs, see Figure 1). Differences between approved PIMs for clinical use and currently marketed PIMs on the pharmaceutical market were not substantial in nearly all countries except TR. For this country, difference reached 19.8% for the EU(7)-PIM list and 21.7% for the AGS Beers 2015 criteria.

Similar findings have also been obtained for absolute numbers of PIMs approved for clinical use in different countries according to the ATC classification [using EU(7)-PIM criteria and AGS Beers 2015 criteria] when conditions of inappropriateness were considered or disregarded (see Figure 2). These absolute numbers for EU(7) criteria (regarding conditions of PIM inappropriateness) ranged from 120 in RS to 200 in ES, and for AGS Beers 2015 criteria, from 47 in RS to 83/84 in ES/TR. The absolute numbers of approved PIMs were substantially higher for PIMs stated on the EU(7)-PIM list in all countries when compared

with AGS Beers 2015 criteria regarding conditions of PIM inappropriateness (+86 in CZ, +94 in HU, +109 in PT, +73 PIMs in RS, +117 in ES, and +105 in TR). According to the ATC classification and EU(7)-PIM list, these absolute numbers of PIMs approved for clinical use were found highest for ATC classes N (central nervous system PIMs; in different countries they ranged $n = 41-75$) and then for ATC class C (cardiovascular PIMs, $n = 19-34$), A (alimentary tract PIMs, $n = 21-32$), M (musculoskeletal PIMs, $n = 14-23$) and R (respiratory tract PIMs, $n = 7-23$). Results not including conditions of PIM inappropriateness yielded nearly the same findings.

Considering the majority of European countries, the availability of marketed PIMs as OTC medications (including conditions of PIM inappropriateness) ranged always below the prevalence of 20% for both explicit criteria (from 9.8% in CZ to 17.9% in RS). The exception was TR, where availability of marketed PIMs as OTC medications reached 46.4–48.1%.

In qualitative longitudinal analyses, only 26/29 PIMs (not including/with regard to the conditions of PIM's inappropriateness) have been withdrawn from pharmaceutical markets and 30/32 PIMs newly approved for clinical use in pharmaceutical markets of analyzed countries between 2016–2018. In CZ ($n = 6$) and TR ($n = 21$), the highest absolute number of PIMs were approved for clinical use in this period, while in other countries, this number was lower (<4). The highest absolute number of PIMs were withdrawn from pharmaceutical markets in RS ($n = 10$), TR ($n = 8$), and HU ($n = 5$; in other countries these were only a few PIMs, <3; see Table 3).

Qualitative analyses discovered some PIMs that have been approved in only one of six analyzed EU countries and may be considered 'unnecessary' (see Table 4). The majority of these PIMs have been approved for clinical use in TR ($n = 14$), but some of these PIMs ($n = 8$) have not been marketed for a long time (see Table 4). More PIMs have been also specifically available on pharmaceutical markets in ES ($n = 12$), and PT ($n = 6$). In CZ and HU, there was only one PIM each (dihydroergotamine and zaleplon, respectively). For more information, refer to Table 4.

Table 4. PIMs approved for clinical use in only one of six analyzed countries.

PIM	ATC code	Country	Most common brand names on the pharmaceutical market	Any other active substance combination	Doses in 1 unit of drug forms	All drug forms available on the pharmaceutical market	Prescriptions limits (Yes = 1/No = 0) and specification
Acepromazine*	N05CX	Turkey	Plegicil	0	3 mg/ml	Liquid drops	0
Alimemazine (trimeprazine)	R06AD01	Spain	Variagil liquid drops	0	Variable dose	Liquid drops	0
Carbinoxamine*	R06AA08	Turkey	Arbitus, Rhinopront, Rhinotussal capsule, Zyriton syrup	Approved but not available			
Clonidine	C02AC01	Portugal	Catapresan	0	0.15 mg	Solid	0
Clotiazepam	N05BA21	Spain	Distensan	0	5 mg, 10 mg	Solid	0
Cyamemazine	N05AA06	Portugal	Tercian	0	100 mg, 40 mg/ml	Solid, oral solution	0
Desipramine	N06AA01	Turkey	Desipram tablet Nortimil tablet	0	25 mg	Solid	Ministry of healths special permission
Dexbrompheniramine*	R06AB06	Turkey	Disophrol	0	6 mg	Solid	0
Dicyclomine (dicycloverine)	A03AA07	Spain	Colchimax	Colchicine	5 mg/0.5 mg	Solid	0
Dihydroergocryptine	N04BC03	Portugal	Striatal	0	5 mg, 20 mg	Solid	0
Dihydroergotogoxine	C04AE01	Czech Republic	Secatoxin Forte	0	Variable dose	Liquid drops	0
Doxepin	N06AA12	Spain	Sinequan	0	25 mg	Solid	0
Estazolam	N05CD04	Portugal	Kaiever	0	2 mg	Solid	MSRM (Medicines subject to medical prescription) Special Narcotic
Eszopiclone	N05CF04	Turkey	Imovane tablet	0	7.5 mg	Solid	neurologist, psychiatrist
Ethylmorphine	R05DA01	Spain	Demusin	0	10 mg	Solid	0
Hydralazine	C02DB02	Spain	Hydrapres	0	20 mg, 25 mg, 50 mg	Solid, powder for injection	0

(Continued)

Table 4. (Continued)

PIM	ATC code	Country	Most common brand names on the pharmaceutical market	Any other active substance combination	Doses in 1 unit of drug forms	All drug forms available on the pharmaceutical market	Prescriptions limits (Yes = 1/No = 0) and specification
Loflazepate	N05BA18	Portugal	Victan	1	2 mg	Solid	0
Lormetazepam	N05CD04	Spain	Aldosomnil, Loramet, Lormetazepam Sandoz, Noctamid	0	1 mg, 2 mg, 0.2 mg/ml, 2.5 mg/ml	Solid, injection, oral drops	0
Meprobamate*	N05BC01	Turkey	Danitrin	0	200 mg	Solid	0
Methyltestosterone	G03BA02	Turkey	Afro	0	25 mg	Solid	0
Oxaprozín (oral)*	M01AE12	Turkey	Duraprox	0	600 mg	Solid	0
Perphenazine	N05AB03	Spain	Decentan	0	8 mg	Solid	0
Pindolol	C07AA03	Turkey	Visken tablet	0	5 mg	Solid,	0
Procaïnamide	C01BA02	Spain	Biocoryl	0	1000 mg	Injection	0
Propiericiazine (periciazine)	N05AC01	Spain	Nemactil	0	10 mg, 50 mg, 40 mg/ml	Solid, oral drops	0
Quazepam	N05CD10	Spain	Quiedorm	0	15 mg	Solid	0
Reserpine	C02AA02	Turkey	Regroton	0	0.25 mg	Solid	0
Terfenadine*	R06AX12	Turkey	Sanofen	0	60 mg	Solid	0
Thioridazine*	N05AC02	Turkey	Approved but not available				
Tolmetin (oral)*	M01AB0	Turkey	Tolectin	0	200 mg	Solid	0
Trifluoperazine	N05AB06	Turkey	Stilizan	0	2 mg	Solid	0
Vinburnine	C04AX17	Portugal	Cervoxan	0	40 mg	Solid	0
Vincamine	C04AX07	Spain	Anacervix	Piracetam	400 mg/20 mg	Solid	0
Zaleplon	N05CF03	Hungary	Andante	0	5 mg	Solid	0

*Approved for clinical use but has not been marketed for a long time.

Discussion

Our study is the first study analyzing in detail cross-country differences in approval rates of PIMs, their actual marketing and availability on prescription or as OTC medications. We also analyzed longitudinal changes in PIM approval rates between 2016 and 2018 (withdrawals from the pharmaceutical markets and new approvals) in six European countries, taking part in the scientific works of the EU COST Action IS1402 WG1b research group. These were ES and PT (long-term member states of the EU), CZ and HU (short-term EU member states), and TR and RS (EU-candidate countries). The aim of our research was to analyze qualitative and quantitative differences in the lists of PIMs approved for clinical use and marketed in these countries, to describe selected differences in regulatory aspects related to PIM approvals, marketing and availability that should be harmonized and better regulated in future decades.

We chose for our analyses two latest EU- and US-explicit criteria of PIMs, namely the EU(7)-PIM list (European tool representing the most comprehensive explicit list of PIMs developed for international European research)⁷ and the AGS 2015 Beers criteria (at the time of our analyses, the latest and the most comprehensive tool in the US from which only the Section 1 was applicable in our regulatory analyses).⁴ Results of our analyses confirmed that PIMs stated on the EU(7)-PIM list were approved for clinical use in participating EU countries more often than PIMs stated in AGS 2015 Beers criteria (approval rates ranged for EU(7)-PIM list from 42.4% in RS to 70.7% in ES and for AGS Beers 2015 Criteria from 36.4% in RS to 64.3% in ES, respectively, with regard to the conditions of PIM inappropriateness). Only in TR, differences between the two analyzed criteria were not substantial, which means lower than 5%. In agreement with our findings, several epidemiological studies in Europe confirmed that PIM prevalence with the EU(7)-PIM list was higher than after application of 2015 AGS Beers criteria. For example, the German study in community-dwelling older patients identified 37.4% PIM users after application of the EU(7)-PIM list and only 26.4% according to AGS Beers 2015 criteria, with longitudinal decrease in 6 years to 36.5% and 23.1%, respectively.⁵² In Lithuania, the study of Grina and colleagues analyzed medication claim data in older outpatients and confirmed that application of the EU(7)-PIM list documented the prevalence of 57.2%, while by the application of the AGS Beers

2015 criteria the prevalence was only 25.9%.⁵³ Also in TR (a European-Asian country), the prevalence of PIM use was found to be 30% after application of the AGS Beers 2015 criteria in community-dwelling older patients,⁵⁴ and 65% when the EU(7)-PIM list was applied in the outpatient setting.⁵⁵ Even if both the EU(7)-PIM list and AGS Beers 2015 criteria have been developed for international research purposes, the EU(7)-PIM list identifies higher PIM prevalence in European countries. However, results of PIM prevalence can be of course influenced by many other factors, for example, preferences in PIM use, regulatory measures, etc.

Moreover, the AGS Beers 2015 criteria include more PIMs defined by clinical conditions of inappropriateness;^{51,52} for instance, the comparison of the AGS Beers 2015 criteria and STOPP version 2 criteria in the clinical setting in one Spanish study yielded nearly the same and very high prevalence, almost 70%,⁵⁶ which confirms that these tools may also be highly applicable in clinical studies in EU countries. Also, our results were influenced by the fact (see Figure 2) that a significantly lower number of PIMs was stated in Section 1 of the AGS Beers 2015 criteria in comparison with the EU(7)-PIM list.

Considering the countries participating in our research, the highest approval rates of PIMs were demonstrated in ES (70.7% of PIMs regarding medication-related conditions of inappropriateness and 71.4% not including conditions of PIM inappropriateness). This is in agreement with the fact that ES was the only country involved in the development of the EU(7)-PIM list⁷ and we discovered during our analyses that many specific PIMs from the EU(7)-PIM list were approved only on the Spanish pharmaceutical market. Higher prevalence of approved PIMs was also documented in PT and TR (according to the EU(7)-PIM list, 67.1% and 67.5%, respectively, not including conditions of inappropriateness). While similar results in PT and ES can be explained by similarities between Spanish and Portuguese pharmaceutical markets, in TR, these findings are most likely more influenced by different drug-regulatory measures.⁵⁷

TR and RS are not EU member states, only EU-candidate countries; therefore, granting marketing authorization to medical products through the centralized authorization procedure

of the EMA or other EU authorization procedures (see Table 2 and the Introduction) are not applied. Even if licensing processes in both of the countries are now harmonized with EU legislation, national authorization procedures still dominate.⁵⁷ Table 2 shows that national authorization procedures in these countries contribute to lower availability of active substances, and in the case of RS, also to lower availability of PIMs. This is fairly different in TR, where the prevalence of approved PIMs was high, and also the total number of registered medicinal products was the highest (see Table 2), as well as the variability of different approved brand names, strengths, and drug forms of PIMs. According to the article of Oner and colleagues, the EMA, US Food and Drug Agency and Turkish Medicines and Medicinal Devices Agency apply different regulatory measures and different authorization procedures, and are autonomous in their decisions.⁵⁷ Many PIMs listed in Table 3 are approved only on the Turkish pharmaceutical market, not in other EU countries. However, some of these PIMs are not marketed anymore (e.g. acepromazine, belladonna alkaloids, buclizine, carbinoxamine, chlordiazepoxide, etc.) This could also mean that TR as an EU-candidate country (the opposite of RS) still does not fully apply the rule of EU legislation called the ‘sunset clause,’ a legal provision stating that the marketing authorization of a medicine will cease to be valid if the medicine is not placed on the market within 3 years of the authorization being granted or if the medicine is removed from the market for 3 consecutive years.^{25–27} In agreement with these findings, TR was the country in our sample with the highest discrepancies between approved and actually marketed PIMs (the difference was 19.8% for the EU(7)-PIM list and 21.7% for AGS Beers 2015 criteria), in other countries, these differences were not substantial. Also, the highest number of PIMs without prescription was available in TR [over 45% using EU(7) or AGS Beers 2015 criteria, compared with less than 18% in other EU countries]. On the other hand, in RS, EU rules were followed more closely and according to local experts from the Medicines and Medicinal Devices Agency of RS, lower numbers of registered medicinal products in this country also highly contributed to the generally lower number of approved PIMs.

In Central and Eastern EU countries (CZ, HU and RS), specificity of the EU(7)-PIM list to local pharmaceutical market and approved PIMs was much

lower than in ES, PT and TR [according to the EU(7)-PIM list, 50.2% PIMs were approved for clinical use in CZ, 55.5% in HU and 42.8% in RS, not including conditions of inappropriateness of PIMs]. In a recently published study in Lithuania, 127 out of 282 from EU(7)-PIMs (45%) and 58 out of 136 of PIMs reported from the 2015 AGS Beers criteria (43%) were available on the Lithuanian pharmaceutical market.⁵³ In a Croatian study, 125 out of 335 EU(7)-PIMs (37.3%)⁵⁸ and in a Belgium study, 178 out of 335 (53.1%) were approved.²⁸ These studies are in agreement with our findings. Our results might show that more comprehensive criteria for EU research are needed. However, it is important to emphasize that the EU(7)-PIM list currently contains many frequently prescribed medications (e.g. zolpidem > 5 mg, zopiclone > 3.75 mg, omeprazole in long-term use, etc.), and for this reason, sensitivity of these criteria is still very high in the majority of EU countries and these criteria enable detection of high prevalence of PIM prescribing also in Central and Eastern Europe. For example, the prevalence obtained with EU(7) criteria was 57.2% in Lithuanian community-residing older patients,⁵³ and 66.7% in a Croatian study assessing prescribing of PIMs in older adults discharged from acute care.⁵⁸

Particularly in Central and Eastern Europe, where many countries except Estonia did not participate in development of the EU(7)-PIM list, ‘other new’ PIMs may be available, not yet defined by the EU(7) and AGS Beers 2015 criteria. These are, for example, tofisopam (N05BA23), cinolazepam (N05CD13), mirabegron (G04BD12), propiverin hydrochloride (G04BD06), etc.⁴⁶ Such PIMs should be first identified through efforts of national expert panels in different countries, and later summarized again in an international European tool. Moreover, our longitudinal analyses confirmed that PIMs are still newly approved on pharmaceutical markets of EU countries and mostly by national authorization procedures. The majority of PIMs evaluated in our research have been authorized by national authorization procedures (95%), while only 5% were approved by the central authorization procedure of the EMA.

According to our findings, some PIMs have been approved in only one out of the six analyzed EU countries. The majority of these specific PIMs have been identified, particularly in PT, ES and TR. These qualitative discrepancies in approval rates of PIMs should be thoroughly studied by

national drug-regulatory institutes, as well as the necessity to distribute such PIMs on pharmaceutical markets for ‘specific situations.’ Seniors will always represent the main users of medicines and the population mostly exposed to unnecessary prescribing of PIMs. While these medications are not needed in the majority of EU countries, what are their specific indications in other countries? In a complimentary article to the 2015 AGS Beers criteria published by Steinman and coauthors,⁵⁹ it was emphasized that ‘...strict regulations, including regulation of drug authorization and reimbursement approaches, can be put in place only for a small number of medications that are “particularly harmful or have few reasonable indications” and most of the PIMs on the list are not absolutely but potentially inappropriate (as they could be appropriate for some patients or certain clinical circumstances) and strict regulations could limit patients’ access to beneficial therapy.’ We can only partially agree with this statement. Our analyses confirmed that some PIMs are no more needed in many EU countries and are still approved and used on some country-specific pharmaceutical markets (see Table 4). Such ‘necessity’ for having these PIMs available on pharmaceutical markets in only some EU countries should be thoroughly evaluated. Based on our EU COST Action IS1402 WG1b discussions, there are no specific measures established to regulate PIM use in all participating countries and in conditions with no regulations; historical approvals of PIMs for clinical use and country-specific prescribing habits prevail. Moreover, SPCs of all known PIMs should be re-evaluated and centrally harmonized by the EMA to include highly relevant recommendations and warnings which will emphasize conditions of appropriate/inappropriate use of these medications in older adults and include for example the statement, ‘This medication is considered a PIM by expert panels in the older population’ and the reasons.

Recently, Ivanova and colleagues⁶⁰ developed a new European repository of explicit criteria of PIMs, particularly for electronic assessment of potentially inappropriate prescribing, by combining the EU(7)-PIM list, the 2015 AGS Beers criteria, also including the STOPP/START criteria version 2 (in total, 650 PIMs;⁶⁰ STOPP/START criteria were included with regard to clinical conditions of their potential inappropriateness). Such a repository can be highly beneficial for utilization in drug consumption studies and analyses of

medication claims data and for e-health studies. However, because we confirmed that applicability of the EU(7) and AGS Beers 2015 criteria are still low on the pharmaceutical markets of many EU countries, more effort in this area is necessary, using a combination of national and international approaches for the development of explicit criteria. For clinicians in individual countries and for the creation of computer-driven prescribing systems to assist appropriate drug prescribing, country-specific and the most comprehensive up-to-date explicit national criteria of PIMs are necessary (not to burden practitioners with extensive lists of all existing PIMs, from which the majority is not approved or used in a particular country). However, for European regulatory measures of the EMA and for international research and surveillance, the most comprehensive summary of all PIMs identified until now is needed to better regulate and screen appropriateness of PIM use and PIM approvals in different EU countries.

There is a lack of studies on PIMs, particularly in Central and Eastern Europe because only a few studies and one explicit PIM criterion have been published in this European region.^{24,53,59,61–63} This problem raised interest of the European project EUROAGEISM FIP7 H2020 (2017–2021),³⁰ focusing on investigating PIM use in Central and Eastern European countries (seven countries: Estonia, CZ, Lithuania, Slovak Republic, RS, Croatia, TR) in comparison with three western European countries (ES, Belgium and Ireland) and two Asian countries (India and United Arab Emirates). The main aim of this project is to describe differences in PIM use, PIM prescribing habits and regulatory measures, to determine strategies to improve rational geriatric prescribing in Central and Eastern Europe, and to identify new PIMs that are not yet available on the EU(7)-PIM list. This project should help to reduce higher rates of PIM use in the Central and Eastern European region.

Study limitations

The main limitation of our study is that it has been conducted in only six European countries and results cannot be simply extrapolated to other EU countries (considering all qualitative and quantitative differences). Thus, before application of our results and the EU(7)-PIM list to other conditions, all discrepancies should always be thoroughly described. The number of PIMs

evaluated in this study by the EU(7)-PIM criteria was twice higher than stated in the AGS 2015 Beers criteria (Section 1), and this fact also substantially contributed to differences in approval rates of PIMs using both methodologies. Because the aim of our study was not to describe in detail all different regulatory measures in participating countries, this issue must be thoroughly studied in other research projects. Also, we have to emphasize that, even if no dramatic changes in approval rates of PIMs have been found in the majority of countries between 2016 and 2018, all data presented have a time-dependent effect. New drugs are continuously approved on, and withdrawn from, different pharmaceutical markets, and our report might become out of date soon, particularly when it stimulates future positive changes in regulatory measures regarding PIMs' availability in participating countries.

We would like to highlight that regulatory measures related to PIMs (even if they are very powerful) are only one of the strategies in the whole puzzle of interventions that may be useful in improving rational drug prescribing in older patients. More-over, some PIMs can be still used appropriately for some specific indications, also in geriatric patients. But, regulations of 'always unnecessary and risky PIMs' were found very beneficial [with regard to regulation of active-substance availability, approved drug doses in drug forms (e.g. in one tablet), or limitation of prescription of PIMs by prescribers not having relevant postgraduate specialty, etc.]. With respect to the fact that some PIMs do not have already a place in prescribed drug regimens in older patients, stronger regulations must be approved for those PIMs, where only 'historical prescribing habits' play a role in their continuous prescribing. In such cases, regulatory measures may present a powerful strategy for how to stop inappropriate use of these PIMs in older patients.

Conclusion

The EU(7)-PIM list has been created for international European research; however, applicability of these criteria in many EU countries is still limited because different PIMs are available on different European pharmaceutical markets, and additional PIMs not listed by these criteria have not been yet identified in many EU countries. High specificity of these criteria was determined for the pharmaceutical market of a country that contributed to the

development of the EU(7)-PIM list (ES), low specificity in Eastern and Central EU countries, where more research effort is needed in this area.

Moreover, the lack of evidence on PIM prescribing in older patients in different settings of health-care, particularly in Central and Eastern Europe, contributes to probably still higher rates of inappropriate prescribing of PIMs in many countries, regions and healthcare facilities. As the area of PIMs is one of very important areas for deprescribing strategies in older patients using poly-pharmacy, regulatory measures and specific aspects of PIM use should gain more interest (of prescribers, educators, and drug-regulatory institutions). The European project EUROAGEISM H2020, FIP7 program (2017-2021), focusing on problems related to PIM use in Central and Eastern Europe with a special focus on aspects of PIM prescribing and relevant regulatory measures, could help to obtain new evidence stimulating the significant change in PIM availability and use in this European region.

Acknowledgements

We are thankful to the co-operation of members of the WG1b group 'Healthy clinical strategies for healthy aging' of the EU COST Action IS 1402 (2015-2018) 'Ageism: a multinational, interdisciplinary perspective' and to the research group 'Aging and Changes in the Therapeutic Value of Medications in the AgeD' (Chair: Associate Professor D Fialová, PharmD, PhD) under the scientific program PROGRESS Q42 of the Faculty of Pharmacy, Charles University, Czech Republic. We also thank local researchers from all academic teams involved in work on data collection and data corrections between autumn 2016 and autumn 2018 and contributing to article revisions in spring 2019. As researchers from individual teams were supported also by local grants, we acknowledge their local grant agencies and support: V Valdíglesias was supported by a Xunta de Galicia postdoctoral fellowship (reference ED481B 2016/190-0).

Funding

This project received funding from the EU COST Action IS1402 initiative 'Ageism: a multi-national, interdisciplinary perspective' (2015-2018), and from the European Union's Horizon 2020 research and innovation program EUROAGEISM H2020 under the Marie Skłodowska-Curie grant agreement no. 764632 (2017-2021). It was also

supported by the project INOMED (reg. no. CZ.02.1.01/0.0/0.0/18_069/0010046): the pre-application research into innovative medicines and medical technologies, cofunded by the EU, by SVV 260 417 and the scientific program PROGRESS Q42 at the Department of Social and Clinical Pharmacy, Faculty of Pharmacy in Hradec Králové, Charles University, Czech Republic.

Conflict of interest statement

All coauthors [except Dr Reissigová, PhD (the project statistician) and Dr Kostřiba, PhD] have been supported in participation at face-to-face scientific meetings by the EU COST Action IS1402 initiative ‘Ageism: interprofessional, multidisciplinary perspectives’ from October 2015 to October 2018. Associate Professor D Fialová, PharmD, PhD, Jovana Brkić, MS, Silvia Grešáková, MS, Professor Soner Dogan, Associate Professor Valentina Marinković and Professor Ljiljana Tasić have been supported to participate at the meeting of the EUROAGEISM H2020 project in Bratislava, June 2018 [EUROAGEISM, no. 764632, H2020-MSCA-ITN (2017–2021)]. Associate Professor D Fialová, PharmD, PhD (Chair of the FIP7 program of the EUROAGEISM H2020 project), and Jovana Brkić, MS (ESR7 in the EUROAGEISM H2020 project) were supported by the EUROAGEISM H2020 project no. 764632 (Horizon 2020-MSCA-ITN 2017–2021, 764632) and Associate Professor D Fialová, PharmD, PhD, also by INOMED project reg. no. CZ.02.1.01/0.0/0.0/18_069/0010046).

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