

Medication use among older people in Europe: Implications for regulatory assessment and co-prescription of new medicines

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Aims: The aim of this study was to elucidate drug prescription patterns in older European people with the objective to support regulatory contextualisation of (1) the suitability of enrolment criteria for new clinical trials; and (2) the understanding of the potential interactions/incompatibilities of newly authorised medicines with those most frequently used by older people.

Methods: Medicines agencies in Portugal, Poland, Slovakia and England were approached to provide a list of the 10 most frequent prescriptions in 2016 for systemically used medicines per active substances (i.e. ATC level 5), in older people. For each active substance and for the most common therapeutic subgroups (i.e. ATC level 2), the percentages of older patients receiving at least one prescription were calculated per older age categories (65–74; 75–84; 85+) and gender.

Results: There was considerable alignment in the most commonly prescribed active substances and therapeutic subgroups represented; these were gastroprotectants (A02), lipid-modifying agents (C10) and analgesics (N02). Some gender differences were observed (A02 and N02 were prescribed more frequently to women), but trends on age categories were consistent; A02 and N02 prescriptions continued to rise with age, while C10 slightly decreased in the 85+ age group in all countries.

Conclusions: The findings of this study are consistent with the major chronic diseases reported in the older European population. Evidence on co-medication of newly applied medicines with the currently identified most commonly used medicines in older people should be generated during the (non)clinical development of new medicines to support regulatory assessment and adequate user information.

KEYWORDS

clinical trials, drug regulation, elderly, geriatrics, prescribing

1 | INTRODUCTION

Older people (≥ 65 years) represent a significant and increasing proportion of the European population and it is expected that they will make up 30% of all Europeans by 2050.¹ Due to the increased co-

occurrence of multiple chronic and acute diseases, older people are the main users of healthcare resources,^{2,3} and it has been estimated that over 10% of the older population receives 10 or more concomitant medicines.^{4,5} However, middle-old (75–84 years) and older-old (≥ 85 years) patients are generally underrepresented in clinical trials

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intended to support the marketing authorisation of new medicines, in spite of existing and upcoming regulatory guidances.^{6–8} The combination of these factors increases the difficulty in reaching firm conclusions on the potential for drug–co-administered drug and drug–coexisting disease interactions in the older and/or multimorbid population. In addition, it also increases difficulty on any medication error problems that could occur, e.g. upon storing products outside their packaging in multi-compliance aid or multi-drug dispensing systems, swapping products upon intake with a similar appearance or the need for a relevant number of additional dosing moments because products may not be taken at the same time.

The European Medicines Agency (EMA) requires that sufficient scientific and clinical evidence supporting the safety, efficacy and quality of a new drug product is established by the sponsor (pharmaceutical company) prior to marketing authorisation. The results of a positive assessment by the EMA supports safe, appropriate and rational prescribing, with relevant information on the benefit–risk profile of the product provided to physicians, patients and health technology assessment bodies in the published European Public Assessment Report (EPAR) and in the authorised product information (i.e. the Summary of Product Characteristics [SmPC] and in the package leaflet [PL]).

Due to the increasing age, multimorbidity and polypharmacy of the typical European patient population, it is generally acknowledged that the regulatory assessment also has to consider that adequate clinical evidence is provided by the sponsor on the potential for drug–co-administered drug as well as drug–coexisting disease interactions.⁶ Studies have been performed in the past to collect prescription data for the older population from individual European countries,^{9–12} but, to the best of our knowledge, a cross-European Union (EU) country parallel analysis of this nature and magnitude has not been conducted, as no data could be found in the indexed literature. In order to do so, the objective of this study was to identify and quantify the most likely prescribed and co-prescribed medicines in the older European patient population. This work was undertaken to support regulatory contextualisation of the suitability of enrolment criteria for new clinical trials. The identification of which medicines have a high probability of being taken by an older patient was also deemed valuable to support prescribers in their dialogue with the patient during medication review, or when considering the addition of a new prescription.

2 | METHODS

2.1 | Data sources and data collection

National Competent Authorities (NCAs) of four EU Member States (Medicines and Healthcare products Regulatory Agency, MHRA, England; Urząd Rejestracji Produktów Leczniczych, URPL, Poland; Autoridade Nacional do Medicamento e Produtos de Saúde, Infarmed, Portugal; and Štátny ústav pre kontrolu liečiv, ŠÚKL, Slovakia) were contacted to provide national prescription data for the

What is already known about this subject

- Older people are the main users of many medications.
- The middle- to older-old (≥75 years) are particularly underrepresented in clinical trials.
- It is currently difficult to reach firm conclusions on the potential for drug–co-administered drug and drug–coexisting disease interactions/incompatibilities in the older multimorbid population.

What this study adds

- Data on frequency of prescriptions in older age groups by ATC and gender in four representative European Union countries is examined.
- The data elucidate the prevalence of likely co-medications in the older patient population, to inform healthcare professionals when (co-)prescribing to older patients, and suggest similarities in the identified top 10 medicines across Europe.
- Data support the evaluation of the external validity of a trial population in regulatory submissions when assessing the potential risk for drug–co-administered drug and drug–coexisting disease interactions between newly developed medicines and the medicines likely to be co-prescribed to older patients.

year 2016 on medicines used for systemic administration (non-topical, excluding flu vaccines) by older people, i.e. ≥65-year-old citizens. Countries were selected on the basis of their geographic spread and size to reflect different geographic regions (northern, eastern, southern and central Europe), and considering data accessibility from different database systems in place in countries that note dispensation of medicines after prescription.

NCAs were asked to provide a list of the 10 most frequent prescriptions for systematic administration as defined by the World Health Organization's Anatomical Therapeutic Code (ATC) level 5, i.e. by active substance¹³ and to provide information on the volume of prescriptions (i.e. number of patients collecting at least one prescription) by gender and by age subsets of the older population (65–74 years, younger-old; 75–84 years, middle-old; and ≥85 years, very-old age).

Data estimates of the number of people per older age group (65–74; 75–84, 85+ years) and gender for 2016 were retrieved from the websites of the national statistical offices for each country: Office for National Statistics (England),¹⁴ which presented data as 2016 mid-year estimates; Statistics Poland (Poland),¹⁵ Pordata (Portugal),¹⁶ and the Statistical Office of the Slovak Republic (Slovakia),¹⁷ which all presented data as of 31 December 2016.

2.2 | Data analysis

The data obtained from each country were qualitatively described and summarised.

In order to contextualise the data, for each of the 10 most commonly prescribed medicines by ATC level 5 (i.e. active substance), the percentage of male and female patients per older age group (65–74; 75–84; 85+) receiving at least one prescription was calculated for each country. This was done by dividing the total number of older male and female patients in each age group receiving at least one prescription, by the total number of older males and females of the same age group in each country.

The therapeutic areas that were most common across the four countries were identified at ATC second level (i.e. by the therapeutic subgroup). They were selected on the basis that all four countries had at least one medicine within that subgroup in their top 10 ranking. To further analyse the data, the percentage of patients in each country and age group that were prescribed at least one medicine in each therapeutic subgroup (i.e. ATC level 2) was calculated, as well as the percentage of male and female patients aged ≥ 65 years in each country receiving at least one medicine in each therapeutic subgroup.

2.3 | Statistics

Descriptive analysis was employed using Microsoft Excel 2016 and, as the objective of the study was to describe prescription patterns for the most frequently prescribed medicines and not to use the data as a sample of a larger population, hypothesis testing was not performed.

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.¹⁸

3 | RESULTS

A list of the 10 most frequently prescribed medicines by ATC level 5 (i.e. active substance) in 2016 from England, Poland, Portugal and Slovakia was received. The data included prescribed and reimbursed

medicines that were dispensed in both the outpatient and inpatient settings in England and Slovakia, and in the outpatient setting only in Poland and Portugal. Population data on people aged ≥ 65 for 2016 were obtained for each of the four countries and categorised by age group and gender (Table 1).

The ATC therapeutic area that was most represented was cardiovascular (ATC C) (Table 2), with the percentage of people aged ≥ 65 years having filled at least one prescription for a cardiovascular medicine varying from 36.9% in Portugal to 64.6% in Poland. Common medicines in other chemical subgroups (i.e. ATC level 4) included **omeprazole** and **pantoprazole** (gastrointestinal; ATC A02BC), both featuring in the top 10 list of three of the four countries; **paracetamol** and **acetylsalicylic acid** (pain and/or cardiovascular usage; ATCs N02BE and B01AC, respectively); **metformin** (diabetes; ATC A10BA); and **amoxicillin** (antibacterial; ATC J01CA and J01CR), with the latter four medicines all featuring in the top 10 list of two of the four countries.

The three most represented therapeutic subgroups at ATC level 2, i.e. where each country had at least one medicine within this therapeutic subgroup prescribed in its top-10 ranking, were ATC A02 (gastroprotectants; including **lansoprazole**, omeprazole and pantoprazole), ATC C10 (lipid-modifying agents; including **atorvastatin**, **rosuvastatin** and **simvastatin**) and ATC N02 (analgesics; including **tramadol**, **metamizole** and paracetamol). Prescription frequencies of top 10 medicines within these therapeutic subgroups varied between countries, but trends with respect to age were consistent (Table 2, Figure 1). For ATC groups A02 (gastroprotectants) and N02 (analgesics), the percentage of patients receiving prescriptions continued to rise with age, whereas for ATC group C10 (lipid-modifying agents), the figures increased between the ages of 65–74 to 75–84, and then slightly decreased in the 85+ age group in all four countries. Additionally, many individual medicines per ATC level 5 in the ranking displayed changing prescription trends with age, which were also consistent across countries: with increasing age, relatively more patients were prescribed acetylsalicylic acid, paracetamol, **furosemide** and amoxicillin, while relatively fewer patients were prescribed metformin. Finally, more patients in the 75–84 age group were prescribed **amlodipine** compared to patients in the two other age groups.

In terms of gender differences in prescriptions in patients aged ≥ 65 , gastroprotectants (ATC A02) and analgesics (ATC N02) were prescribed to a higher proportion of females relative to males in all four countries, with the difference particularly marked for the analgesics (Table 2, Figure 2).

TABLE 1 2016 population data on people aged ≥ 65 in four EU countries

Country	65–74 years		75–84 years		85+ years	
	Female	Male	Female	Male	Female	Male
England	2,805,321	2,608,023	1,729,354	1,412,051	856,696	471,396
Poland	2,019,654	1,552,997	1,275,519	712,716	537,908	204,611
Portugal	607,762	496,951	461,221	313,302	190,381	89,119
Slovakia	282,757	211,612	159,008	84,835	55,143	21,304
Total	5,715,494	4,869,583	3,625,102	2,522,904	1,640,128	786,430

TABLE 2 The ten most prescribed medicines in patients ≥65 years by age group and gender in four EU countries in 2016 (in per cent per country)

ATC5	Active substance(s)	England						Poland					
		65–74		75–84		85+		65–74		75–84		85+	
		F	M	F	M	F	M	F	M	F	M	F	M
A02BC01	Omeprazole	21.9	19.5	25.1	23.3	25.2	25.8	25.2	21.2	29.2	33.1	31.5	
A02BC02	Pantoprazole	14.3	14.3	18.1	18.7	19.9	21.2	27.0	27.6	29.0	16.1	15.1	
A02BC03	Lansoprazole	18.0	6.3	30.0	12.1	41.0	20.9	27.2	20.3	31.9	25.2	17.2	
A10BA02	Metformin	11.8	22.0	21.7	32.5	27.4	35.7	27.2	20.3	22.1	25.2	17.2	
A11CC05	Colecalciferol	15.7	21.2	21.4	23.7	21.7	21.3	22.0	21.3	31.3	29.7	22.3	
B01AC06	Acetylsalicylic acid	11.9	19.3	16.7	23.0	17.2	22.7	28.1	31.6	38.3	40.6	38.7	
C03BA11	Indapamide	17.3	24.4	25.4	32.3	24.1	31.5	15.7	13.5	23.1	20.0	20.9	
C03CA01	Furosemide	20.0	27.6	24.6	28.8	17.1	21.4	32.5	32.7	39.7	28.2	32.2	
C07AB02	Metoprolol							19.0	15.3	15.6	7.0	6.8	
C07AB07	Bisoprolol							24.1	4.5	20.2	5.7	5.2	
C08CA01	Amlodipine	15.4	13.8	17.8	18.0	21.1	22.3						
C09AA05	Ramipril												
C10AA01	Simvastatin												
C10AA05	Atorvastatin												
C10AA07	Rosuvastatin												
H03AA01	Levothyroxine sodium												
J01CR02	Amoxicillin and beta-lactamase inhibitor												
J01CA04	Amoxicillin	15.4	13.8	17.8	18.0	21.1	22.3						
M01AB05	Diclofenac												
M01AE01	Ibuprofen												
N02AX02	Tramadol, combinations							13.0	9.0	21.7	13.5	21.8	
N02BB02	Metamizole, sodium salt												
N02BE01	Paracetamol	16.9	12.8	32.4	24.4	51.0	38.5						
N05BA12	Alprazolam												

F, female; M, male.

TABLE 2 Continued

ATC5	Portugal						Slovakia					
	65-74		75-84		85+		65-74		75-84		85+	
	F	M	F	M	F	M	F	M	F	M	F	M
A02BC01	26.9	18.9	32.5	23.5	41.1	31.7	13.8	10.9	16.6	13.3	17.8	14.5
A02BC02	19.4	16.7	25.4	22.6	32.4	31.1	11.8	11.4	16.3	15.7	17.4	16.9
A02BC03												
A10BA02	17.5	21.3	18.2	20.2	14.5	15.0						
A11CC05												
B01AC06							28.3	29.4	39.5	38.0	43.5	40.6
C03BA11												
C03CA01	9.9	9.7	24.0	22.7	48.4	46.9	8.6	10.1	22.7	22.1	36.4	36.1
C07AB02							12.4	10.9	18.3	15.8	19.6	16.0
C07AB07							19.6	16.7	24.2	19.9	23.2	18.3
C08CA01							15.7	15.9	20.5	18.9	20.1	16.0
C09AA05												
C10AA01	35.4	30.1	41.4	35.0	40.9	33.9						
C10AA05	24.2	25.2	24.8	24.2	20.1	19.2	29.0	27.8	31.8	31.4	21.2	22.8
C10AA07												
H03AA01												
J01CR02	19.3	18.8	21.5	23.1	34.8	36.9						
J01CA04												
M01AB05							20.8	15.4	21.2	15.8	16.6	13.2
M01AE01	18.4	15.0	13.4	12.1	11.2	10.9						
N02AX02												
N02BB02							21.9	15.3	30.8	21.1	33.9	24.2
N02BE01	28.7	21.1	36.5	28.6	47.2	41.0						
N05BA12	17.3	9.3	18.8	10.7	21.7	13.5						

F, female; M, male.

FIGURE 1 Prescription frequencies to patients aged ≥ 65 years of top-10 medicines in three therapeutic areas and by age group across four EU countries

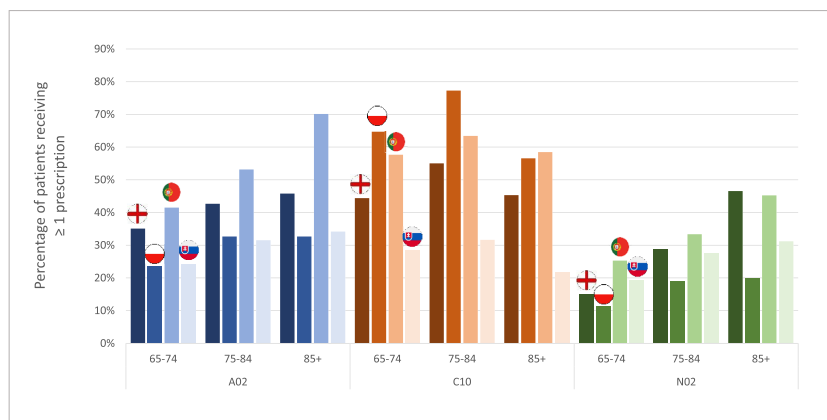
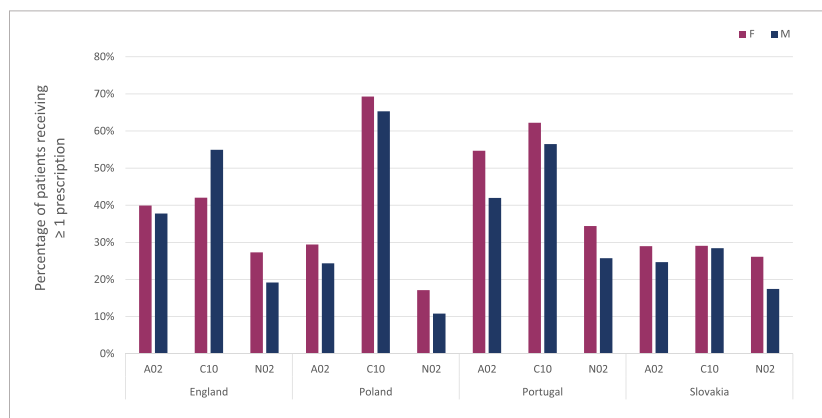


FIGURE 2 Prescription frequencies of top-10 medicines in male and female patients aged ≥ 65 years by therapeutic area and EU country



4 | DISCUSSION

4.1 | Prescription patterns in older Europeans

This study provides an overview of the 10 most prescribed medicines by ATC level 5, i.e. at the active substance level, to older people in four EU countries. Only medicines for systemic use were considered, as this study focused on medicines with an increased risk for drug-co-administered drug and drug-coexisting disease upon multi-medication or polypharmacy. The data indicate broadly similar drug prescription patterns across the four different EU countries with regards to the main therapeutic areas represented and gender.

The results confirm previous data from individual EU countries. For example, out of the most commonly dispensed medicines by active substance in this study, seven (acetylsalicylic acid, simvastatin, paracetamol, amlodipine, metformin and omeprazole) were also found in the ranking from a Spanish study conducted between April 2011 and March 2012 focusing on older patients aged 75 and older.¹⁰ There is also agreement with Italian and Swedish studies listing the most commonly prescribed medicines by ATC level 4 (Italy) and ATC level 3 (Sweden) in the ≥ 65 population in 2013 and 2008, respectively.^{9,12} These findings provide evidence on the similarity of

prescription patterns across European countries, suggesting that these classes of medicines should indeed be assumed as highly likely co-medications during regulatory assessment performed at the European level, as well as being considered as potential co-medications when newly prescribing medicines to older patients.

The therapeutic classes featuring in the top-10 rankings of the four countries are relatively consistent, reflecting the major chronic diseases reported in the older population in Europe, while individual prescribed chemical substances display some variability. This may be in part explained by differences in national therapeutic guidelines, as well as in reimbursement status due to health technology assessment (HTA) bodies' reimbursement decisions, dispensing status (prescription-only vs over-the-counter; OTC) and differences in pack size. The type, dosage form and frequency of the prescription influence the accessibility to patients and the traceability, and therefore may impact the national rankings.¹⁸

The list of the most frequently prescribed medicines at ATC level 5 includes some that are considered as potentially inappropriate for older patients due to increasing risk of adverse events in this population, namely gastroprotectors (omeprazole, pantoprazole) and non-steroidal anti-inflammatories (acetylsalicylic acid, paracetamol).^{19,20} This highlights the importance to evaluate the potential interactions with these medicines when designing a clinical trial and non-clinical

studies, and during regulatory assessment of the benefit–risk profile so that adequate information for clinical practice will become available to prescribers through the authorised product information (SmPC, PL). This includes evaluating the specific potential for both pharmacokinetic and pharmacodynamic interactions, including, e.g., the effect on absorption due to gastric pH changes from proton pump inhibitors.

Another notable finding is that a significant proportion of patients aged ≥ 85 years are prescribed statins, which varies from approximately 20% of patients in Slovakia to just short of 60% in Poland and Portugal. Clinical evidence in this group has been questioned,²¹ and these data reflect the importance to contextualise the reality of daily clinical practice in which a new medicine will be used.

The differences in prescription between genders observed in this analysis were largely in line with expectations and generally consistent between countries. The significantly higher use of analgesics in females compared to males in all countries may be explained by women being at increased risk of many chronic pain conditions compared to males, with women having also been reported to exhibit higher sensitivity to pain.^{22–24} Statins were prescribed to a higher proportion of men than women in England, a trend that differed from the other three countries but that has been observed elsewhere.^{25–29} Still, a significant proportion of women aged ≥ 65 in all the four EU countries analysed were also prescribed statins and, as women have been underrepresented in clinical trials,^{30–32} the data generated in this study confirm the need to generate clinical evidence in a relevant patient population.

4.2 | Implications for medicines authorisation and prescription

Overall, the data presented here are useful across the medicines' life-cycle in two ways. Firstly, they provide important information on the prevalence and type of medicines used by the older and multimorbid population, as these have a high probability to be co-administered with any newly authorised medicine in this patient population. Thus, pharmaceutical companies need to consider at an early stage, also through regulatory advice on development plans, the need to generate broad (non)clinical evidence on potential drug–co-administered drug or drug–coexisting disease interactions. These data will comprehensively support the regulatory authorisation process and clarify potential implications for the benefit–risk profile of the product within real-life usage.

Secondly, the data are important for transparent and effective communication of the regulatory assessments' conclusions to healthcare professionals, patients, caregivers and other stakeholder parties in clinical practice. Reflecting the available (non)clinical data in the authorised product information (SmPC and PL) and the additional product information in the European Public Assessment Report (EPAR) is essential to support physicians in evidence-based prescribing in older and multimorbid patients, and hence to the development of evidence-based clinical practice therapeutic guidance.

4.3 | Strengths and limitations of the study

Prescription data categorised by age and gender are not easily obtainable from public databases and are often presented at different levels of granularity according to the data source. This study presents data that was directly received from the relevant NCAs of four EU countries, which provide a structured and comprehensive data set on prescription patterns therewith supplementing the single-country analyses in the literature, and confirming similarities within various national prescribing settings. Another strength of our study is that the ranking obtained does not represent volumes/packages, but rather number of older persons obtaining at least one prescription, which gives a clearer picture on the actual real-life systematic use “exposure” to active substances.

This study has some limitations. Firstly, while the top-10 medicine ranking in this study is based on the number of patients collecting at least one prescription, it does not provide a full picture of the total (at least once) use of some of the top-10 active substances, i.e. does not capture total at least once “exposure”. This is because some of the same active substances are also often contained within the medicines which are fixed dose combinations of two or more active substances, and have not reached top-10 entry as could be expected considering disease epidemiology in older age (e.g. antidiabetics other than metformin). Consequently, active substances emerging on our top-10 ranking that exist and are marketed in the form of fixed dose combination medicines (often used for typical older age chronic conditions), could also be underrated and ranked even higher (e.g. statins, metformin, amlodipine, indapamide, ramipril, etc.) or reach the top-10 entry. In addition, although OTC products are normally not for chronic use/diseases, some of the top-10 active substances are available as OTC medicines for acute use and thus not captured in the prescription scheme (e.g. acetylsalicylic acid, ibuprofen, paracetamol, colexicalferol, certain gastroprotectives); however, OTC status specifics can vary between the countries.

Another limitation of this study relates to the data background, which showed some diversity towards the type of dispensing setting (inpatient and/or outpatient). Considering that the number of hospitalised patients is small in comparison to the overall number of older patients, and considering that it is rather likely that top-10 medications will be for chronic diseases that need both treatment in the inpatient and outpatient setting, we consider that the difference in the data unit between inpatient and outpatient setting can be accepted.

It should also be acknowledged that differences between countries may be due to aspects such as different screening and/or treatment protocols for chronic diseases, or differences in the prevalence of diseases due to differences in lifestyles and dietary patterns among countries. However, we consider that rather than focusing on the differences among prescription rates, it is important to focus on the similarities. These indicate that a high proportion of older people across Europe are taking similar medicines for chronic conditions, i.e. on a long-term basis.

Finally, while the data included in this study are from 2016, the good alignment of our findings with those from individual EU countries from previous years (dating back to 2008) supports the

assumption that the study conclusion is sufficiently up to date and shows data time consistency. The similar patterns observed between the countries included in our study and those in previous single-country analyses also seem to indicate that, while the results from the present cross-European study may have been strengthened by data from additional EU countries (the retrieval of which is a non-trivial task, when done at the age group and gender granularity), our results do reflect broad European trends. The data presented here are therefore worthy of regulatory and prescribers' attention and the reflections derived from the data are still topical.

5 | CONCLUSIONS

The findings of this study corroborate anecdotal evidence and single EU country studies previously performed, by shedding light on prescription patterns in the population over 65 years in EU countries. The study highlighted that the 10 most prescribed medicines are prescribed with a probability of 5–50% to older patients in four European countries.

The high degree of prescription probability of the top 10 medicines to the older patient population including medicines that are considered as potentially inappropriate for older patients is an important finding. These findings are relevant for the design of clinical studies as well as non-clinical supportive data in order to provide suitable overall evidence for clinical safety and efficacy in the patient populations that will eventually use a newly authorised medicine. Accordingly, the data support the regulatory assessment and guidance process to establish the best benefit–risk profile as well as to provide the necessary information on a new medicine to healthcare professionals, caregivers and patients through adequate information within the authorised information for each specific product (EPAR, SmPC and PL).

The data obtained in this study consolidate some of the previous findings in national studies, demonstrating a high degree of alignment in prescription patterns in therapeutic classes between the four representative EU Member States included in this evaluation. This suggests that the potential risk for drug–co-administered drug and drug–coexisting disease interactions of the identified top 10 medicines with any new medicine is similar across Europe. This emphasises the importance of considering the likelihood for any interactions between newly developed medicines and the medicines that are likely to be co-prescribed to older patients. Where a mechanistic understanding does not exclude any relevant interactions, the potential for any relevant interactions should be broadly investigated in (non)clinical trials before the medicinal product reaches the prescribers. In addition, the likelihood that the newly developed medicine may be co-packed in a multi-compartment compliance aid or multi-drug dispensing system should be considered for any relevant incompatibilities. Finally, the product appearance and any specific user instructions should be balanced against those of the medicines that are likely co-prescribed in order to avoid medication errors and ensure an acceptable number of dosing moments per day.

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COMPETING INTERESTS

Katarina Vučić was a member of the CHMP and the chair of the EMA Geriatric Expert Group. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organisations with which the authors are affiliated.

CONTRIBUTORS

All authors contributed to the design of the study and to collecting the data. A.S. analysed the data and wrote the manuscript with input from F.C. and K.V.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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