Risk Management and Healthcare Policy

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ORIGINAL RESEARCH

Potentially Inappropriate Medication Dispensing in Outpatients: Comparison of Different Measurement Approaches

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Purpose of the Research: This paper aims at comparing different approaches to measure potentially inappropriate medication (PIM) with routinely collected data on prescriptions, patient age institutionalization status (ie in nursing home or in the community). A secondary objective is to measure the rate and prevalence of PIM dispensing and to identify problematic practices in Switzerland.

Material and Methods: The studied population includes about 90,000 insured over 17 years old from a Swiss health maintenance organization in 2019 and 2020. We computed and compared the number of PIM per patient for Beers criteria, Priscus list, Laroche, NORGEP and Prescrire approaches. We also created a composite indicator that accounts for the specificities of the Swiss context (adaptation to the Swiss drugs' market, recommendations in force related to sleeping pills, anxiolytics and NSAIDs). We also stratified the analysis per physician, including initiation and cessation of PIM prescription.

Results: Our comparison revealed similarities between the approaches, but also that each of them had specific gaps that provides further motivation for the development of a composite approach. PIM rate was particularly high for sleeping pills, anxiolytics, NSAIDs, even when analyses were limited to chronic use. Drugs with anticholinergic effect were also frequently prescribed. Based on our composite indicator, 27% of insured over 64 years old received at least one PIM in 2020, and 8% received more than one. Our analyses also reveal that for sleeping pills and anxiolytics, half of the volume (or prevalence?) occurs in the <65 population. We observed strong variations between physicians and a significant proportion of new users among patients with PIM.

Conclusion: Our results show that PIMs prescribing is very frequent in Switzerland and is driven mostly by a few drug categories. There is important physician variation in PIM prescribing that warrants the development of intervention targeted at high PIM-prescribers.

Keywords: low-value care, inappropriateness, medication, outpatients, Switzerland

Introduction

Countries generally authorize market access for new medicines if the treatment demonstrates its efficacy, without generating disproportionate undesirable effects.[1–3] Recommendations can then restrict prescription if the benefit-risk balance for specific indications and/or patient groups is not favorable, ie if the medication is unnecessary or dangerous. The elderly population (>64 years old) is particularly at risk of using inappropriate treatments, as they are more vulnerable to adverse drug events. In addition, polypharmacy, the concurrent use of multiple medications, which increases the risk of interactions, is common in this population, costly and harmful.[4] Some types of medication, such as anxiolytics or sleeping pills, might also be inappropriate in younger patients especially in chronic use. Many implicit (ie, judgment-based) and explicit (ie, criterion-based) approaches are available to identify potentially inappropriate medications (PIM) and provide reference guides for comprehensive medication reviews.[5,6]

Implicit approaches rely on expert professional judgement, are patient-oriented, and address entire medication regimen. These instruments are time consuming to implement and might have a low reliability.[7] For instance, the

Received: 20 July 2023
Accepted: 13 October 2023
Published: 23 November 2023

Medication Appropriateness Index[8,9] provides a comprehensive list of criteria with corresponding scores to assess the appropriateness of drugs prescriptions. Such tools can be useful to support medical decision-making,[10] but they require in-depth information on the clinical context. Since data on diagnoses or labs results are not routinely collected, those tools are not suitable to build monitoring indicators.

Explicit approaches have been developed from literature reviews, expert opinions, and consensus techniques. Based on lists of drugs, drug-classes, and dosages known to cause harmful effects, such approaches are easy to implement, not costly, and need regular updates.

To date, few studies investigated PIM dispensing in Switzerland. For instance, an insurance company used Beers and Priscus lists independently to raise awareness of doctors about inappropriate prescriptions of drugs.[11] They found a prevalence of 22.5% of PIM in a managed care sample (N = 49,668)[12] and of 79% among nursing homes residents (N = 72,106).[13] Another Swiss study, combining Beers and NORGEP approaches found that 30% of consumed drugs were potentially inappropriate among nursing home residents.[14]

In this paper, we retained five approaches: Beers criteria, Priscus list, Laroche, NORGEP, and Prescrire approaches (references in the Method section) because they rely on explicitly listed substances, which is a necessary condition to automatize computation. Our source of information in the Swiss system is insurance claims data. Thus, another rationale for the use these tools is that they do not require information on comorbidities (except, to a limited extent, for the Beers criteria). PIM-approaches relying on clinical and physiological criteria,[15–19] were not retained, as such information (hypokalaemia, hypertension, history of myocardial infarction, renal failure for instance) are is rarely available in claims data.

The aim of our paper consists in assessing and comparing different potentially inappropriate medication (PIM) measurement approaches based on routinely available data on drugs dispensed to more than 90,000 individuals enrolled in an Health Maintenance Organization (HMO) plan in Switzerland. Our analysis was conducted in light of the Swiss context (ie product availability, local guidelines, etc.), potentially justifying the design of an adapted tool. A secondary objective was to measure the rate and prevalence of PIM and to identify problematic practices (differences between physicians, initiating or stopping PIM).

Methods

Study Population and Setting

In Switzerland, the population has a mandatory basic health care insurance package. Insured can lower their premium by choosing an HMO contract with a primary care physician as gatekeeper. The Delta Network is such an HMO, established in 1992 in the French-speaking part of Switzerland (canton of Geneva, Vaud, Fribourg, Valais, and Jura), proposing a network of 700 gate keepers (primary care physicians).[20] The Delta Network is available in for enrollees of any health insurance company. We focused on enrollees from Geneva and Vaud that represents 95% of Delta enrollees. In 2019 and 2020, more than 250,000 individuals were enrolled in the Delta Network. Delta network gatekeeping physicians (GP), all paid fee-for-service, agreed to be accountable for the quality, cost, and overall care of HMO beneficiaries. GP committed to a smart medicine philosophy, ie "doing only necessary care, but all necessary care, based on both scientific medicine and patients' preferences".

Our setting included 91,739 insured over 17 years old contracting with Swiss insurance companies, enrolled in the Delta network in 2020, and having received at least one drug with oral route of administration in 2020 (insured <18 or without those drugs prescriptions were excluded). To analyze the frequency of PIM stopping or initiating, we also analyzed the data of 85,894 insured from the year 2019.

The data used for this research were anonymous, without any possibility to identify patients (no birth date or precise residence information for instance). Patient-level information collected included anonymous identifiers, age (years), gender, canton of residence, year of insurance contract (2019, 2020), an anonymous identifier of the primary care physician, and data on medication, products code, and the quantity of delivered packages. From the medication data, the Delta network derived defined daily dose (DDDs) by Anatomic Therapeutic Chemical codes (ATC), the classification system of the World Health Organization. We created a flag for PIM for each approach as described below (ie Beers, Priscus, Laroche, etc.).

The analysis was limited to all patients receiving oral drugs prescriptions. Anesthetic and healing products, contraceptive, disinfectant, antiseptic, diagnostic tests, nutriments, and vaccines were not considered as drugs and therefore excluded. We also excluded homeopathy and herbal medicine, because they were not included in most PIM lists studied here.

PIM Criteria

All approaches relied on a list of substances to be avoided, sometimes for specific conditions (age, institutionalization status, Table 1). According to the Swiss drug market specificities, we excluded some substances (not included in the PIM list, see Appendix A).

Beers Criteria

We used the American Society of Geriatrics 2019 updated list[21] for patients older than 64 years. Those recommendations included substances that should be avoided, sometimes with specific criteria (eg, treatment duration, minimal dose). It provided for each criterion the quality of the evidence and the strength of recommendations and was also used in several European countries. If the recommendation was to avoid chronic use only, we applied the condition of at least 90 days of treatment (deduced from DDD) during the year.

Priscus List

A similar approach, named Priscus, was developed in Germany, with a simple list of substances to avoid in patients 65 years and over.[22] Drugs combining several substances with at least one included in Priscus list were also considered as PIM.[14]

Table 1 Comparison of the Different Approaches, by Class of PIM

PIM classes	Beers	PRISCUS	Laroche	NORGEP	Prescrire®	Composite Indicator	
Residence				**Nursing home**			**Ages**
Age (years)	**>64**	**>64**	**>74**	**> 70**	**>0**		
Benzodiazepines and analogs							
Sleeping pill	Partial	Partial	Partial	Partial	No	All*	>17
Anxiolytic	Partial	Partial	Partial	Partial	Partial	All*	>17
Hypnotics (not benzodiazepine)	Partial	Partial	Partial	Partial	Partial	All	>17
Barbiturics	Yes	No	No	No	No	Yes	>17
Non-steroidal anti-inflammatory drug							
Indomethacin	Yes	Yes	Yes	Yes	No	Yes	>17
Other NSAIDs	Partial	Partial	Partial	Partial	Partial	All**	> 64
Acetylsalicylic acid	Yes	No	No	No	No	Yes*	>17
Anticholinergic drugs							
Tricyclic anti-depressant	Partial	Partial	Partial	Partial	No	All, except amitriptyline	> 64
Antispasmodic anticholinergic	No	Yes	Yes	Yes	No	Yes	Nursing home
Neuroleptic phenothiazine	All	Partial	Thioridazine	All	No	All	> 64
Anticholinergic antihistaminic	Partial	Partial	Yes	No	Partial	All	> 64
Other anticholinergic	Partial	Partial	Partial	Partial	No	All (high and moderate)	Nursing home
Cardiovascular drugs							
Centrally acting antihypertensive	Partial	Partial	Partial	No	No	All	> 64
Anti-hypertensive - alpha receptors	Partial	Partial	Partial	No	No	All	> 64
Peripheral vasodilators	Partial	Partial	Yes	No	Partial	All	> 64
Immediate release calcium channel blocker	Partial	No	Partial	No	No	All	> 64
Digoxin	Yes	No	Yes	Yes	No	Yes	> 64
Endocrine drugs							
Long-acting hypoglycaemic suflamides	Partial	No	Partial	No	Partial	All	> 64
Estrogen	Yes	No	No	No	Yes	Yes	> 64
Megestrol	Yes	No	No	No	No	Yes	> 64

(*Continued*)

Table 1 (Continued).

PIM classes	Beers	PRISCUS	Laroche	NORGEP	Prescrire®	Composite Indicator	
Residence				**Nursing home**			**Ages**
Age (years)	**>64**	**>64**	**>74**	**> 70**	**>0**		
Other drugs							> 64
Anti-dementia	No	Yes	Yes	No	Yes	Yes	> 64
Pethidine	Yes	Yes	No	No	No	Yes	> 64
Codeine and paracetamol	No	No	No	Yes	No	No	> 64
Nitrofurantoin	Yes	Yes	Yes	No	No	Yes**	> 64
Centrally acting muscle relaxants	Partial	Partial	Yes	No	Partial	Yes	> 64
Stimulating laxatives	Yes	No	No	No	No	Yes	> 64
Mineral oil	Yes	No	No	No	No	No	> 64
1st generation antihistaminic	Partial	Partial	Yes	Partial	Yes	Yes	> 64

Notes: The class of PIM might be included in different approaches' lists (yes) or not (no). Sometimes, only a part of corresponding substances available in the Swiss market are included (partial), other times they are systematically included (all). *Only with more than 30 days of treatment dispensing. **Only with more than 90 days of treatment dispensing.

Laroche Criteria

In France, Laroche et al developed a list of drugs to be avoided, targeting people aged 75 and over, based on a consensus panel.[23] The goal of the list was to propose safer or more effective therapeutic alternatives, with a particular attention to drug interactions.

This approach was more challenging to implement, due to a lack of clarity in its description. To obtain explicit ATC codes, we used all substances with a high or moderate anticholinergic burden from a recent review of the literature on this topic[24] (34th Laroche criteria). We had also to specify drugs considered as anticholinesterase, namely: tacrine, donepezil, rivastigmine, galantamine, ipidacrine, neostigmine, pyridostigmine, distigmine, ambenonium and associations with one the listed substances.

We used the dates of delivery as first day of treatment, DDD and prescribed doses to estimate the duration of treatment (last day of treatment) to identify prescriptions with overlapping periods. Doing this, we assumed that patients took the prescribed drugs regularly and completely.

NORGEP-NH Criteria

In Norway, another list of drugs to avoid in people over 70 in nursing home was developed, paying some attention to drug interactions.[25] It also identifies PIMs based on simultaneous use of other drugs.[17] Deprescribing criteria including bisphosphonates, statins, antidepressants, were not implemented, since the recommendation was only to reassess regularly their use.

The same rules than Laroche were applied to detect concomitant use of drugs. We computed all interactions, most of them being of first order (criteria 12–25) and one of second order with a triple interaction (criteria 26).

Prescrire List

In France, a collective of independent pharmacists and physicians established a list of drugs, whose prescriptions should be avoided regardless of the age of the patients.[26] They developed a list based on a continuous review of the literature during the last 15 years (Prescrire review), claiming independence from pharmaceutical companies. They did not formally consider them as PIMs, but we examined this approach to understand similarities and differences with the other approaches.

We considered all medications that the Journal Prescrire recommends avoiding. Of note, more than half of the substances advised against were not present on the Swiss market in 2020.

Quantitative Analysis and Outcomes

To build indicators on the quality of drug prescribing, it is necessary to define numerators (occurrence of PIM) and denominators (eligible population).

A PIM corresponds to at least one inappropriate prescription for a given ATC code during the year. Some patients may therefore have several PIM at the same time. The rationale of this definition is that PIM of different ATC codes correspond to independent decisions. The rate of PIM is the sum of the prevalence of PIM (at least one PIM par patient) and of the frequency of multiple PIM per patient.

We used two types of numerators, one static, counting the number of PIM per patient (PIM rate), and another one as a score that takes into account the dynamic of prescriptions.

A primary outcome was the rate of PIM over one year (2020) according to each approach in the delta network, categorized by age, computed by counting PIMs of different ATC codes and dividing this sum by the 2020 eligible population. We also computed the proportion of the eligible population receiving at least one drug prescription (prevalence). We computed PIM rates globally and per physician to analyze its variation among prescribers.

As secondary outcome we built a score to reflect changes in prescription patterns between 2019 and 2020. This score is based on points assigned to various situations, with higher points reflecting poorer prescribing and less physician effort to limit PIM. Initiating a new PIM between 2019 and 2020 is assigned 2 points. The most favorable situation (−2) consists in PIM discontinuation between years. One point is attributed if a PIM was maintained during both years. If no PIM was prescribed over both years, the score does not change. The proposed score considers that it is more difficult to stop a PIM (−2) than not to start such a prescription (0). We computed scores among insured eligible for the two years (2019 and 2020) and identified PIM with our composite approach.

Despite higher rates among elderly, we did not standardize these per GPs' indicators for age because we consider that adverse events are potentially at least as harmful among old people than younger individuals and that potential interactions are more frequent in the elderly (more polypharmacy). In other words, we consider that doctors must be even more careful with elderly patients, even if it is perhaps more challenging to avoid PIMs among them.

Results

Comparison of PIM Lists and Creation of a Composite PIM Indicator

The comparison of the various approaches showed that most relied on common PIM classes (Table 1), but often with partial lists of ATC codes, despite similar undesirable effects. We observed that the various lists included similar classes of drugs (sleeping pills, anxiolytics, non-steroidal anti-inflammatory drugs (NSAIDs), anticholinergic drugs, etc.,) but also that the list of ATC codes were different without medical reasons. Thus, we built a composite indicator to include them systematically (see Appendix B for details and rationale). According to usual recommendations in place in Switzerland, we considered sleeping pills, anxiolytics, and NSAIDs as PIM only if they were used for >90 days (chronic use). A third difficulty was related to the justification of the limitations (age, nursing home residence, etc.). We considered for instance that chronic use of sleeping pills and anxiolytics should be avoided in the same way among young and old people, because the problem of addiction does not depend on age. Consequently, the composite indicator was extended to people under 65 for benzodiazepines and analogs, indomethacin and acetylsalicylic acid (chronic use only). We included most medications of the Prescrire list as it overlapped quite well with the other lists. However, we excluded from our composite list more controversial substances included in Prescrire, such as nasal decongestants, combinations of hypoglycaemics, renin inhibitors, other anti-depressants (see Appendix C). We analyzed them separately but did not include them in the composite approach.

Frequency of PIM

Table 2 gives the frequency of PIM according to the different approaches, with the corresponding eligible populations. We observe the same frequency of PIM in 2020 according to the criteria of Beers and Priscus (0.360 and 0.334 PIM/patient respectively), even if targeted substances are not identical. The population at risk was the same, 16,927 eligible insured for both methods, corresponding to the population aged 65 and over having received at least one prescription for oral medication. Laroche's approach targets about the half of this population (8705 insured aged 75 and over), while the NORGEP method addressed an even smaller eligible population (1583 nursing homes residents, aged 70 and over). For these last two approaches, the frequency is

Table 2 Occurrence of PIM (One per ATC Code) per Eligible Insured (2020)

Types of insured	Number of PIM*						Prevalence of PIM**
	Beers	Priscus	Laroche	NORGEP	Prescrire	Composite	Composite
Number of PIM:							
18–64 years old					16,941	6018	4877
65–69 years old	1362	1239			1562	1127	882
70–74 years old	1292	1210		112	1581	1172	949
>74 years	3447	3208	7893	1231	3767	3675	2822
Total	6101	5657	7893	1343	23,851	11,992	9530
Eligible population:							
18–64 years old					74,812	74,812	74,812
65–69 years old	4251	4251			4251	4251	4251
70–74 years olds	3971	3971		97	3971	3971	3971
>74 years	8705	8705	8705	1486	8705	8705	8705
Total	16,927	16,927	8705	1583	91,739	91,739	91,739
Rate of PIM*:							
18–64 years old					0.226	0.080	0.065
65–69 years old	0.320	0.291			0.367	0.265	0.207
70–74 years old	0.325	0.305		1.155	0.398	0.295	0.239
>74 years	0.396	0.369	0.907	0.828	0.433	0.422	0.324
Total	0.360	0.334	0.907	0.848	0.260	0.131	0.104

Notes: *Possibly several PIM per patient. **Only one PIM per patient.

0.907 and 0.848 PIM/patient respectively. The Prescrire approach had the highest proportion of PIM, especially among the youngest.

The global prevalence measured with the composite approach was about one in 10 enrollees (10.4% with at least a PIM) with 2.7% having multiple PIM, leading to the global PIM rate of 0.131 (Table 2 people above 18 years old). Considering only enrollees over 64 years, the prevalence was 27.5% (at least a PIM) with 8% received more than one (computed from Table 2 outcomes) leading to a global PIM rate of 0.353.

With the composite indicator, PIM rates increased with the age of patients, with a prevalence of 32.4% among older patients (>74 years old). However, the composite approach, extended to younger people, show that the half of PIM occurred among people under 65 years old, which include much more eligible people.

The detailed analysis by PIM class makes it possible to compare the different approaches for a better understanding of their specificities (Table 3).

Globally, the composite indicator indicates a frequency of 0.35 PIM par patient among patients older than 64 years old. Sleeping pills, anxiolytics, and hypnotics represented almost the half of those cases. No consumption of barbiturate was identified as this drug is not on the market. The only hypnotics delivered was clometiazole.

Non-steroidal anti-inflammatory represented another frequent type of PIM, especially in the Laroche approach; limiting PIMs to chronic use in the composite approach reduced significantly their prevalence. Inappropriate prescriptions of acetylsalicylic acid (chronic intake > 325 mg) were not observed.

PIM related to cardiovascular, hormonal or anticholinergic drugs are relatively rare. Several classes of PIM are never prescribed in Switzerland as corresponding substances (pethidine, first generation antihistamines for example) were not available in the Swiss market. PIM related to anti-dementia drugs were relatively rare (rate of 0.01).

A large part of the PIM according to the Laroche's approach concerned the delivery of nitrofurantoin. Such PIM were much less frequent in the composite approach because only chronic consumption (more than 90 days per year) is considered problematic.

Table 3 Detailed Occurrence of PIMs (One per ATC Code) per Eligible Insured (2020, >64 Years Old)

PIM_Class	Beers	PRISCUS	Laroche	NORGEP	Prescrire®	Composite[a]	
	PIMs	PIMs	PIMs	PIMs	PIMs	PIMs	Rate
Benzodiazepines and analogs							
Sleeping pill	1860	2052	1134	32		1621	0.0958
Anxiolytic	2941	1341	1263	47		1867	0.1103
Hypnotics				206		360	0.0213
Barbiturics							
Non-steroidal anti-inflammatory drug							
Indomethacin	29	17	14			29	0.0017
Other NSAIDs	568	1106	2439	354	1688	844	0.0499
Acetylsalicylic acid							
Anticholinergic drugs							
Tricyclic anti-depressant	125	125	69	9		126	0.0074
Antispasmodic anticholinergic		320	183			19	0.0011
Neuroleptic phenothiazine		12	13			15	0.0009
Anticholinergic antihistaminic	25	26	3			23	0.0014
Other anticholinergic	181		42			62	0.0037
Cardiovascular drugs							
Centrally acting antihypertens.		1	105			160	0.0095
Anti-hypertensive - alpha receptors	24	24				23	0.0014
Peripheral vasodilators		26	20		18	26	0.0015
Immediate release calcium channel blocker			162			224	0.0132
Digoxin	38	121	102			37	0.0022
Endocrine drugs							
Long-acting hypoglycaem. sulf.	122					122	0.0072
Estrogen	176				89	176	0.0104
Megestrol							
Other drugs							
Anti-dementia			609		198	198	0.0117
Pethidine							
Codeine and paracetamol				73			
Nitrofurantoin	7	7	562			7	0.0004
Centrally acting muscle relaxants	5	30	13		5	35	0.0021
Stimulating laxatives			35			0	0.0000
Mineral oil							
1st generation antihistaminic							
Other[b] and interactions		449	1125	622	4910[c]		
Total	6101	5657	7893	1343	6908	5974	0.3529

Notes: [a]This table do not include PIMs occurring for younger people (<65 years old), which represent 2431 supplémentary PIMs for sleeping pills, 3417 for anxiolytics, 54 for hypnotics and 116 for indomethacin. [b]Mainly flecainide (165), fluoxetine (130), solatol (96), clozapine (33), prasugrel (16) in Priscus list. [c]Substances of Prescrire® list, not mentioned in other lists: see Appendix B.

Initiating and Stopping PIM Dispensation

PIM scores are given in Table 4. Most PIM (6782) occurred during both 2019 and 2020 years. About a third of PIM were stopped in 2020 [=3449/3449+6782]. A little bit more was initiated in 2020 (3751), mostly driven by sleeping pills and anxiolytics (see column "excess").

There is a great variability in the frequency of PIM dispensing among physicians (Figure 1). Physicians dispensing a lot of PIM are set on the left with about 1.0 PIM per patient in elderly, and the lowest PIM prescriber on the right (0.25 PIM par patient). Only physicians with at least 10 eligible enrollees are included in the figure, to avoid too much random variation. The same variation is observed among younger insured, from 0.5 to less than 0.1 PIM/insured. The PIM scores

are given by the grey line, also showing great variability between physicians, between about +1 and −1. However, there was no clear correlation between low PIM prescribing (frequencies) and the effort to stop PIM (scores), except perhaps for some physicians shown on the far right (Figure 1). However, the difference of average scores among young and old people was not statistically significant (0.36 probability that they were due to hazard according to bilateral *t*-test).

Discussion

Main Findings

To the best of our knowledge, this is the first study comparing five approaches for PIM identification in the same setting. The comparison of PIM frequencies is difficult because it can be biased by various factors[27] (country, age of patients, and possible overlap between PIM lists) and patient selection. For instance, it is difficult to compare our results with a study focusing on hospitalized patients (higher rates[5]) or another taking into consideration only certain duplicated prescriptions (lower rates[28]). Our study has the advantage to compare PIM approaches from the same data set, with explicit explanations of the differences.

Our results are in line with a previous study and confirm the high rate of PIM in Switzerland, using data from an HMO.[29] The rates are slightly higher than the prevalence of PIM per patient (considering only one PIM per patient) with the composite approach.[30]

We found similarities between the different approaches in the choice of listed drugs categories, mainly sleeping pills, anxiolytics, NSAIDs and drugs with anticholinergic effects. However, the lists of substances included in these categories differed across approaches for unclear reasons. Such discrepancies probably reflect different drug markets. We also identified categories of drugs such as nitrofurantoin or anti-dementia drugs, that are not consistently listed in all the approaches. Possible explanation includes the lack of evidence for some these recommendations; this might alter the interpretation of the results. Indeed, some interventions fall into a grey zone for which the balance of benefits and harms varies substantially among patients and are backed by little evidence to help decide which patients may benefit. We have therefore proposed a composite approach that systematically includes substances with analogous effects. Several substances considered as PIM were not prescribed because they were not or no longer authorized on the Swiss market. Furthermore, we introduced some restrictions to comply with the best practices in Switzerland, by tolerating certain short-term treatments (sleeping pills, anxiolytics, NSAIDs) for example. Conversely, we considered that long-term sleeping pills and anxiolytic treatments were not appropriate in younger patients either. Globally, the composite indicator indicates a frequency of 0.35 PIM par patient among patients older than 64 years old.

Benzodiazepines (BZD) used as sleeping pills and/or anxiolytics are the main reported PIM irrespectively of the approach used, accounting for about a quarter of PIM in the group of elderly people. Of note, it must be emphasized that this BZD rate was not higher using the new composite indicator even if we extend the list to all substances because short-term prescriptions were tolerated in our approach. The problems associated with the abuse of sleeping pills and anxiolytics are well known.[31,32] BZD overuse is endemic in western countries, especially in hospital settings for insomnia disorders. Studies showed that up to 30% of inpatients[33] and about 20% of outpatients[34] had at least one BZD prescription in Switzerland. It is interesting to note that sleeping pills are precisely the ones that gave rise to a greater number of new treatments as opposed to discontinuations (Table 4). A recommendation would therefore be to educate doctors to stop treatment before addiction sets in.[30] If this proves too difficult, perhaps they should be encouraged to initiate these types of treatments less often. Among different strategies, a recent meta-analysis revealed that patient education interventions were promising for BZD deprescription.[35] Even a small reduction of sleeping pills and anxiolytics prescription rate may have a significant impact in reducing potential serious complications of BZD such as cognitive impairment, delirium, falls and hip fractures and possibly readmissions.[36–38]

Our results based on the composite score highlighted that such problems also concern younger patients, for whom we observed half of the total PIM volume. It is interesting to note that 60% of inappropriate sleeping pills and anxiolytics were observed in patients under 65, even if the prevalence of PIM was much lower. Knowing that a lot of consumption began before retirement, this result shows that it is important to monitor this issue among younger individuals as well.

Table 4 PIM Scores

Scores	Stopped in 2020 (−2 Score)	During the 2 Years (1 Score)	Initiated in 2020 (2 Score)	Excess (=Initiated-Stopped)
Sleeping pill	956	2432	1131	175
Anxiolytic	1406	2985	1615	209
Hypnotics	110	175	172	62
Indomethacin	111	30	82	−29
Other NSAIDs	502	400	367	−135
Tricyclic anti-depressant	31	66	52	21
Antispasmodic anticholinergic	6	8	8	2
Neuroleptic phenothiazine	4	9	4	0
Anticholinergic antihistaminic	12	6	14	2
Other anticholinergic	26	20	38	12
Centrally acting antihypertens.	37	107	44	7
Anti-hypertensive - alpha receptors	5	9	11	6
Peripheral vasodilators	6	21	4	−2
Immediate release calcium channel blocker	130	91	112	−18
Digoxin	5	27	9	4
Long-acting hypoglycem. sulf.	21	94	16	−5
Estrogen	28	147	12	−16
Anti-dementia	42	136	44	2
Nitrofurantoin	5	3	3	−2
Centrally acting muscle relaxants	6	16	13	7
Total	3449	6782	3751	302

This study confirms PIM are frequent in the HMO but there is also a large variation among GP working within Delta network, from 0.25 per patient to 1.0 per patient in elderly. The same variation is observed among younger insured, from 0.5 to less than 0.1 PIM/insured. Clinical variation is an accepted way to identify whether there is overuse in medicine among practitioners. Variation analyses can show significant differences that are warning signs of overuse and a strong quality indicator. Clinical variation can play as catalysts for change by stimulating debate, engaging all participants in the health system so that patient-focused care can be achieved. Process standardization can dramatically decrease variation and eventually improve performance. Furthermore, the case mix of studied populations has little importance when interpreting variation results, which avoids some bias and makes benchmarking between providers easier. For this purpose, data measurement and reporting are again essential and represent a powerful tool.

The average of PIM score also varied, between about +1 and −1, with lower values (more PIM stopped) for physicians with rare PIM among young people (Figure 1). We note though that stopping NSAIDs treatments is observed more frequently.

PIM related to anti-dementia drugs were fairly common. The effects of anti-dementia drugs are modest, symptomatic, and limited to short-term.[39,40] Thus, they should it be avoided for a prolonged period, this being not observed currently (Table 4). The frequent use of clometiazole might similarly be questionable because it also generates dependence and undesirables effects.[41]

It is interesting to note that substances belonging only to the Prescrire list were not typically PIMs, but rather substances which might be substituted by others with less side effects (olmesartan for instance) or low added value.

Perspective and Limitations of the Study

Irrespectively of the approached used, PIM seem high enough to consider that it is a public health issue, requiring corrective measures. It is interesting to note that if one targeted the analysis on BZD (and analogues), on NSAIDs and anti-dementia drugs, one would address 83% of PIM detected by the composite approach.

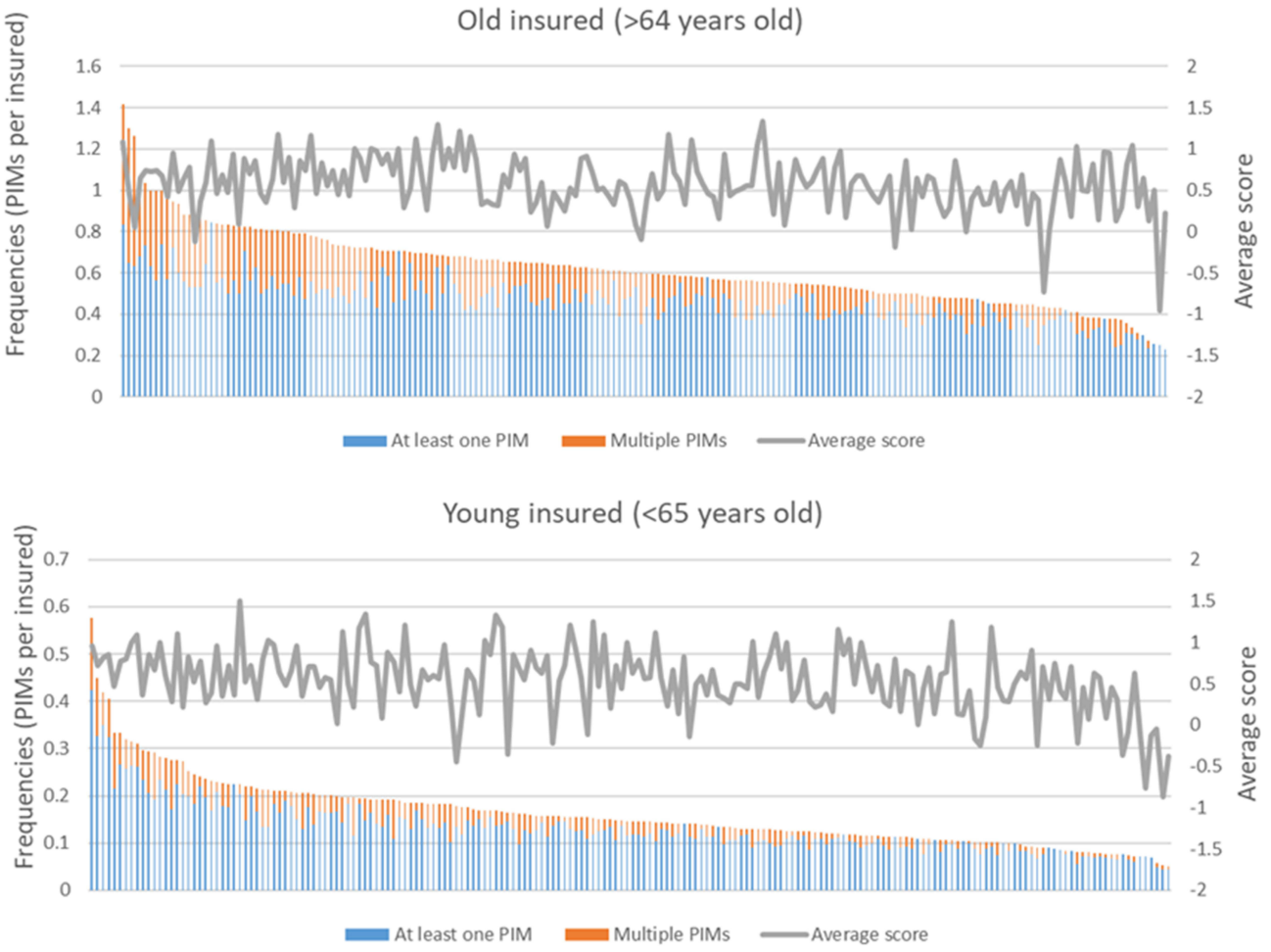

Figure 1 Variations in PIM frequencies and scores among 190 physicians with at least 10 eligible insured.

An approach targeting these three drug classes could therefore be effective in reducing the number of PIM in Switzerland. There are many actions to take:

- Informing and raising awareness of doctors working in the Delta network, by preparing documentation on the disadvantages of these treatments and recommendations for alternative treatments;
- Targeted mail to doctors with a particularly high rate of PIM (Figure 1), with the list of patients and PIM identified;
- Continuous training and physicians pharmacists peer review groups (meeting regularly[42]) to discuss these four themes to promote alternative treatments.

The effectiveness of each of these measures might be evaluated by the evolution of the PIM rates.

The dissemination of guidelines alone does not appear to change physician behavior. Only multifaceted interventions may have an impact to reduce PIM.[43] Behavioral interventions with provider assessment and feedback have proven to affect practice in medicine.[44]

A recent study published in the same setting, suggests that among primary care practices working in the delta network, thematic quality circle intervention with data feedback and peer comparison resulted in lower mean of PPI prescription and statin prescriptions over age 75 years of age.[27] Another study using the same approach with audit and data feedback revealed a modest but statistically significant effect of a multifaceted educative intervention in reducing the BZD prescription rate at discharge in hospitalized patients.[45]

General information aimed at patients would probably also be necessary to raise their awareness of the dangers of PIMs, as well as to participate in campaigns targeted at the general population.

Several methodological choices are also worth discussing. We did not adjust the results for patients' characteristics, as we were not able to capture the clinical context from our data; the consequence might be ignoring some PIM. For instance, opioids might be considered inappropriate in certain circumstances (history of falls, cognitive impairment for example[21]) but justified in a palliative context. Determining whether the use of opioids – even chronically – could be avoided by other effective treatments without knowing all clinical information is difficult. We hypothesized that patients were taking the full amount of delivered drugs, while this is not necessarily the case; the prevalence of PIM might thus be overrated, especially for sleeping pills or inappropriate painkillers. We know that elderly patients have more PIM than young people. One might advocate that old people are more often ill and more frequently suffer from multiple pathologies. However, we considered that the problem of PIM is then also more serious because of the greater risk of side effects (in the event of renal failure or interactions between drugs, for example). Another point is the question of the quantification of PIM. We could have calculated the proportion of patients with at least one PIM; however, we preferred to count all PIM because their accumulation can be harmful for patients. We adopted a 90-day criterion to define chronic medication intake. This complicated the calculation of the indicators because it is necessary to calculate the DDDs, which is not always easy, in particular for drugs combining several substances. We preferred this measure to others such as the number of packages per quarter, which do not take into account the number of tablets and the dosages and which pose problems of delimitation (treatment started at the end of the quarter and continued at the beginning of the following quarter, for example).

Furthermore, we have circumscribed the analysis to drugs administered orally. It could perhaps be interesting to extend the approach to other administration routes, especially for patches (estrogen, anti-inflammatory for example), provided however that the side effects are significant, which is not always the case.[46]

The drugs have been allocated to primary care physicians, who have a gatekeeping role. It is possible that some PIM were prescribed by subcontracted physicians (psychiatrists for example). Although some approaches (Laroche for example) emphasize drug interactions, we did not retain such drugs' combinations in the composite model, considering that it was beyond the aim of our study. Similarly, we ignored the issue of polypharmacy and deprescribing.[47] We have limited ourselves to drugs that should in principle not be prescribed because their effectiveness is too low in relation to their disadvantages. This reflection can contribute to reducing polypharmacy, but it is not the only the question of the justification of medications according to the indications, which depend on detailed clinical information.[48] Since our approach is limited to an indicator that can be calculated from routinely available data, this aspect was not addressed. Doctors will be able to justify this or that exception. For example, the prescription of nitrofurantoin may be justified as first choice treatment if there are no severe side effects and no renal failure (frequent among elderly).[49] Another example concerns the prescription of certain anticholinergic treatments, which can be justified in some circumstances.[50] Such PIM are relatively infrequent in Switzerland, so it seems appropriate to focus on areas where overuse of drugs seems clearly established.

Finally, we examined all the prescriptions advised against by the *Prescrire* journal, apart from the PIM mentioned above. This type of approach could be useful for reducing polypharmacy, but none of the substances concerned appeared sufficiently harmful to be added to the list of PIM (see list in Appendix C).

We focused on two cantons insured of a Swiss HMO and cannot be inferred to other regions, even if there is some evidence of overuse of benzodiazepine in most French speaking cantons.[33] A comparison with other countries, other languages speaking regions in Switzerland and non-HMO insurance might be interesting.

Overall, our results show that PIM prescribing is very common with more than 0.5 PIM prescribed per patient in half of the doctors, and that prescription rates tend to increase over time. Also, there is no evidence that doctors seek to stop these treatments even among those who prescribe few. It should be noted that this high prevalence of PIM delivery was obtained after excluding short-term prescriptions for benzodiazepines and NSAIDs. On the brighter side, we observe that:

- There are doctors who rarely prescribe PIM; it is therefore feasible reducing their occurrence;
- There is a about one-third patients who are newly receiving PIM per year, which means that if fewer new prescriptions are made, there should be a gradual reduction in the prevalence of PIM;
- PIM concentrate on four types of medicine only, which allows for targeted information.

Conclusion

Our comparison highlighted broad convergences between the different PIM approaches. However, as most of these lists were incomplete, combining them in a composite tool was of interest. The main result shows that the PIM rate is too high in Switzerland for sleeping pills, anxiolytics, NSAIDs and drugs with an anticholinergic effect. There are strong variations between doctors and we recommend to provide feedback to doctors who have particularly high rates. The dynamics of prescriptions show that a score measuring the efforts of physicians to limit PIMs could constitute an interesting indicator, particularly for sleeping pills and anxiolytics in the context of an increasing rate.

Ethics Approval and Informed Consent

We confirm that the data accessed complied with relevant data protection and privacy regulations. The rules applicable in Switzerland in terms of ethics specify that an authorization by an Ethics Commission is not required for a study with anonymous data where it is not possible to identify patients by crosschecking of data. Reference: Federal Act on Research involving Human Beings (HRA) of 30 September 2011 (Status as of 26 May 2021, article 2 paragraph 2c). The data used in the study was anonymized before its use.

Acknowledgments

The authors thank Henrique da Costa (Delta network) for collecting and validating the data.

Disclosure

The authors report no competing interests in this work.

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