Current Therapeutic Research 95 (2021) 100650

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Impact of Pharmaceutical Interventions in Hospitalized Patients: A Comparative Study Between Clinical Pharmacists and an Explicit Criteria-Based Tool

Akram Farhat, PhD[1,2,3,*], Rime Abou-Karroum, MSc[4,5], Alice Panchaud, PhD[6], Chantal Csajka, PhD[1,2,3], Amal Al-Hajje, PhD[4]

[1] Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[2] Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Switzerland
[3] School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland
[4] Clinical and Epidemiological Research Laboratory, Faculty of Pharmacy, Lebanese University, Hadat, Lebanon
[5] Department of Pharmacy, Clemenceau Medical Center, Beirut, Lebanon
[6] Service of Pharmacy, Lausanne University Hospital, Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 10 August 2021
Accepted 22 October 2021

Keywords:
CLEO
pharmaceutical interventions
PIM-Check
potentially inappropriate medication list
prescribing errors

ABSTRACT

Background: It has been well recognized that pharmaceutical interventions (PIs) can prevent patient harm related to prescribing errors. Various tools have been developed to facilitate the detection and the reduction of inappropriate prescriptions and some have shown benefit on clinical outcomes.
Objective: The objective of this study was to evaluate the clinical, economical, and organizational impact of interventions generated by clinical pharmacists in hospitalized patients, and to evaluate the performance of an explicit tool, the Potentially Inappropriate Medication Checklist for Patients in Internal Medicine (PIM-Check), in detecting each pharmacist's intervention.
Methods: A cohort retrospective study was conducted on hospitalized patients. The impact of PIs based on pharmacists' standard examination was evaluated using the Clinical, Economic, and Organizational (CLEO) tool. The performance of PIM-Check in detecting each intervention was assessed by conducting a retrospective medication review based on available information collected from patients' records. A qualitative analysis was also conducted to identify the types of PIs that PIM-Check failed to detect.
Results: The study was performed on 162 patients with a median age of 68 years (interquartile range = 46–77 years) and a median hospital stay of 5 days (interquartile range = 4–7 days). The pharmacists generated 1.9 PIs per patient (n = 304) of which 31% were detected by PIM-Check. The acceptance rate of the interventions by physicians was 84% (n = 255). Among the accepted interventions, 53% (n = 136) had a clinical impact graded CL $\geq$ 2C (moderate or major), whereas the majority of them were not detected by PIM-Check (63%; 86 out of 136). In addition, 46% of accepted interventions (n = 117) were associated with a cost decrease, among which 62% were not detected by PIM-Check (73 out of 117). The qualitative analysis shows that PIM-Check mostly failed to detect PIs related to dose adjustment, overprescribing, and therapy monitoring.
Conclusions: According to the CLEO tool evaluation of PIs, our results show that clinical pharmacists' interventions are associated with improved clinical outcomes. In comparison with pharmacists' interventions, PIM-Check failed in detecting the majority of interventions associated with a moderate or major impact.

© 2021 The Author(s). Published by Elsevier Inc.
This is an open access article under the CC BY-NC-ND license
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

* Address correspondence to: Akram Farhat, PharmD, MSc, PhD.
E-mail address: akram.farhat@hotmail.com (A. Farhat).

https://doi.org/10.1016/j.curtheres.2021.100650
0011-393X/© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

Knowledge into Practice

- Very little is known regarding the clinical and economic potential impact of explicit tools in detecting prescribing errors.
- The majority of pharmaceutical interventions detected by pharmacists were not detected by the electronic explicit tool PIM-Check.
- These findings suggest that tools' detection rate and impact should be assessed carefully to prevent underdetection and gaps improvement should be taken into consideration.

Introduction

Drug-related problems are of major concern in hospitalized patients. Medication errors can concern different stages of the medication process, including prescriptions.[1] The reported prevalence of prescribing errors is widely variable, ranging between 2% and 94% depending on medicines' management process.[2] Data from 7 hospitals in Lebanon identified that 40% of medication orders had at least 1 prescribing error.[3]

Prescribing errors may lead to patients' injuries and may be a source of increased morbidity, mortality, and health care costs.[4–8] Harm related to medication errors, among which are prescribing errors, are called preventable adverse drug events (pADEs).[8]

The incidence of pADEs might be reduced by medication reviews led by clinical pharmacists.[9,10] Among the major outputs of medication review is the generation of pharmaceutical interventions (PIs) and recommendations to health care professionals. A PI is defined as "any activity undertaken by the pharmacist which benefits the patient."[11] PIs can interfere on prescribing errors to prevent their negative outcomes and optimize therapy. PIs can significantly reduce pADEs, hospital length of stay, costs, and increases efficacy of drug therapy.[12–14]

Several tools have been developed to help detect prescribing errors, some of which exist in electronic support forms.[5,14–16] In the present study, we focus on a recent electronic explicit criteria-based open-source tool, the Potentially Inappropriate Medication checklist for Patients in Internal Medicine (PIM-Check) (www.pimcheck.org), which is a prescription-screening checklist developed by an international panel of experts to help detect prescribing errors in adult inpatients. PIM-Check contains 160 criteria: 74 related to underprescribing; 36 related to overprescribing; 16 related to drug-drug interactions; and 34 related to other criteria concerning drug monitoring, dose adjustment, and choice of medication.[5,15]

The benefit of explicit tools in detecting and reducing the number of inappropriate prescriptions has been well examined,[17,18] yet few reports have been able to prove the clinical impact of such interventions.[14] The assessment of the impact of PIs is essential to evaluate and emphasize their value in enhancing medication safety.[19] The Clinical, Economic, and Organizational (CLEO) tool is a multidimensional, validated tool developed by the French Society of Clinical Pharmacy to assess the potential impact of PIs.[20] The CLEO tool[20] was developed to evaluate the potential effect of PIs and includes 3 independent dimensions: clinical dimension from the patient's point of view (CL), economic dimension from the hospital setting point of view (E), and organizational dimension from the health care providers' point of view (O).

The primary objective of this study was to evaluate the clinical, economical and organizational impact of PIs generated by clinical pharmacists in hospitalized patients, and to evaluate the performance of PIM-Check in detecting each PI. This comparison will identify potentially missing criteria with relevant impact. The secondary objective was to characterize the type of PIs not detected by the explicit tool.

Patients and Methods

Study population

A cohort retrospective study was conducted including patients hospitalized between April and June 2018 in a 158-bed hospital in Lebanon. Patients aged 18 years and older, admitted to acute medical care in the internal medicine ward and who beneficiated from a PI documented by the clinical pharmacists in patients' records were included, whereas patients not subject to PI during this period were excluded. The institutional review board approved the study protocol. Informed consent from patients was not required because the interventions were considered part of the hospital patients' care.

Data

Patient information was extracted from computerized patient records by a clinical pharmacist and anonymized. Collected data included information on sociodemographic characteristics (eg, sex, age, body mass index), lifestyle (eg, alcohol use and smoking), medications, comorbidities, laboratory results, and the documented PI.

PI evaluation

As a part of routine clinical patient care in the examined hospital, medication reviews are conducted by clinical pharmacists. When relevant, PIs are generated and communicated to physicians through the computerized patient records. PIs are considered as accepted by physicians if a change in the patient's management or therapy is done.

In this study, each included patient had at least 1 PI. For the purpose of this analysis, medications related to a PI were classified by the pharmacist, using the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization.[21] PIs were categorized according to the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) classification scheme:[22] therapy initiation, overprescribing, substitution, dose adjustment, therapy monitoring, change of administration route, optimization of administration, counseling of patient/training, information to caregivers, clarification in the patient record, and report to pharmacovigilance center. The development of the GSASA classification system was based on the instrument for documentation of clinical pharmacists' interventions of the French Society of Clinical Pharmacy [23] and the Pharmaceutical Care Network Europe classification system.[24]

PIM-Check evaluation

For each included patient, a medication review was performed retrospectively by a clinical pharmacist using PIM-Check based on the information collected from the patient record. If at least 1 inappropriate prescription detected by PIM-Check corresponded to a PI generated by the pharmacist, the latter was considered as "detected by PIM-Check," otherwise it was considered as "not detected by PIM-Check."

CLEO evaluation

Only PIs accepted by physicians were assessed using the CLEO version 3 tool[20] to classify their potential impact in the 3 dimensions (clinical, economic, and organizational). Each dimension consists of several numeric levels (negative, zero, and positive values) and an open level "not determined" representing the significance level of the interventions: clinical (6 numeric levels: from −1C to

4C), economic (3 numeric levels: from –1E to 1E), and organizational (3 numeric levels: from –1O to 1O). The analysis was performed separately by 3 clinical pharmacists and the interrater reliability was measured. The analysis was performed first for all accepted PIs and then for PIs "detected by PIM-Check" and "not detected by PIM-Check." Impact was also presented for the subgroup of patients aged 65 years and older.

Evaluation of the type of PI

A qualitative analysis was conducted to identify the types of PIs that PIM-Check failed to detect. This analysis was considered as a first step to improve this explicit tool in detecting prescribing errors.

Statistical Analysis

Descriptive statistics were used to summarize the sociodemographic and clinical characteristics of the study population, the ATC classes of medications related to the PI, the acceptance rate of PIs, the percentages of PIs detected or not by PIM-Check, and the types of PIs. The interrater reliability was measured using Krippendorff's alpha,[25] which is useful when there are multiple raters and multiple possible ratings. The proportion of accepted PIs "detected by PIM-Check" and those "not detected by PIM-Check" were compared using a χ^2 test. All analyses were performed with Statistical Package for the Social Sciences version 23 (IBM-SPSS Inc, Armonk, NY). An association was considered significant with a P value < 0.05.

Results

A total of 162 patients were included during the 3-month study period of which 56% (n = 90) were female patients; the population median age was 68 years (interquartile range [IQR] = 46–77) among which the majority (n = 90; 56%) was aged ≥ 65 years. The median hospital stay was 5 days (IQR = 4–7 days). The majority of patients were overweight or obese (body mass index ≥25), and a minority were smokers and alcohol consumers (**Table 1**).

Table 1
Sociodemographic and clinical characteristics of the study population.

Baseline characteristic	Result
Sex*	
Male	72 (44)
Female	90 (56)
Age, y†	68 (46–77)
20–64*	72 (44)
65–100*	90 (56)
BMI†	27 (24–31)
Underweight < 18.50*	0 (0)
Normal range 18.50–24.99*	59 (36)
Overweight 25.00–29.99*	50 (31)
Obese ≥ 30.00*	53 (33)
Alcohol use*	
Yes	15 (9)
No	145 (90)
Previous	2 (1)
Smoking*	
Yes	43 (27)
No	99 (61)
Exsmokers	20 (12)
Hospital stay, d†	5 (4–7)
< 5*	90 (56)
≥ 5*	72 (44)
Total	162 (100)
ATC class of medication targeted by PI*	
Anti-infective for systemic use	70 (23)
Alimentary tract and metabolism	68 (22)
Cardiovascular system	50 (16)
Blood and blood forming organs	42 (14)
Nervous system	30 (10)
Antineoplastic and immunomodulating agents	17 (6)
Other medications	8 (3)
Respiratory system	7 (2)
Systemic hormonal preparations, excluding sex hormones and insulin	6 (2)
Musculoskeletal system	6 (2)
Total	304 (100)

ATC = anatomical therapeutic chemical. BMI = body mass index; PI = pharmaceutical intervention.
* Values are presented as n (%).
† Values are presented as median (interquartile range).

PIs

The number of PIs generated by the clinical pharmacist was 304 (1.9 PI/patient), with an acceptance rate by physician of 84%; that is, 255 PIs in 162 patients (1.6 PI/patient).

PIM-Check detected 31% of these PIs (94 among the 304 PIs) with 77% of them labeled "accepted by the physician" (72 among the 94 PIs identified). Similar percentages were identified in the subgroup of patients aged 65 years and older (**Table 2**).

The most common drugs targeted by PIs according to the ATC classification (**Table 1**) were: anti-infective for systemic use (23%; n = 70), alimentary tract and metabolism (22%; n = 68), cardiovascular system (16%; n = 50), blood and blood-forming organs (14%; n = 42), and nervous system (10%; n = 30).

The most common types of PI according to GSASA classification (**Table 3**) were: dose adjustment (31%; n = 93), overprescribing (23%; n = 71), therapy initiation (11%; n = 32), information to caregivers (10%; n = 30), clarification in the patient record (8%; n = 25), and therapy monitoring (8%; n = 25).

Potential clinical, economic and organizational impact of PIs

Potential impact of all accepted PIs

Among the accepted PIs (n = 255), 53% (n = 136) had a potential clinical impact graded ≥ 2C (moderate or major). No lethal (4C) clinical impact was identified. In addition, 46% of accepted PIs (n = 117) were associated with a potential cost decrease ("a decrease of cost" 1E). Regarding the care process, 34% of accepted PI (n = 86) had a favorable (1O) potential impact on the organization.

Among the accepted PI in patients aged 65 years and older (n = 147), 60% (n = 88 PIs) had a potential clinical impact graded ≥ 2C (moderate or major). In addition, 47% of accepted PIs in patients aged 65 years and older (n = 70) were associated with a potential cost decrease. Regarding the care process, 33% of accepted PIs in patients aged 65 years and older (n = 48) had a favorable (1O) potential impact on the organization (**Table 4**).

Potential impact of accepted PIs "not detected by PIM-Check"

The majority of accepted PIs graded ≥ 2C were "not detected by PIM-Check" (63%; 86 out of 136 PIs). In addition, 62% of accepted PIs associated with a cost decrease were "not detected by PIM-Check" (73 out of 117 PIs).

Among the accepted PIs graded ≥ 2C in patients aged 65 years and older, the majority were "not detected by PIM-Check" (58%; 51 out of 88 PIs). In addition, 56% of accepted PIs associated with a cost decrease in patients aged 65 years and older were "not detected by PIM-Check" (39 out of 70 PIs) (**Table 4**).

Interrater evaluation

The classification of PI impact was reliable with Krippendorff's $\alpha = 0.898$ (95% CI, 0.875–0.920) for clinical impact, Krippendorff's $\alpha = 0.929$ (95% CI, 0.897–0.959) for economic impact and Krippendorff's $\alpha = 0.794$ (95% CI, 0.739–0.846) for organizational impact.

Table 2
Classification of pharmaceutical interventions (PIs).

Variable	PI*	Not detected by PIM-Check	Detected by PIM-Check
Full sample			
Accepted	255 (84)	183	72
Not accepted	49 (16)	27	22
Total	304 (100)	210 (69)	94 (31)
Subgroup of older patients (age ≥ 65 y)			
Accepted	147 (83)	98	49
Not accepted	30 (17)	17	13
Total	177 (100)	115 (65)	62 (35)

PIM-Check = Potentially Inappropriate Medication Checklist for Patients in Internal Medicine.
* Values are presented as n (%).

Table 3
Number of pharmaceutical interventions (PIs) by category, class, and clinical impact.

Type of intervention	PI	Accepted PI	Accepted PI (No. with CL ≥ 2)*	
			Not detected by PIM-Check	Detected by PIM-Check
Categories present in the tool				
Dose adjustment	93	75	47 (23)	28 (18)
Overprescribing	71	59	40 (18)	19 (15)
Therapy initiation	32	22	5 (1)	17 (12)
Therapy monitoring	25	20	12 (10)	8 (5)
Optimization of administration	17	17	17 (6)	0
Change of administration route	6	5	5 (2)	0
Substitution	5	4	4 (4)	0
Categories not present in the tool				
Information to caregivers	30	28	28 (20)	0
Clarification in the patient record	25	25	25 (2)	0
Total	304	255	183 (86)	72 (50)

CL = clinical impact; PIM-Check = Potentially Inappropriate Medication Checklist for Patients in Internal Medicine.
* CL ≥ 2 indicates a clinically relevant PI.

Table 4
Impact of accepted pharmaceutical interventions using the Clinical, Economic, and Organizational (CLEO) tool.

CLEO result	Accepted PI(n = 255)	Not detected(n = 183)	Detected(n = 72)	*P* value
Full sample				
Clinical impact (score)				**< 0.001**
Harmful (−1C)	0 (0)	0 (0)	0 (0)	
Null (0C)	37 (15)	36 (20)	1 (2)	
Minor (1C)	82 (32)	61 (33)	21 (29)	
Moderate (2C)	70 (27)	54 (30)	16 (22)	
Major (3C)	66 (26)	32 (17)	34 (47)	
Vital (4C)	0 (0)	0 (0)	0 (0)	
Not determined	0 (0)	0 (0)	0 (0)	
Economic impact (score)				**< 0.001**
Increase of cost (−1E)	87 (34)	60 (33)	27 (38)	
No change (0E)	51 (20)	50 (27)	1 (1)	
Decrease of cost (1E)	117 (46)	73 (40)	44 (61)	
Not determined	0 (0)	0 (0)	0 (0)	
Organizational impact (score)				0.751
Not favorable (−1O)	71 (28)	51 (28)	20 (28)	
Null (0O)	98 (38)	68 (37)	30 (42)	
Favorable (1O)	86 (34)	64 (35)	22 (30)	
Not determined	0 (0)	0 (0)	0 (0)	
Subgroup of older patients (age ≥ 65 y)	(n = 147)	(n = 98)	(n = 49)	
Clinical impact (score)				**< 0.001**
Harmful (−1C)	0 (0)	0 (0)	0 (0)	
Null (0C)	15 (10)	15 (15)	0 (0)	
Minor (1C)	44 (30)	32 (33)	12 (24)	
Moderate (2C)	45 (31)	32 (33)	13 (27)	
Major (3C)	43 (29)	19 (19)	24 (49)	
Vital (4C)	0 (0)	0 (0)	0 (0)	
Not determined	0 (0)	0 (0)	0 (0)	
Economic impact (score)				< 0.001
Increase of cost (−1E)	54 (37)	36 (37)	18 (37)	
No change (0E)	23 (16)	23 (23)	0 (0)	
Decrease of cost (1E)	70 (47)	39 (40)	31 (63)	
Not determined	0 (0)	0 (0)	0 (0)	
Organizational impact (score)				0.772
Not favorable (−1O)	42 (28)	29 (29)	13 (26)	
Null (0O)	57 (39)	36 (37)	21 (43)	
Favorable (1O)	48 (33)	33 (34)	15 (31)	
Not determined	0 (0)	0 (0)	0 (0)	

PI = pharmaceutical interventions.

Evaluation of the type of PI

The 183 PIs "not detected by PIM-Check" were related to different types of intervention (**Table 3**): information to caregivers and clarification in the patient record (n = 53), dose adjustment (n = 47), overprescribing (n = 40), therapy monitoring (n = 12), optimization of administration (n = 17), change of administration route (n = 5), therapy initiation (n = 5), and substitution (n = 4).

Among interventions on dose adjustment, the most common PIs "not detected by PIM-Check" were related to indications (eg, the need of high-intensity statin instead of low-intensity statin), to laboratory test results (eg, absolute neutrophil count), and to therapy monitoring of medication with narrow therapeutic index (eg, antiepileptics). Among interventions on overprescribing, the most common PIs "not detected by PIM-Check" were related to unnecessary anticoagulant agents (eg, in patients with low risk of developing a venous thromboembolism) and to drug contraindications due to specific patients' conditions (eg, nonsteroidal anti-inflammatory drugs). Among interventions on therapy monitoring, the most common PIs "not detected by PIM-Check" were related to therapeutic drug monitoring (eg, antiepileptic agents), to monitoring of some laboratory tests (eg, potassium and platelets) and to monitoring of electrolytes in case of electrolytes replenishment. Among interventions on optimization of administration, the most common PIs "not detected by PIM-Check" were related to drug dilution and drug infusion rate to prevent burning sensation, phlebitis, or allergies (eg, vancomycin, intravenous immunoglobulin, and potassium chloride). Among interventions on change of administration route, PIM-Check failed to detect PI related to cost-effectiveness pharmacoeconomics of route switching when possible. Among interventions on therapy initiation, PIM-Check failed to detect PIs related to the need of proton-pump inhibitors, to the addition of certain medication according to patients' vital signs (eg, beta blockers in patients with tachycardia), and to the requirement of vitamins and minerals (eg, vitamin D and calcium). Among interventions on substitution, PIM-Check failed to detect PIs related to drug allergies.

The qualitative analysis shows that among the PI with a significant clinical impact that were not detected by PIM-Check (86 PIs graded $\geq$ 2C), 59% were related to dose adjustment, overprescribing, and therapy monitoring.

Discussion

This study evaluated the potential impact of PIs generated by the pharmacists and show the partial usefulness of supporting tools. Among the PIs suggested to physicians, an important proportion was indeed "not detected by PIM-Check" and among the undetected PIs, an important percentage was considered of moderate or major clinical impact (ie, $\geq$2C).

Our findings regarding the significant potential clinical impact of PIs are consistent with the existing limited data.[26] Some studies demonstrated a positive impact of pharmacists' interventions on clinical outcomes. The limited amount of evidence on the clinical impact of such intervention is probably due to the complexity in conducting such studies requiring large cohorts of patients. The overall results of the potential impact of PIs in our study is in good agreement with a study[26] that assessed the potential impact of PI using CLEO on 150 hospitalized patients in a French university hospital. In that study, the number of PIs was inferior (1.1 vs 1.9 PI/patient), whereas the percentage of PIs with a potential clinical impact $\geq$ 2C was higher than our results (68% vs 53%). This could reflect the variability in the pharmacist's assessment, some will generate fewer PIs but of higher impact. Similar to our findings, the overall prescriber's acceptance rate was 86%. The inter-rater reliability for the clinical impact score was lower (0.822 vs 0.898). The PIs with high potential impact emphasize the utility of such interventions.

Another study compared the acceptance rate of PIs generated by a standard pharmacist evaluation on treatment plans stemming from 102 patients hospitalized in a geriatric psychiatry in a Swiss University Hospital to PIs generated by the explicit Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) version 1 criteria.[27] In that study, the number of PIs generated by the pharmacist (4.4 PI/patient) was higher than STOPP/START (2.4 PI/patient). It was performed in a different setting (enrolled population mean age and length of stay: 80 years and 15 days vs 68 years and 5 days in our study) resulting in a higher number of PIs. Similarly, to our observation, the PIs detection rate was higher with the standard pharmacist evaluation, then with the explicit tool alone. Unlike our findings (acceptance rate of 84%), the higher number of PIs was associated to a lower global acceptance rate of 68% (78% based on standard pharmacist examination and 47% based on STOPP/START). The 4 most common types of accepted PI based on standard pharmacist evaluation in both studies, according to GSASA classification, were information to caregivers (23% in this study vs 11%), dose adjustment (17% vs 29%), overprescribing (15% vs 23%), and clarification in the patient record (12% vs 10%). Because the impact of PIs was not evaluated in this study, it is impossible to determine whether or not this lower acceptance rate was correlated to higher number of PIs with low impact.

The available literature evaluating the use of PIM-Check includes 3 studies, among which 2 studies compared retrospectively the rate of detection of prescribing errors between 2 tools, PIM-Check and STOPP/START. The first was conducted in a geriatric population[28] and the second in internal medicine settings.[29] The third study evaluated the variation of inappropriate prescribing, during hospitalization, using PIM-Check.[30] These studies did not evaluate the impact of PIM-Check on clinical outcomes.

In our study, PIM-Check did not detect a proportion of PI with low (null or minor) and important (moderate or major) clinical impact. If it is acceptable to exclude those with low impact (CL $<$ 2) to increase specificity and decrease superfluous alerts, PIs with high impact (CL $\geq$ 2) should be detected by explicit tools to raise sensitivity and increase patient safety. Thus, additional criteria enabling the detection of some types of interventions could be added to improve the clinical impact of the explicit tool. If it is obvious that an explicit tool cannot generate PIs related to "information to caregivers" and "clarification in the patient record" (**Table 3**), these PIs remain significant, which reinforces the need for pharmacists in hospital services. Other types of PI could be easily added to an explicit tool, especially because it is built on an electronic support. Our study identified 3 types of PIs associated to a high undetection rate and important clinical impact using PIM-Check: "dose adjustment," "overprescribing," and "therapy monitoring." These 3 types constitute 59% of the PIs graded $\geq$ 2C not detected by PIM-Check (51 PIs among 86 PIs).

PIM-Check detected a relatively low percentage of PIs (31%). PIM-Check detected a minority in all types of PI (**Table 3**), except in "therapy initiation," it detected the majority (17 vs 5). This could be explained by the fact that PIM-Check tool targets preferentially underprescribing (prescribing omission) and thus tends by design to recommend treatment initiation.[28]

This study had some strength because it is the first study that identified missed PIs with an explicit tool, and classified them according to their types and impact but had some limitations, too. First, the study design did not allow us to evaluate the impact (using CLEO) of interventions "detected by PIM-Check" but missed by the pharmacist. Second, the observational and retrospective nature of the study did not allow us to assess the added potential benefit of using PIM-Check by a clin-

ical pharmacist (prospectively), on prevalence of pADEs and on pharmacoeconomics.

Conclusions

This study shows that PIs have a significant clinical impact and hence are essential in preventing patient harm related to prescribing errors. The electronic, explicit tool PIM-Check did not detect a significant proportion of PIs of moderate or major clinical impact. The risk of underdetection associated with the inherent characteristics of explicit tools should be carefully assessed in clinical settings. However, PIM-Check and other such tools can be viewed as a supportive approach for the systematic evaluation of medication in reducing time and cost of pharmaceutical management.

Acknowledgments

The authors thank Maissa Issa, B.Comm. for English editing.

Author contribution statements

Study design was conducted by A. Farhat, R. Abou-Karroum, A. Panchaud, C. Csajka, and A. Al-Hajje; data collection conducted by R. Abou-Karroum; data analysis was conducted by A. Farhat and R. Abou-Karroum; drafting of the manuscript was conducted by A. Farhat; and revision of the manuscript was conducted by A. Farhat, R. Abou-Karroum, A. Panchaud, C. Csajka, and A. Al-Hajje.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

1. Société Française de Pharmacie Clinique. Dictionnaire français de l'erreur médicamenteuse. [1ère édition]. Available from: http://www.optimiz-sih-circ-med.fr/documents/dictionnaire_sfpc_em.pdf. Accessed January 11, 2021.
2. Assiri GA, Shebl NA, Mahmoud MA, Aloudah N, Grant E, Aljadhey H, et al. What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature. *BMJ open*. 2018;8(5).
3. Al-Hajje A, Awada S, Rachidi S, Chahine NB, Azar R, Zein S, et al. Medication prescribing errors: data from seven Lebanese hospitals. *Le Journal medical libanais The Lebanese medical journal*. 2012;60(1):37–44.
4. Boeker EB, Ram K, Klopotowska JE, de Boer M, Creus MT, de Andres AL, et al. An individual patient data meta-analysis on factors associated with adverse drug events in surgical and non-surgical inpatients. *British journal of clinical pharmacology*. 2015;79(4):548–557.
5. Desnoyer A, Blanc AL, Pourcher V, Besson M, Fonzo-Christe C, Desmeules J, et al. PIM-Check: development of an international prescription-screening checklist designed by a Delphi method for internal medicine patients. *BMJ open*. 2017;7(7).
6. Di Giorgio C, Provenzani A, Polidori P. Potentially inappropriate drug prescribing in elderly hospitalized patients: an analysis and comparison of explicit criteria. *International journal of clinical pharmacy*. 2016;38(2):462–468.
7. Hudhra K, Garcia-Caballos M, Casado-Fernandez E, Jucja B, Shabani D. Bueno–Cavanillas A. Polypharmacy and potentially inappropriate prescriptions identified by Beers and STOPP criteria in co-morbid older patients at hospital discharge. *Journal of evaluation in clinical practice*. 2016;22(2):189–193.
8. Mark SM, LJ Geller S, Weber RJ. *Pharmacotherapy: a pathophysiologic approach 8e*. Principles and practices of medication safety. New York: McGraw-Hill; 2011.
9. Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *The American journal of medicine*. 1996;100(4):428–437.
10. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. *Archives of internal medicine*. 2003;163(17):2014–2018.
11. Bright JM, Tenni PC. The clinical services documentation (CSD) system for documenting clinical pharmacists' services. *Aust J Hosp Pharm*. 2000;30:10–15.
12. Blassmann U, Morath B, Fischer A, Knoth H, Hoppe-Tichy T. [Medication safety in hospitals: Integration of clinical pharmacists to reduce drug-related problems in the inpatient setting]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*. 2018;61(9):1103–1110.
13. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Archives of internal medicine*. 2006;166(9):955–964.
14. Farhat A, Al-Hajje A, Csajka C, Panchaud A. Clinical and economic impacts of explicit tools detecting prescribing errors: A systematic review. *J Clin Pharm Ther*. 2021;46(4):877–886 Epub 2021 Mar 25PMID:33765352 . doi:10.1111/jcpt.13408.
15. Hôpitaux Universitaires de Genève, Université de Genève. PIM Check. [v1.2; 26.09.2016]. Available from: http://pimcheck.org/. Accessed July 20, 2018.
16. Lang PO, Farhat A, Csajka C. [Optimizing one's prescriptions: Which approach, which tool to use?]. *Rev Geriatr*. 2017;42(4):207–218.
17. Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, et al. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. *Drugs & aging*. 2014;31(4):291–298.
18. Pazan F, Burkhardt H, Frohnhofen H, Weiss C, Throm C, Kuhn-Thiel A, et al. Changes in prescription patterns in older hospitalized patients: the impact of FORTA on disease-related over- and under-treatments. *European journal of clinical pharmacology*. 2018;74(3):339–347.
19. Farhat A, Al-Hajje A, Rachidi S, Zein S, Zeid MB, Salameh P, Bawab W, Awada S. Risk factors and quality of life of dyslipidemic patients in Lebanon: A cross-sectional study. *J Epidemiol Glob Health*. 2016 Dec;6(4):315–323. doi:10.1016/j.jegh.2016.10.001.
20. Vo TH. *Evaluation of the potential impact of pharmacist interventions: development and validation of the CLEO multidimensional tool* [PhD thesis]. Université Grenoble Alpes; 2015.
21. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. *ATC/DDD index*; 2019 Available from: *http://www.whocc.no/atc_ddd_index/* Accessed november 10, 2019.
22. Maes KA, Tremp RM, Hersberger KE, Lampert ML. Demonstrating the clinical pharmacist's activity: validation of an intervention oriented classification system. *International journal of clinical pharmacy*. 2015;37(6):1162–1171.
23. Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. *Pharmacy world & science: PWS*. 2006;28(4):181–188.
24. Pharmaceutical Care Network Europe. Classification for drug related problems V6.2. 2010. Available from: http://www.pcne.org/upload/files/11_PCNE_classification_V6-2.pdf. Accessed January 11, 2021.
25. McHugh ML. Interrater reliability: the kappa statistic. *Biochemia medica*. 2012;22(3):276–282.
26. Mongaret C, Quillet P, Vo TH, Aubert L, Fourgeaud M, Michelet-Huot E, et al. Predictive factors for clinically significant pharmacist interventions at hospital admission. *Medicine*. 2018;97(9):e9865.
27. Hannou S, Voirol P, Pannatier A, Weibel ML, Sadeghipour F, von Gunten A, et al. Pharmacist intervention acceptance for the reduction of potentially inappropriate drug prescribing in acute psychiatry. *International journal of clinical pharmacy*. 2017;39(6):1228–1236.
[61]. Farhat A, Panchaud A, Al-Hajje A, Lang PO, Csajka C. Ability to detect Potentially Inappropriate Prescriptions in older patients: Comparative analysis between PIM-Check and STOPP/STARTv2. *European journal of clinical pharmacology*. 2021;77(11):1747–1756 Epub 2021 Jun 30. PMID: 34191107; PMCID: PMC8528795. doi:10.1007/s00228-021-03171-4.
29. Blanc AL, Spasojevic S, Leszek A, Théodoloz M, Bonnabry P, Fumeaux T, et al. A comparison of two tools to screen potentially inappropriate medication in internal medicine patients. *J Clin Pharm Ther*. 2018 Apr;43(2):232–239. doi:10.1111/jcpt.12638.
30. Blanc AL, Guignard B, Desnoyer A, Grosgurin O, Marti C, Samer C, et al. Prevention of potentially inappropriate medication in internal medicine patients: A prospective study using the electronic application PIM-Check. *J Clin Pharm Ther*. 2018 Dec;43(6):860–866. doi:10.1111/jcpt.12733.