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PIM-Check: development of an international prescription-screening checklist designed by a Delphi method for internal medicine patients

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ABSTRACT

Objectives Potentially inappropriate medication (PIM) occurs frequently and is a well-known risk factor for adverse drug events, but its incidence is underestimated in internal medicine. The objective of this study was to develop an electronic prescription-screening checklist to assist residents and young healthcare professionals in PIM detection.

Design Five-step study involving selection of medical domains, literature review and 17 semistructured interviews, a two-round Delphi survey, a forward/back-translation process and an electronic tool development.

Setting 22 University and general hospitals from Canada, Belgium, France and Switzerland.

Participants 40 physicians and 25 clinical pharmacists were involved in the study. Agreement with the checklist statements and their usefulness for healthcare professional training were evaluated using two 6-point Likert scales (ranging from 0 to 5).

Primary and secondary outcome measures Agreement and usefulness ratings were defined as: >65% of the experts giving the statement a rating of 4 or 5, during the first Delphi-round and >75% during the second.

Results 166 statements were generated during the first two steps. Mean agreement and usefulness ratings were 4.32/5 (95% CI 4.28 to 4.36) and 4.11/5 (4.07 to 4.15), respectively, during the first Delphi-round and 4.53/5 (4.51 to 4.56) and 4.36/5 (4.33 to 4.39) during the second (p<0.001). The final checklist includes 160 statements in 17 medical domains and 56 pathologies. An algorithm of approximately 31 000 lines was developed including comorbidities and medications variables to create the electronic tool.

Conclusion PIM-Check is the first electronic prescription-screening checklist designed to detect PIM in internal medicine. It is intended to help young healthcare professionals in their clinical practice to detect PIM, to reduce medication errors and to improve patient safety.

Strengths and limitations of this study

- A screening checklist for potentially inappropriate medication detection in internal medicine patients was developed by an international and multidisciplinary panel of experts, using a validated consensus method.
- Results from this study should be robust, because the number of experts involved in the Delphi survey and the participation rate were high (n=40 experts and 97.5%, respectively) and the reliability of a Delphi survey is directly proportional to the size of the expert group.
- As participants involved in this study came from French-speaking countries, further work will be needed to assess the effectiveness of the English version of the tool in non-French-speaking areas.

BACKGROUND

Improving medication safety and optimising drug prescribing are fundamental to patient safety and are priority goals of healthcare systems worldwide.[1 2] Drug-related problems (DRPs) defined as an event or circumstance involving a patient's drug treatment that actually or potentially interferes with the achievement of an optimal outcome are common in internal medicine: approximately 80% of the inpatients have at least 1 DRP, with a mean of 2–3 DRPs per patient.[3–7] DRPs include subtherapeutic dosage, failure to receive drugs, adverse reactions and potentially inappropriate medication (PIM), defined as the prescribing of medications without a valid indication or with a contraindication (overprescription); failure to prescribe a clinically indicated drug (underprescription); the occurrence of unwanted drug–drug or drug–disease interactions or the incorrect prescribing of an indicated drug (misprescription), such as duplicate prescribing, inappropriate follow-up and incorrect medication dose or duration.[8] PIM is a well-known risk factor for adverse drug events and is therefore a source of morbidities

and sometimes mortality, imposing clinical and economic burdens on patients and healthcare systems.[9]

Many prescription-screening checklists, such as the Beers Criteria (North America),[10–14] the Assessing Care of Vulnerable Elders indicators (United States),[15 16] a set of criteria developed in Australia[17] and the STOPP/START criteria (Europe),[18 19] have been developed to detect PIM in geriatric patients.[8 20–22] Application of STOPP/START combined with education of physicians and pharmacists has been shown to be effective in minimising PIM in this population.[23] However, no such checklist has been developed for general internal medicine patients. Nevertheless, multimorbidity and polypharmacy are frequent in this population[4–7] and are independent risk factors for the occurrence of DRPs, whereas age is not.[4 24] Geriatric checklists can be used for patients admitted in internal medicine, but such checklists are often much more focused on geriatric pathologies, not necessarily relevant in internal medicine (eg, dementia and Alzheimer's disease). Some pathologies and interventions commonly encountered in internal medicine are almost never covered by geriatric checklists (eg, obesity, contraception, infectious diseases, transplantation, renal failure and neuropathic pain).

Therefore, we have developed a new international electronic prescription-screening checklist for use with adults in general internal medicine. Specifically, we adapted the approach used by Gallagher *et al*[18] with the aim of achieving an international, multidisciplinary consensus on a checklist of statements that includes all types of PIMs, covers pathologies commonly observed in internal medicine and is available as an electronic version to assist and train junior healthcare professionals, in PIM detection in their daily practice and to improve medication safety.

METHODS

This study was split into five steps (figure 1).

First step: Selection of medical domains

A multidisciplinary international research group consisting of four internists, five clinical pharmacists, and three clinical pharmacologists from France and Switzerland was constituted to supervise the project. The group was responsible for selecting the medical domains (eg, medical specialties and medical acts, such as vaccinations and transplants) and subdomains (including pathologies, therapeutic classes and medical procedures (eg, prevention/prophylaxis, analgesia)) to be addressed in the draft version of the checklist. Selections of medical domains and subdomains were based on the main diseases observed in patients admitted to internal medicine,[25] the therapeutic classes associated with adverse drug events in these patients,[7] the Institute for Safe Medication Practices' list of high-alert medications that includes drugs that bear an increased risk of causing significant patient harm when they are used in error[26] and some of the pathologies included in previously published geriatric prescription-screening checklists.[20 22 25 27] AD led the project and is the principal investigator in this study.

Second step: Literature reviews, semistructured interviews and draft criteria agreement

During this step, statements of potential interest for a prescription-screening checklist dedicated to adults

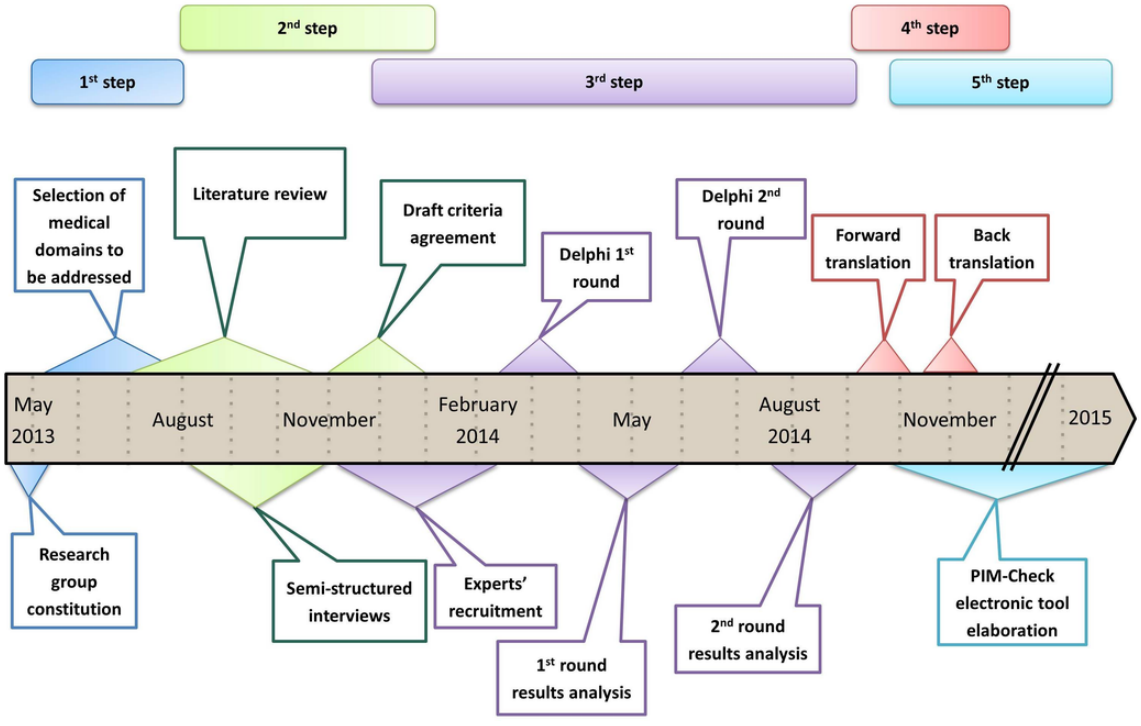

Figure 1 Study workflow.

in internal medicine (excluding pregnant women and inpatients with low life expectancy or requiring palliative care) were identified and selected for inclusion in the draft checklist.

Literature reviews and semistructured interviews

For each medical domain and subdomains selected during the first step, an extensive literature review of evidence-based optimal and inappropriate medication prescriptions was conducted. It preceded a semistructured interview, with a specialist physician of the domain to be addressed during the interview, working in the Geneva University Hospitals. The literature review process is detailed in the online supplementary appendix 1. Each interview comprised four parts: (1) project presentation, (2) presentation of statements previously published in geriatric prescription-screening checklists and statements related to the medical field addressed during the interview, (3) submission to the specialist of the pathologies and statements formulated during the literature review and (4) suggestions by the specialist of pathologies and statements to be added to the draft version. The semistructured interview topics and guide are provided in the online supplementary appendix 1 and supplementary table 1.

Draft criteria agreement

After semistructured interviews, redundant statements related to two or more domains and validated by at least two medical specialists were merged and the formulation of each remaining statement was standardised by the principal investigator. Finally, the statements were submitted to five members of the research group—three internists, one clinical pharmacist and one clinical pharmacologist—who anonymously rated the usefulness of the statements for practice in internal medicine by using a 5-point Likert scale ranging from 1 (not useful at all) to 5 (very useful). Statements with a mean rating greater than or equal to 3 were retained for the next step.

Third step: Delphi study

A two-round Delphi method was used to generate a consensual validation of the statements that were included in the draft checklist (figure 2).

Experts' recruitment

To represent the views of the professional groups engaged in medication management in internal medicine, a panel of experts in French-speaking countries was recruited in roughly equal numbers by profession (internists and clinical pharmacists with a practice in internal medicine), hospital teaching status (university

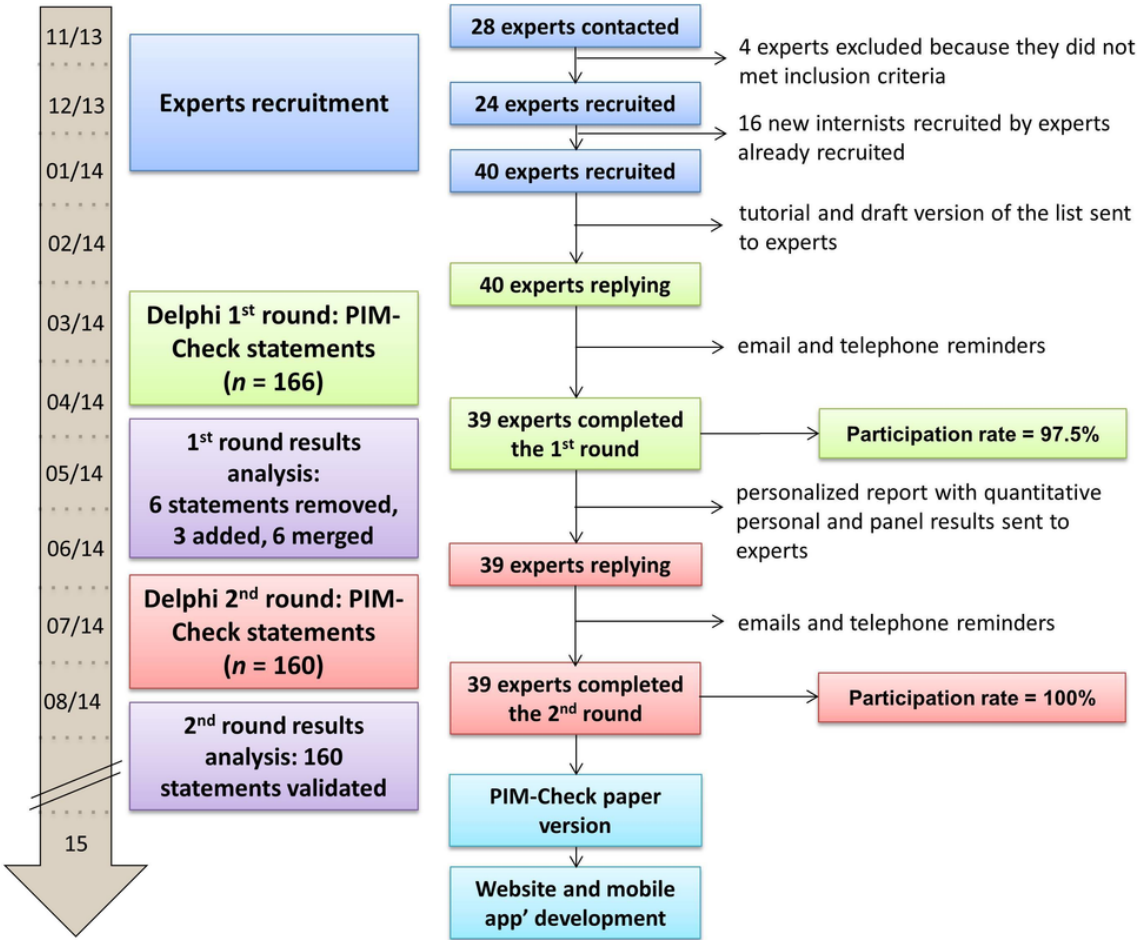

Figure 2 Delphi flowchart.

and non-teaching hospitals) and country (Canada (Québec), Belgium, France and Switzerland). The recruitment process is described in the online supplementary appendix 1.

Delphi rounds

We used the SurveyMonkey website to conduct the Delphi survey. As detailed in the online supplementary appendix 1, 1 week before each round, experts received by email the relevant documents to validate statements. For each round, the experts had to indicate their level of agreement with each statement using a 6-point Likert scale: 0, no opinion; 1, strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree and 5, strongly agree. Using a second 6-point Likert scale, ranging from 1 (not useful at all) to 5 (very useful) (0, no opinion), the experts also had to rate the usefulness of each statement for daily practice and for training of students, residents and young healthcare professionals in internal medicine or clinical pharmacy. Finally, the experts were invited to add propositions including comments, modifications, references and useful links to each statement.

In accordance with previous studies, we used the following two validation rules. Statements that received the agreement (rating 4 or 5) of more than 65% of the experts after the first round were retained, were eventually modified according to the experts' comments and were subjected to the second round.[28 29] Statements with a lower percentage of experts' agreement were excluded (ie, ≤65% of the experts rating 4 or 5 the statement). After the second round, only statements that received the agreement of more than 75% of the experts were retained for the final version of the checklist. The usefulness rating was considered a secondary endpoint and was not used to exclude statements. The expected durations of the first and second rounds were 3 and 2 weeks, respectively. For each round, reminders were sent to the experts, as described in the online supplementary appendix 1.

Integration of experts' propositions

To reduce potential bias due to a single person doing all the data management, we used investigator triangulation to integrate comments and propositions from the experts.[30] This triangulation process is detailed in the online supplementary appendix 1.

Fourth step: Forward/back-translation process

A forward/back-translation process was applied to translate the checklist in English.[31] Briefly, the checklist was forward-translated into English by a bilingual native-English-speaking physician from Elsevier Translation Service who was familiar with French-speaking culture and with the terminology of internal medicine. Then, a bilingual native-French-speaking internist back-translated the checklist into French. Finally, three members of the research group identified and resolved any instances of inadequate expression between the back translation and the original version.

Fifth step: Electronic tool development

To facilitate the use of the tool in daily practice, an electronic version was created. A web-designer and a webmaster were involved in the development of a website and a web-mobile application. A 'Screening' function, allowing to select for a specific patient, his/her comorbidities and/or medications and to present only relevant statements, a 'Favourite' function to give quick access to statements identified as favourite and a 'Learning' function to allow users to follow their progress in the acquisition of recommendation knowledge were included in the application. To develop the 'Screening' function, members of the research group identified medications, and corresponding anatomical therapeutic chemical code, from Belgium, France, Quebec and Switzerland, using national databases.[32–35] A dictionary of synonyms of subdomains included in the tool was also created. Then, an algorithm combining each validated statement with corresponding subdomains and medications was developed.

Statistical methods

Analyses were performed with Prism 6 software (GraphPad Software, San Diego, California, USA). Variables were summarised as numbers (percentages) for categorical variables, the mean and 95% CI for continuous variables. During each Delphi round and for each statement, the mean agreement rating, the mean usefulness rating, the percentage of experts who rated each statement as 4 or 5, the participation rate and the mean number of experts who responded with 'no opinion' (0) were evaluated. For each statement, the mean agreement and usefulness ratings were compared between the first and the second rounds using Mann–Whitney tests. p Values are two-tailed, with a significance level of 0.05.

Ethics considerations

The Swiss Law on Medical Research Involving Human Subjects did not require us to seek ethical approval as no participation by patients or use of patients' data, human tissue or animals were involved in this study.

RESULTS

First and second steps

The principal investigator conducted 17 semistructured interviews, one each with 17 specialist physicians. Seventeen medical domains and 69 subdomains associated with pathologies, therapeutic classes, medical procedures and DRPs commonly observed in internal medicine were identified. After the semistructured interviews and suppression or merging of redundant statements, 187 statements remained. Among them, 21 mean ratings were less than 3 (2.44 (2.33 to 2.55)) and were considered to be not useful for practice in internal medicine. These statements were excluded from the draft checklist (eg, statements related to sleep apnoea, cystic fibrosis, polymyalgia rheumatica and myasthenia gravis). The remaining 166 statements involved 17 medical domains and 65

Table 1 Characteristics of Delphi panel of experts

Characteristic	
Sex: male/female, n (%)	23 (57.5%)/17 (42.5%)
Profession: n (%)	
Internist	20 (50%)
Clinical pharmacist	20 (50%)
Years of professional experience: median (CI)	9 (4–14)
Teaching status of hospital: n (%)	
University hospital	23 (57%)
Non-teaching hospital	17 (43%)
Country of expert: n (%)	
Belgium	9 (22.5%)
France	13 (32.5%)
Canada (Québec)	8 (20%)
Switzerland	10 (25%)

subdomains that received a mean usefulness rating of 3.99/5 (3.89 to 4.08).

Third step: Delphi survey

Forty experts from 22 hospitals met the inclusion criteria and agreed to join the Delphi survey (table 1). During the first round, participation rate was 97.5% (39/40). A median of 37 (IQR 25%–75%: 36–38) experts rated their agreement for each statement, with a median of 2 experts with 'no opinion' per statement. Only one statement was evaluated by fewer than 30 experts (n=28); because this statement completed the first-round validation rule, it was clarified and modified according to the experts' comments and submitted for the second round of Delphi. The mean agreement and usefulness rating were 4.32/5 (95% CI 4.28 to 4.36) and 4.11/5 (4.07 to 4.15), respectively according to the 0–5 Likert scales. Six statements were removed according to the validation rule for the first round (table 2). Of the 166 statements evaluated in the first Delphi round, 152 (91.5%) were rated by more than 65% of the experts as useful or very useful for the training of students, residents and young healthcare professionals in internal medicine and clinical pharmacy. The experts made 677 comments, which led the investigator triangulation group to add 3 new statements, modify 84, and merge 3 pairs of statements. The remaining 160 statements were retained and subjected to the second round.

All the experts who completed the first round completed the second round (participation rate 100% (39/39)). They rated their level of agreement for 100% of the statements, without selecting the 'no opinion' option. The mean agreement and usefulness ratings were 4.53/5 (95% CI 4.51 to 4.56) and 4.36/5 (4.33 to 4.39), respectively (see online supplementary table 1). Both ratings were higher than the corresponding ratings from the first round (p<0.001). After the second round, all 160 submitted statements were validated according to validation rule for this round. Of these statements, 156 (97.5%) were rated as useful or very useful by more than 75% of the experts (see online supplementary table 2). During the second round, the experts made 399 propositions and on the basis of these propositions, 74 statements were clarified.

The final checklist includes 160 statements, divided into 17 medical domains and 52 subdomains (table 3). Seventy-four (46%) statements are related to underprescription,

Table 2 Statements rejected by the expert panel during the first round of the Delphi survey

Type of PIM	Medical domain and subdomain	Rejected statement	Proportion of experts who agreed or strongly agreed with the statement (%)
Underprescription	Cardiology: Dyslipidaemia and hypolipidemics	Prescribe fibrates as a first-line treatment in case of isolated hypertriglyceridaemia when pharmacological treatment is necessary*	56.4
Overprescription	Pneumology: Chronic respiratory diseases	Avoid prescribing BZD or opiates in patients with chronic respiratory disease when an alternative is available or monitor respiratory function closely	63.2
Underprescription	Nephrology: Renal failure	Prescribe or continue treatment with statins in patients with chronic renal failure*	57.1
Other	Neurology: Epilepsy and antiepileptics	When possible, keep the same antiepileptic brand name in hospitalised patients or re-evaluate treatment with a specialist	55.3
Underprescription	Psychiatry: Insomnia, sedatives and hypnotics	Prescribe BZD or a BZD-like drug as a first-line treatment in case of insomnia when pharmacological treatment is necessary	57.9
Overprescription	Psychiatry: Insomnia, sedatives and hypnotics	Avoid prescribing drugs that may exacerbate insomnia* in patients with chronic insomnia	53.8

*Additional information provided to experts.

Table 3 Final list of statements included in PIM-Check

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine

This tool is designed for quick detection of underprescription: UP, overprescription: OP, drug interaction: DDI or other kind of potentially inappropriate medications (eg, therapeutic adaptations, treatment re-evaluations, improper drug use): OTH, that may be dangerous for patients hospitalised in internal medicine (excluding pregnant women and patients with low life expectancy or requiring palliative care).
It is organised by major physiological systems and pathologies.
This is not a replacement for a clinical and biological evaluation by a clinician. The proposals are only applicable in the event there is no patient-specific contraindication.
This tool was validated using a Delphi method including 40 international experts from Belgium, France, Québec and Switzerland.
Some drugs listed may not be available in each country.

CARDIOLOGY	
Heart failure	
1 UP	Start ACEI or ARB Prescribe or continue long-term ACEI treatment in patients with HF (or ARB in case of intolerance)
2 UP	Start beta-blocker treatment Prescribe or continue long-term beta-blocker treatment* in patients with HF
3 UP	Start aldosterone antagonist when LVEF≤35% despite optimal treatment Consider prescribing an aldosterone antagonist in HF patients with LVEF≤35% despite treatment with ACEI, or ARB and beta-blocker at the recommended or maximum tolerated doses
4 OP	Drugs that may exacerbate HF Avoid prescribing drugs* that may exacerbate HF, drugs that are rich in sodium** and antiarrhythmics (except for digoxin and amiodarone) in HF patients
Dyslipidaemia and hypolipidemics	
5 UP	Dyslipidaemia and high cardiovascular risk: start statins Prescribe or continue treatment with statins in patients with a high cardiovascular risk or adapt lifestyle and dietary measures and the treatment intensity based on that risk (moderate, high or very high)
6 UP	Dyslipidaemia, hypercholesterolaemia: start statins as a first-line treatment Prescribe statins as a first-line treatment in case of mixed dyslipidaemia or hypercholesterolaemia when pharmacological treatment is necessary*
7 DDI	Statins and DDI Evaluate the risk of DDIs and adapt the treatment if statins are introduced or if treatment is modified in patients receiving statins
8 OP	Avoid combining statins and fibrates Avoid combining statins and fibrates and prohibit the statin/gemfibrozil combination
Stable ischaemic heart disease	
9 UP	Start beta-blocker treatment Prescribe or continue beta-blocker treatment in patients with ischaemic heart disease
10 UP	Start low-dose aspirin Prescribe or continue treatment with low-dose aspirin in patients suffering from ischaemic heart disease (when there is no contraindication*)
11 UP	Start statins Prescribe or continue statins in patients suffering from stable ischaemic heart disease
Secondary prevention of acute STEMI or NSTEMI	
12 Other	Start lifestyle and diet modifications Encourage patients having undergone a STEMI or NSTEMI to participate in a secondary prevention programme, specifically aiming to adapt their diet, control their weight, engage in physical activity, stop smoking and improve compliance with treatment
13 UP	Start beta-blocker treatment Prescribe or continue long-term beta-blocker treatment after a STEMI or NSTEMI
14 UP	Dual antiplatelet therapy? Prescribe or continue treatment by dual antiplatelet therapy for up to 12 months after a STEMI or NSTEMI, followed by long-term antiplatelet monotherapy (first-line treatment = low-dose aspirin)

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
15 UP	Start statins Prescribe or continue statins after STEMI or NSTEMI
16 UP	Start ACEI or ARB Prescribe or continue treatment with ACEI for at least 30 days following a STEMI or NSTEMI and then, on a long-term basis, in particular in the presence of an aggravating factor* (or an ARB in case of intolerance)
	High blood pressure
17 UP	Start antihypertensive drug treatment Begin antihypertensive drug treatment with a first-line drug* alone or in combination if pharmacological treatment of BP is necessary**. Combine it with lifestyle and diet modifications***
18 Other	Favour ACEI or ARB in patients with diabetes/CKD/HF/STEMI/NSTEMI and HBP Favour an ACEI or ARB combined or without another first-line antihypertensive drug to treat high BP in patients with diabetes or in patients with microalbuminuria/proteinuria, CKD, HF or history of STEMI or NSTEMI
19 UP	Resistant high BP Seek a secondary cause of high BP and then optionally add an aldosterone antagonist*, amiloride or an alpha 1 blocker in case of true resistant HTN**
20 OP	Drugs that can exacerbate high BP Exercise caution in using drugs that may increase BP* or that are rich in sodium** in patients with high BP
21 OP	Avoid loop diuretic as a first-line treatment Do not prescribe a loop diuretic as a first-line treatment to treat high BP
	Non-cardioembolic stroke and transient ischaemic attacks
22 UP	Start statins Prescribe statins in patients with non-cardioembolic and non-haemorrhagic TIA or stroke
23 UP	Start antiplatelet therapy Prescribe a preventive antiplatelet therapy* in patients with non-cardioembolic and non-haemorrhagic TIA or stroke
	Arrhythmias, atrial fibrillation and antiarrhythmics
24 Other	Adjust digoxin dose Reduce or adjust digoxin dose depending on the digoxin serum levels in elderly patients or patients with renal failure; favour an alternative when possible
25 DDI	Digoxin and DDIs Evaluate the risk of DDIs and adapt treatment in case new treatment is introduced in a patient receiving digoxin (in particular with Pgp inhibitors)
26 UP	Start oral anticoagulation Prescribe or continue oral anticoagulation* in patients suffering from non-valvular AF whose CHA_2DS_2-VASc** is≥1. In case of treatment with VKA, adapt the doses to obtain an INR between 2 and 3
	ANGIOLOGY/HAEMOSTASIS
	Oral anticoagulants
27 Other	Anticoagulation: start patient education Provide patient education for patients receiving oral anticoagulation (or the caregiver)
28 Other	Anticoagulation: prevent the inappropriate administration of anticoagulant Verify the appropriateness of the administration for an oral anticoagulant taken by a patient (dosage, frequency and time of administration) with the indication, the usual treatment and the prescribed molecule (in particular for DOACs: the number of doses/day and the administration conditions)
29 Other	VKAs: Vitamin K1 administration Favour the OR in case of VKA overdose requiring the administration of Vitamin K1. Favour low doses (1–5 mg) when there is VKA overdose with no bleeding or minor bleeding but requiring the administration of Vitamin K1
30 OP	Switching from VKA to DOAC Consider a DOAC switch in patients who were already treated with VKA only if the INR is not kept in the target zone despite monitoring and correct observance or in case of intolerance. Continue VKA treatment if the latter is effective and well tolerated

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
31 Other	Anticoagulation and renal function Evaluate renal function* and adjust the doses to the CrCl if a DOAC is introduced in a patient. Favour VKA treatment if the CrCl is<30 mL/min
32 DDI	Anticoagulation and DDIs Evaluate the risk of DDIs* and adapt the treatment if a new drug is introduced in patients receiving an oral anticoagulant
Deep vein thrombosis, pulmonary embolism, venus thromboembolism	
33 UP	DVT/PE: start anticoagulation Prescribe or continue anticoagulation for at least 3 months* in case of proximal DVT and/or PE. In case of treatment with VKA, adapt the doses to obtain an INR between 2 and 3
34 UP	Idiopathic VTE: start anticoagulation Prescribe or continue anticoagulation for at least 3 months or long term with annual re-evaluation in case of idiopathic VTE or with a major persistent risk factor*
35 UP	DVT/PE/VTE: start prophylactic anticoagulation Prescribe prophylactic anticoagulation* in patients who are hospitalised for acute medical affection for an anticipated duration of>3 days and with a high risk of thrombosis** and/or in patients who are hospitalised for surgical procedure with a moderate or high risk of thrombosis
PNEUMOLOGY	
Chronic respiratory diseases	
36 Other	New inhalation drug delivery device: start patient education Provide individualised patient education (or caregiver) if a new inhalation drug delivery device is prescribed and ensure that it is used properly
37 Other	Use of the holding chamber Favour the use of a holding chamber for the administration of products in a metered-dose inhaler in the event of worsening chronic respiratory disease or poor hand-lung coordination
38 Other	ICS mode of administration Favour taking ICS before meals and rinse out the mouth and gargle or brush teeth after inhalation
39 Other	Caution with non-cardioselective beta-blocker Favour a cardioselective beta-blocker* when it is indicated in patients with asthma or COPD
Asthma	
40 UP	Asthma and long-term treatment: start ICS as a first-line treatment Prescribe, as a first-line treatment, low-dose ICS in patients with mild persistent asthma* requiring background treatment
41 OP	Asthma and long-term treatment: avoid long-acting beta2-agonists as a first-line treatment or as monotherapy Do not prescribe as first-line treatment or as monotherapy a long-acting beta2-agonists to treat asthma
42 UP	Asthma and long-term treatment: add long-acting beta2-agonists as a second-line treatments Add long-acting beta2-agonists (favoured) or increase the inhaled corticosteroid doses in patients with asthma for whom taking a low dose ofICS alone is not sufficient
Chronic obstructive pulmonary disorder	
43 UP	COPD and long-term treatment: start a beta2-agonist or anticholinergics as a first-line treatment Prescribe an inhaled bronchodilator (β2-mimetic or anticholinergics) as a first-line pharmacological treatment for COPD
44 OP	COPD and long-term treatment: avoid ICS as a first-line treatment or as a monotherapy Do not prescribe ICS as a first-line treatment and as a monotherapy to treat COPD
NEPHROLOGY	
Renal failure	
45 Other	Adjust drug doses Adjust drug doses if a new treatment is introduced in a patient with renal failure or in case of a significant modification of renal function

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
46 OP	RF: be careful with nephrotoxic drugs and or adjust doses of drugs that are excreted by the kidneys Avoid nephrotoxic drugs* and exercise caution in prescribing drugs that are excreted by the kidneys in chronic renal failure patients or patients having a pathology that may cause acute renal failure, or adjust doses and check renal function
47 UP	Correct iron deficiency before starting ESA treatment Correct any iron deficiency before starting ESA treatment and then prescribe a sufficient iron supplement* in combination with ESA treatment
48 UP	ESA and Hb target Prescribe, if needed and in collaboration with a nephrologist, an ESA in chronic renal failure patients with a Hb level<10 g/dL or bothersome symptoms, despite sufficient iron supplementation. The Hb target is approximately 11.5 g/dL (between 10 and 12 g/dL) while avoiding exceeding 12 g/dL
49 UP	Calcium, vitamin D and/or phosphate-binding agents Continue or adjust calcium, vitamin D supplementation and/or phosphate-binding agents (to be taken with food) in chronic renal failure patients
50 UP	Start ACEI or ARB Prescribe or continue treatment with ACEI or ARB in chronic renal failure patients with albuminuria* or chronic renal failure patients with diabetes and microalbuminuria**
	Benign prostatic hyperplasia
51 OP	Drugs that may exacerbate BPH Avoid anticholinergic* or sympathomimetic drugs in patients with BPH or use with caution and under monitoring
	GASTROENTEROLOGY
	Peptic ulcer disease and proton pump inhibitors
52 OP	Peptic ulcer disease prevention: PPI treatment started before hospitalisation Re-evaluate the continuation of PPI treatment that started more than 8 weeks before hospitalisation
53 OP	PPI treatment started during hospitalisation Stop PPI treatment before patient discharge if that treatment started during hospitalisation to prevent bleeding
54 OP	PPI re-evaluate treatment dose and duration Do not exceed a dose equivalent* to 20 mg/day of oral esomeprazole if empiric PPI treatment is started during hospitalisation and do not extend past 8 weeks without gastroenterologist opinion or endoscopic evaluation
55 OP	PPI: prescription with no valid indication Do not prescribe a PPI to prevent lesions that are caused by taking NSAIDs, CS or aspirin alone in the absence of a risk factor*
56 OP	Be careful with drugs that may exacerbate ulcer disease Avoid prescribing drugs that may cause digestive bleeding* in patients suffering from peptic ulcer disease or make sure that it is combined with a PPI
	Hepatic impairment and cirrhosis
57 OP	Hepatic impairment and cirrhosis: avoid or adjust doses of hepatotoxic drugs or of drugs that are metabolised by the liver Avoid the use or adjust doses of potentially hepatotoxic drugs or of drugs that are metabolised by the liver* when started in patients with hepatic impairment
58 UP	Hepatic encephalopathy: lactulose and lactitol Consider prescribing disaccharides that are not generally absorbable at high doses in patients suffering from hepatic encephalopathy
	Diarrhoea
59 OP	Diarrhoea without investigation: avoid antimotility agents Do not use antimotility agents* in case of mucohaemorrhagic diarrhoea, diarrhoea combined with high fever or postantibiotic diarrhoea without additional investigation
60 Other	Testing for *Clostridium difficile* infection Systematically look for a *C difficile* infection in case of nosocomial diarrhoea (>72 hour), postantibiotic diarrhoea or diarrhoea with no other aetiology

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
61 UP	Treatment of Clostridium difficile infection Prescribe as a first-line treatment for a first episode of Clostridium difficile infection: ► metronidazole (OR or intravenous), in the case of a mild to moderate episode ► vancomycin (OR), in the case of a severe episode
	Constipation
62 OP	Drugs that may exacerbate constipation Avoid or use with caution drugs that may cause iatrogenic constipation* in patients suffering from constipation, or monitor and treat any aggravation
	RHEUMATOLOGY
	Gout
63 UP	Acute gout: NSAID and/or colchicine or glucocorticoid as a first-line treatment Prescribe as a first-line treatment an NSAID and/or oral colchicine or even a glucocorticoid* to patients suffering from acute gout
64 UP	Gout and long-term treatment: start allopurinol as a first-line treatment Prescribe allopurinol as a first-line treatment to patients for whom pharmacological treatment seeking to reduce uric acid levels is necessary*
65 UP	Gout and long-term treatment initiation: add an NSAID or low-dose colchicine To avoid a gout attack, prescribe an NSAID or low-dose colchicine for the titration duration of a hypouricaemic background treatment or if the dose is changed
66 OP	Drugs that may exacerbate gout When an alternative is available, avoid or use with caution drugs that may cause an increase in uric acid levels and gout attacks* in patients suffering from gout
	Rheumatoid arthritis
67 Other	MTX and monitoring Monitor hepatic transaminases, complete blood count and renal function before starting treatment with MTX and then regularly during treatment (in particular if combined with other hepatotoxic, haematotoxic or nephrotoxic drugs*)
68 UP	MTX: start folic acid Prescribe preventive treatment with daily or weekly folic acid in patients receiving long-term MTX
69 OP	Avoid long-term CS Re-evaluate with a specialist and optionally stop long-term corticosteroid treatment in patients with RA with prolonged remission
	Corticosteroids and osteoporosis
70 Other	Long-term CS: start patient education Provide patient education* to those receiving new long-term corticosteroid treatment (or caregivers)
71 UP	Long-term CS and prevention of osteoporosis: start calcium/vitamin D Evaluate intake and prescribe calcium and vitamin D if needed to patients receiving corticosteroid treatment for an anticipated duration of≥3 months (irrespective of the dose)
72 UP	Long-term CS and prevention of osteoporosis: start bisphosphonates Prescribe bisphosphonates to patients receiving CS with an increased risk of fracture* or to patients with a high risk of osteoporosis receiving long-term CS**
73 UP	CS and bisphosphonates: prevent inappropriate administration Correct any hypercalcaemia or vitamin D deficiency* before beginning treatment with bisphosphonates. Prescribe bisphosphonates in the morning on an empty stomach** with a large glass of lowly mineralised water, separate from other medicines***, informing the patient to remain seated or standing for at least 30 min
	NEUROLOGY
	Epilepsy and antiepileptics
74 OP	Drugs that may exacerbate epilepsy Avoid or use with caution treatments that may lower the seizure threshold* in an patient with epilepsy if an alternative is available

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
75 DDI	Antiepileptic and DDIs Evaluate the risk of DDIs, and adjust the treatment if a new treatment is introduced in patients receiving antiepileptics (in particular with CYP and/or Pgp inducers/inhibitors*)
76 UP	Antiepileptic and DDIs with contraception Use effective contraception means* if possible other than combined oral or intra-vaginal contraceptives, patches and pure progestogen pills in women of childbearing age who are treated with an enzyme-inducing anti-epileptic** and who have not planned to become pregnant
	Parkinson's disease and Parkinson's medications
77 UP	Prevent the inappropriate administration of Parkinson's disease treatment Continue treatment for Parkinson's disease at the usual doses, times and dosing forms in case of hospitalisation. Adapt the dosing form and the dose in case of fasting or difficulty swallowing
78 OP	Parkinson's disease and antinausea neuroleptics: prefer domperidone Avoid using dopamine antagonist antinausea medications crossing the haematoencephalic barrier to treat nausea and vomiting in patients with Parkinson's disease. Prefer domperidone
	PSYCHIATRY
	Psychotropic illness and drugs
79 OP	Avoid prescribing two psychoactive drugs from the same therapeutic class Avoid prescribing two psychoactive drugs from the same therapeutic class without seeking a specialised opinion
	Depression and antidepressants
80 UP	Optimise the dose of an antidepressant medication if a suboptimal response is observed Do not stop an insufficiently effective antidepressant treatment before optimising the dose up to the effective dose and verifying patient observance, except in the case of side effects
81 UP	Severe depression: start SSRI as a first-line treatment Prescribe an antidepressant* with or without combining psychotherapy in patients suffering from severe depression
	Insomnia, sedatives and hypnotics
82 OP	Hypnotics: Treatment duration and re-evaluation Re-evaluate hypnotic treatment every 2 weeks and on hospital discharge. Do not stop hypnotic treatment abruptly
83 OP	Hypnotics: drugs to avoid as a first-line treatment Do not prescribe sedative neuroleptics or antihistamines as a first-line treatment for insomnia (except with specific indications)
	Schizophrenia and neuroleptics
84 DDI	Neuroleptics: Drugs that prolong the QT interval Avoid prescribing drugs that may prolong the QT interval* in patients receiving a neuroleptic, in particular if their pre-treatment QT interval is long or when there is a risk of torsade de pointes
	PAIN and ANALGESIA
	Neuropathic pain
85 UP	Neuropathic pain: start an anticonvulsant* or an antidepressant** as a first-line treatment Prescribe as a first-line treatment an anticonvulsant* or an antidepressant** to treat chronic neuropathic pain requiring pharmacological treatment
86 UP	Neuropathic pain: combine analgesics as a second-line treatment Potentially combine an opiate antalgic with a first-line drug* in case of chronic neuropathic pain after the failure of two monotherapies or a bi-therapy of first-line drugs
	Acute pain and opiates
87 UP	Start opioids in the case of acute moderate to severe pain Prescribe an opiate antalgic in the case of moderate (level 2) to severe (level 3) acute pain, preferably orally, when allowed by the patient's clinical situation (VAS>4 according to the WHO scale)
88 Other	Analgesia and opioids: switching and equianalgesic dose ratios Switch opioids* and apply the rules of equianalgesic dose ratios to determine the initial dose to be administered in patients with side effects, in case of inefficacy despite correct titration, in case of harmful drug interactions or if a change in the administration route is necessary

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
89 DDI	Combine opioids of different release rates Avoid combining two opioids with the same release kinetics or combining pure agonists–partial agonists
90 UP	Opioids: start prophylactic measures* to prevent constipation Take prophylactic measures* to prevent constipation from the start of an opioid treatment
	Migraines
91 UP	Start a triptan for patients not responding to NSAIDs +/– in combination Prescribe a triptan in the case of a migraine attack not responding to NSAIDs +/– in combination* or in case of severe migraine
92 UP	Start migraine prophylaxis Prescribe a background treatment for migraines in patients with more than two incapacitating migraines/week or very frequently using migraine medication*
	INFECTIOLOGY
	Urinary infections
93 Other	Urinary tract infection: replace the urinary catheter before starting antibiotic treatment* Remove the urinary catheter or change it before starting suitable antibiotic treatment* in patients with urinary infection with a catheter in place for more than 2 weeks
	Pulmonary-related and tuberculosis-related infections
94 UP	Pneumonia: use beta-lactam, macrolide and/or fluoroquinolone as empirical therapy Prescribed an antibiotic from the family of beta-lactam, macrolide and/or fluoroquinolone, depending on the gravity factors and local recommendations, in empirical therapy for community-acquired pneumonia in hospitalised patients
95 UP	Tuberculosis: treatment for at least 6–18 months Continue antituberculosis treatment for at least 6–18 months (depending on the location and the germ) in patients who are treated for active tuberculosis
96 OP	Anti-tuberculosis drugs: be careful with potentially hepatotoxic drugs* Avoid or use with caution potentially hepatotoxic drugs* in patients who are treated with antituberculosis drugs, and monitor the hepatic function closely
97 DDI	Rifampicin and DDIs Evaluate the risk of DDIs and favour the use of drugs not interacting* with rifampicin or adapt treatment in patients treated with rifampicin
	Abdominal infections
98 UP	Intra-abdominal infection: antibiotics covering anaerobic germs* Prescribe an antibiotic covering, in particular, anaerobic germs* as an empirical treatment of a serious acute intra-abdominal infection
	Endocarditis
99 OP	Endocarditis prophylaxis: only in patients at very high risk* and undergoing a very high-risk procedure** Prescribe preventive endocarditis treatment only in patients at very high risk* and undergoing a very high-risk procedure** for bacterial endocarditis
	Osteoarticular infections
100 UP	Osteoarticular infection: antibiotics with correct bone penetration* Prescribe a highly bioavailable antibiotic with correct bone penetration* that is suitable for the germ and its sensitivity when it is identified during an osteoarticular infection
	HIV infection
101 DDI	HIV infection: HAART and DDIs Evaluate the risk of DDIs and favour the use of drugs with no interaction with HAART, or adjust the doses if a new treatment is started in patients infected with HIV who are treated with HAART
102 UP	HIV infection and cardiovascular risk: start statins Prescribe statins to patients infected with HIV, considering the DDIs. The therapeutic objective in those patients is determined based on their cardiovascular risk level*
	Hepatitis C virus infection

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
103 DDI	HCV infection: direct-acting antivirals against HCV and DDIs Evaluate the risk of DDIs*, and adapt the treatment if a new treatment is introduced in patients infected with HCV receiving direct-acting antiviral therapy
	Hepatitis B virus infection
104 UP	HBV infection: do not suspend long-term antiviral therapy Do not suspend long-term antiviral therapy with nucleosidic analogues in patients who are infected with HBV without an evaluation by a specialist
	Prevention/prophylaxis
105 UP	Prophylaxis for *Pneumocystis jiroveci* pneumonia and bone marrow transplant Prescribe or continue prophylactic treatment against *Pneumocystis* pneumonia in patients having received a bone marrow transplant
106 UP	Prophylaxis for *P jiroveci* pneumonia and solid organ transplant Prescribe or continue prophylactic treatment against *Pneumocystis* pneumonia in patients having received a solid organ transplant and receiving immunosuppressants
107 UP	Prophylaxis for *P jiroveci* pneumonia and HIV infection Prescribe or continue prophylactic treatment against *Pneumocystis* pneumonia in patients who are HIV-infected with a CD4 count of<200 cells/mm3
108 UP	Prophylaxis for *P jiroveci* pneumonia and highly immunosuppressive drugs Consider prophylactic treatment against *Pneumocystis* pneumonia in patients receiving highly immunosuppressive treatments*
109 UP	Isoniazid and the prevention of peripheral neuropathy: start vitamin B6 Prescribe a vitamin B6 supplement in patients who are treated with isoniazid and with a risk of deficiency* or showing signs of peripheral neuropathy
	Proper use of antibiotics
110 Other	Re-evaluate empiric antibiotic treatment within 24–72 hours Re-evaluate empiric antibiotic treatment within 24–72 hours after it is started and adapt it based on the patient's clinical condition and the results of bacteriological samples
111 Other	Antibiotics through parenteral route: re-evaluate the route of administration Favour the OR* as soon as the patient's clinical condition allows it, considering the bacteriological documentation and choosing an antibiotic with good oral bioavailability*
112 OP	Proper use of antibiotics: re-evaluate the duration of therapy Re-evaluate the continuation of effective antibiotic treatment after 5–7 days. Continuation of the treatment past 10 days should be reserved for certain serious infections or situations*
113 Other	Aminoglycoside and vancomycin: therapeutic drug monitoring Monitor plasma concentrations for antibiotics with a dose-dependent toxicity* in the case of suspicion of toxicity or risk situation for toxicity** and/or in the case of risk of underdosing**. Then, adjust the dosing regimens
114 DDI	Macrolides and long QT syndrome or drugs that prolong the QT interval Exercise caution when using macrolides, in particular azithromycin, in patients with a high cardiovascular risk*, especially if combined with drugs with the potential to cause QT prolongation
115 Other	Aminoglycosides and once-daily dosing Preferably use an aminoglycoside with a once-daily dosing regimen by intravenous route (30 min perfusion) combined with another antibiotic and for a duration of≤5 days (unless there is a particular situation*)
	ENDOCRINOLOGY
	Diabetes mellitus
116 UP	DM: adjust therapy according to HbA1c targets Adjust the antidiabetic treatment in a customised manner, optionally combining several molecules, to obtain a HBA1c target that is adapted to the patient*
117 OP	DM: avoid drugs that may alter the blood glucose level* Exercise caution in using drugs that may alter the blood glucose level** in patients with diabetes and perform a close monitoring of blood glucose* in case of use
118 Other	DM: CS and blood glucose monitoring Monitor blood glucose closely if CS are introduced to patients with diabetes or patients with glucose intolerance, and optionally adjust the antidiabetic treatment

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
119 Other	DM or microalbuminuria*/proteinuria and HTN: start ACEI or ARB (nephroprotective effects) Favour an ACEI or ARB combined or not with another first-line antihypertensive drug to treat HTN in patients with diabetes or patients with microalbuminuria*/proteinuria
120 UP	DM: start statins in patients with a high or very high cardiovascular risk Prescribe or continue statins in patients with diabetes with a high or very high cardiovascular risk*
121 UP	DM: start low-dose aspirin in patients with a high cardiovascular risk or as secondary prevention Consider a low-dose aspirin treatment* in patients with diabetes with a high cardiovascular risk**. Prescribe it as secondary prevention of cardiovascular events
122 UP	T2DM: start metformin as a first-line treatment Prescribe metformin as a first-line treatment for pharmacological treatment for T2DM
123 OP	T2DM and metformin: withhold metformin in unstable conditions If necessary, withhold metformin in hospitalised patients with diabetes in unstable conditions, in case of surgery or in case of the injection of an iodine contrast product, particularly with polymorbidity or renal failure
124 Other	T2DM and sulfonylurea: monitor blood glucose in unstable conditions Monitor blood glucose closely in the case of treatment using sulfonylurea* in hospitalised patients with diabetes with unstable conditions (particularly in the case of renal failure, frequent hypoglycaemia or difficulties perceiving the signs of hypoglycaemia)
125 Other	DM and renal failure: adjust the doses of antidiabetics Monitor blood glucose and adjust the doses of antidiabetics* in the case of impaired renal function
Thyroid disorders	
126 Other	Hypothyroidism: measure the serum TSH 6 weeks after changing the levothyroxine dose Measure the serum TSH 6 weeks after changing the levothyroxine dose or after any change in a levothyroxine-based agent and assess whether a new titration of the dose is necessary
127 Other	Hypothyroidism: levothyroxine and usual mode of administration Continue treatment with levothyroxine under the usual mode of administration. In the case of initiation, favour the administration on an empty stomach in the morning* in the absence of substances that may decrease its absorption**
128 OP	Hypothyroidism: levothyroxine and OR unavailable It is not necessary to administer levothyroxine parenterally to dysthyroidal patients with stable euthyroidism who are unable to receive oral treatment for an anticipated duration of<7 days
129 OP	Thyroid disorders: be careful with drugs that may induce hypothyroidism or hyperthyroidism* Monitor the TSH before and 6 weeks after the introduction of a treatment that may induce thyroid disorders*
130 UP	Hyperthyroidism: start a beta-blocker Consider prescribing a beta-blocker in patients with hyperthyroidism, particularly at the beginning of pharmacological management
Contraception	
131 DDI	Contraception and DDIs Verify contraceptive use in all hospitalised women of childbearing age, and if necessary monitor the lack of DDI with the treatments* that are received or started during hospitalisation
OPHTHALMOLOGY	
Glaucoma	
132 UP	Glaucoma and medication history at admission: continue ophthalmic drop treatment Verify ophthalmic drop intake during drug medication history at admission and continue glaucoma treatment in patients who are treated for that indication
133 OP	Acute angle-closure glaucoma: drugs that may exacerbate acute glaucoma Avoid the use of drugs that may induce acute closed-angle glaucoma* in at-risk individuals who have not had an iridotomy
DEPENDENCIES	
Addictions and hospitalisation	
134 Other	Addiction: rapid interview and brief intervention Perform a rapid interview to detect addiction if an addiction problem is suspected, and if needed, perform a brief intervention to address the addiction problem

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
Alcohol dependence	
135 Other	Alcohol dependence: rapid identification test for alcohol dependence and brief intervention In case of suspicion, perform a rapid identification test for alcohol dependence in hospitalised patients
136 UP	Alcohol withdrawal: start close monitoring and optional prophylaxis with a BZD* Provide close monitoring using a predictive evolution scale and optionally prescribe an appropriate oral BZD* in hospitalised patients with a risk of alcohol withdrawal. If close monitoring is not feasible, prescribe an appropriate oral BZD*
137 UP	Alcohol dependence: start vitamin B1 and multivitamins Prescribe treatment with vitamin B1 in alcohol-dependent patients and multivitamins in case of malnutrition
Tobacco use and tobacco withdrawal	
138 UP	Tobacco dependence: start nicotine replacement therapy if needed If needed, prescribe treatment with a nicotine replacement therapy for hospitalised smokers
139 UP	Tobacco dependence and chronic ischaemic heart disease/respiratory diseases: start smoking cessation intervention Offer assistance for tobacco cessation to any patient suffering from ischaemic heart disease or chronic respiratory disease
Benzodiazepine dependence	
140 UP	BZD dependence: continue BZD treatment at the usual dose during the acute phase of hospitalisation Continue BZD treatment at the usual dose for hospitalised patients with BZD dependency. Suggest a progressive tapering out of the acute phase of hospitalisation
Opioid dependence	
141 UP	Opioid dependence: continue maintenance opioid substitution Continue opioid substitution treatment at the usual doses or an equivalent treatment, while respecting the rules of dose equivalence, in hospitalised patients with an opioid dependency and receiving a substitution treatment
142 DDI	Opioid dependence and buprenorphine: be careful when prescribing opioid analgesics Avoid or be careful when prescribing methadone or a step 2 or 3 opioid analgesic in patients receiving buprenorphine substitution
OBESITY	
Proper use of drugs in the case of obesity	
143 Other	Obese patients: increase doses of injectable antithrombotic agents (LMWH/heparin/fondaparinux) Increase the doses of heparin or fondaparinux in obese patients requiring antithrombotic treatment
144 Other	Obese patients: prefer oral and intravenous routes Favour the oral and intravenous routes in obese patients when they are appropriate for the patient and the drug
145 Other	Obese patients: Adjust initial doses of aminoglycosides according to the adjusted body weight* Adjust the initial dose of aminoglycosides in obese patients according to the adjusted body weight* and then re-evaluate the dose based on the plasma concentrations
146 Other	Obese patients: Adjust the initial doses of vancomycin according to the total body weight Adjust the initial dose of vancomycin in obese patients according to the total body weight and then re-evaluate the dose based on the plasma concentrations
PHARMACOLOGY and TOXICOLOGY	
Clinical pharmacology	
147 OP	Allergies and new medication: rule out allergies Verify the absence of allergies when a new medication is introduced in patients
148 OP	QT prolongation: drugs that prolong the QT interval Avoid the use of drugs* that may prolong the QT interval in patients suffering from congenital long QT syndrome or at risk of torsade de pointes**
149 DDI	Serotonin syndrome: drugs that are associated with serotonin syndrome Avoid prescribing two drugs that may induce serotonin syndrome* when an alternative is available or monitor patients closely
150 OP	Drug-induced Parkinsonism: drugs that may induce extrapyramidal symptoms Avoid prescribing drugs that may induce extrapyramidal symptoms in patients with that syndrome

Continued

Table 3 Continued

PIM-Check: Potentially Inappropriate Medication checklist for Patients in Internal Medicine	
151 OP	G6PD deficiency: drugs that may cause haemolytic anaemia* Avoid or use with caution drugs that may cause haemolytic anaemia* in patients with G6PD deficiency
152 UP	Antifolates* and haematotoxicity: start folinic acid Prescribe folinic acid to patients with haematotoxicity related to taking antifolates*
	Drug–drug interactions
153 DDI	DDI: strong enzyme inducers and inhibitors* Adapt the doses of substrate drugs as needed if a strong enzyme inducer or inhibitor* is introduced, and monitor the clinical response
154 DDI	DDI: re-evaluate drug doses within 15 days following the discontinuation of a strong enzyme inducer Re-evaluate doses of substrate drugs within 15 days following the cessation of a strong enzyme inducer
	TRANSPLANTS
155 UP	Immunosuppressive drugs*: therapeutic drug monitoring Continue immunosuppressive treatment* in transplanted patients; do not modify that treatment without consulting the referring physician but monitor the plasma or blood concentrations** in case of altered renal function or in the presence of a health condition that may influence the plasma or blood concentrations
156 DDI	Immunosuppressive drugs and DDIs Evaluate the risk of DDIs, and optionally monitor plasma or blood concentrations* if a new treatment is introduced or if a drug is removed from a transplanted patient receiving immunosuppressants (in particular with CYP and/or Pgp inducers/inhibitors**)
	VACCINATIONS
157 UP	Annual influenza vaccination Offer an annual influenza vaccination to patients with a high risk of complications*
158 UP	Pneumococcal vaccination: high-risk patients* Offer pneumococcal vaccination to patients at high risk of invasive pneumococcal infection*
159 OP	Vaccination and immunocompromised patients*: avoid live attenuated vaccines Avoid the use of live attenuated vaccines in immunocompromised patients*
160 UP	Vaccines: check vaccination status Verify the vaccination status of hospitalised patients, and suggest catch-up for mandatory and recommended vaccines, if necessary*

Colour code of PIM: green stands for UPs, red for OPs, amber for DDIs and grey for other kind of PIM.
*, **, *** Stars refers to information that is available in online supplementary table 2.
ACEI, angiotensin conversion enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor antagonists; BP, blood pressure; BPH, benign prostatic hyperplasia; BZD, benzodiazepine; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; CrCl, creatinine clearance; CS, corticosteroids; CYP, cytochrome P450; DDI, drug–drug interaction; DOAC, direct-acting oral anticoagulant; DM, diabetes mellitus; DVT, deep vein thrombosis; ESA, erythropoiesis-stimulating agent; G6PD: glucose-6-phosphate dehydrogenase; GDU, gastroduodenal ulcer; HAART, highly active antiretroviral therapy; Hb, haemoglobin; HBA1c, glycated haemoglobin; HBV, hepatitis B virus; HCV: hepatitis C virus; HF, heart failure; HTN, hypertension; ICS, inhaled corticosteroids; INR:,international normalised ratio; LVEF, left ventricular ejection fraction; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drug; OP, overprescription; OR, oral route; PE, pulmonary embolism; Pgp, P-glycoprotein, PPIs, proton pump inhibitors; RA, rheumatoid arthritis; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack; TSH, thyroid-stimulating hormone; T2DM, type 2 diabetes mellitus; UP, underprescription; VAS, visual analogue scale; Vitamin B1, thiamine; Vitamin B6, pyridoxine; VKA, vitamin K antagonist; VTE, venous thromboembolism.

36 (23%) to overprescription, 16 (10%) to interactions and 34 (21%) to other PIM (eg, insufficient drug monitoring, incorrect dose adjustment, wrong choice of medication). The rationales for the statements are presented in online supplementary table 2, along with 233 references, 116 recommendations (eg, dose adjustment, alternatives and monitoring), 93 remarks (eg, definitions, reminders and useful lists of drugs) and 24 useful web links.

Fourth step: Forward/back-translation

Among the 160 statements that were forward/back-translated, 16 were identified as having inadequate expression and were then corrected. The tool is available, both in French and in English (http://app.pimcheck.org/#/accueil/en).

Fifth step: electronic tool development

One hundred and ninety-three synonyms of the 52 subdomains included in the tool and 1635 medications were identified. To create the 'Screening' function, each statement was associated with corresponding subdomains and medications and an algorithm of approximately 31 000 lines was developed. This algorithm allows to 'switch on', or 'switch off', statements, depending on comorbidities and medications selected by the user. The 'Favourites' function created gives quick access to statements identified as

favourite, and the 'Learning' function gives access to the list of all statements included in PIM-Check, those unread and those already read. Details regarding the conception of the tool, direct access to the references (n=333) and useful links (n=29) (through URL links), publications related to the tool and a contact section, are also available (http://www.pimcheck.org/en/).

Interpretation

PIM-Check was specifically designed to assist residents and young healthcare professionals in the detection of PIM in patients typically admitted in internal medicine (excluding pregnant women, patients with low life expectancy and patients requiring palliative care). The checklist consists of 160 statements for pathologies and drugs commonly encountered in internal medicine. The checklist does not replace the judgement of physicians and pharmacists but is intended to help young healthcare professionals to improve the medication review process and to reduce the incidence of PIM. Owing to the additional data and references associated with the statements, PIM-Check should also be helpful for training students and residents in prescribing-optimisation. Because most of the statements are based on current international clinical evidence and were validated by European and North American experts, we expect that the English version of PIM-Check will be useful in many healthcare settings. Finally, the availability of an electronic version should facilitate the use of PIM-Check in daily practice.

Comparison with other studies

PIM-Check includes more medical domains (n=17) and subdomains (n=52) than do the published geriatric checklists.[20] Some of the domains and subdomains commonly found in geriatric checklists are not included in PIM-Check (eg, falls, dementia, orthostatic hypotension and sleep apnoea). In contrast, PIM-Check includes statements related to domains, such as transplantation, dependencies, obesity, antiviral therapy and proper use of antibiotics that are not generally covered by geriatric checklists. This last domain should be useful because interventions implemented in hospitals to improve the use of antibiotics have succeeded in preventing PIM.[36] PIM-Check also includes therapeutic classes and drugs commonly associated with preventable hospitalisation and with PIM in internal medicine (eg, non-steroidal anti-inflammatory drugs, anticoagulants, antihypertensive or antidiabetic treatments, statins, proton pump inhibitors and corticosteroids).[7 37 38] PIM-Check is also more focused on underprescription than are geriatric checklists. Seventy-four (46%) statements in PIM-Check are related to underprescription versus 18 (37%), 34 (27%) and 71 (18%) in the Australian checklist, STOPP/START v2, and Assessing Care of Vulnerable Elders indicators v3, respectively.[16 17 19] This can be explained by the fact that recommending preventive treatment in older populations is sometimes inappropriate. In contrast, underprescription in internal medicine patients is not rare, and occurred 1.8 times as often as overprescription[7]; thus, PIM-Check should be more helpful than other checklists for preventing PIM in this population.

Strengths and limitations

The Delphi method is a robust method for reaching a consensus of opinion and is commonly used for validating PIM checklists.[14 19 20 29] The reliability of a Delphi survey is directly proportional to the size of the expert group.[39] Therefore, we are confident that results from this study are robust, because the number of experts involved in our Delphi survey was high, as was the participation rate. As previously demonstrated by Chang *et al*, checklists with higher numbers of statements, therapeutic classes and medical domains tend to show higher rates of PIM detection, although the use of long checklists can be time-consuming.[21] However, PIM-Check is the first checklist available as an electronic device. The 'Screening' function allows users to perform an analysis for a specific patient, restricting the statements displayed to those that are most relevant to that patient, depending on his/her comorbidities and prescribed medications. This function should enable users to review a prescription in less than 5 min, as can be done with STOPP/START.[9 37 40] However, these issues need to be addressed in the future, as the ability of PIM-Check to prevent PIM.

Implications for clinicians and policymakers

In our study, experts rated the statements as being highly useful for the training of students and residents. The inclusion of additional data and references with the statements can be expected to make PIM-Check helpful for improving trainee awareness of good prescription practices. Moreover, as previously demonstrated, interactive techniques in medication education and training in the use of systematic tool to reduce PIM are effective in improving prescribing-skill and patient care.[41 42] The progressive learning function included in the electronic version of PIM-Check may constitute an effective intervention to improve prescribing performance. Finally, PIM-Check could be helpful for researchers and policymakers because it could be used to estimate the incidence of PIM in various settings, to evaluate prescription quality and safety and to evaluate factors and costs associated with PIM, as it has been proposed for STOPP/START and the Beers Criteria.[9 43–48]

Unanswered questions and future research

The next step will be to evaluate the incidence of PIM detected and prevented using PIM-Check in various healthcare settings. It will also be of interest to determine whether the use of PIM-Check, like the use of STOPP/START, is significantly associated with reductions in adverse drug events and improvement in young healthcare professionals prescribing training.[23 40 49] We will test the English version of PIM-Check in non-French-speaking countries.[50] Another project might be to integrate PIM-Check as a clinical decision support system in electronic health records, to assist physicians and pharmacists in their clinical practice. Finally, like geriatric checklists,[10–14 16 18 19 51] PIM-Check will need to be updated in a

few years as new research is published and new drugs are licensed.

CONCLUSION

In conclusion, this study offers an electronic prescription-screening checklist, including 160 statements. The application of this checklist combined with clinical judgement should contribute to help young physicians and pharmacists in their training and clinical practice, to detect and reduce PIM. In the context of expansion of the prevalence of multimorbidity and polypharmacy, PIM-Check could be a complementary strategy to reduce PIM and to improve patient safety.

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