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THERAPEUTIC DECISION SUPPORT

Translation of the REMEDI[e]S (Review of potentially inappropriate MEDIcation pr[e]scribing in Seniors) explicit criteria into seminatural language for use in prescription support systems: A multidisciplinary consensus

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KEYWORDS
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Summary
Background. — By recovering data in an ordered manner and at the right time, clinical decision support systems (CDSSs) are designed to help healthcare professionals make decisions that improve patient care.

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Potentially inappropriate drugs ;
Prescription support systems ;
Seminatural language

Objectives. — The aim of the present study was to translate the REMEDI[e]s tool's explicit criteria, France's first reference list of potentially inappropriate drugs for the elderly, into seminatural language, in order to implement these criteria as alert rules and then enable their computer coding in a CDSS.
Methods. — This work was carried out at Lille University Hospital by a team of clinical pharmacists with expertise in the use of pharmaceutical decision support systems, in collaboration with the authors of the REMEDI[e]s tool. A total of 3 multi-professional consensus meetings were required to discuss the construction of each rule in seminatural language and the coding choices.
Results. — All REMEDIES criteria ($n = 104$) were translated into seminatural language. This study is the first to have translated the 104 REMEDI[e]s explicit criteria into seminatural language.
Conclusions. — One of the study's strengths relates to the close collaboration between the authors of the REMEDI[e]s tool and experts in CDSS programming rules; this ensured the exactitude of the seminatural language translations and limited (mis)interpretations.

Abbreviations

ACEIs	angiotensin-converting enzyme inhibitors
ARBs	angiotensin receptor blockers
ATC	anatomical therapeutic chemical
CDSS	clinical decision support systems
ICD10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICD-11	International Statistical Classification of Diseases and Related Health Problems 11th Revision
LOINC	Logical Observation Identifiers Names & Codes
NSAIDs	nonsteroidal anti-inflammatory drugs
STOP/START	Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment
REMEDI[e]S	Review of potentially inappropriate MEDIcation pr[e]scribing in Seniors
UCD	*unité commune de dispensation*

Introduction

By recovering data in an ordered manner and at the right time, clinical decision support systems (CDSSs) are designed to help healthcare professionals make decisions that improve patient care. The CDSSs used to identify potentially inappropriate prescriptions can draw on knowledge about how to resolve problems related to the treatment in question. These tools can be built by leveraging either machine learning (i.e. a type of artificial intelligence that learns from prior experience and/or identifies the models to be applied) [1] or knowledge bases that are expressed as sets of rules [2]. These rules can be based on local experience or an expert consensus. For example, the ''Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment'' (STOPP/START) criteria have recently been converted into algorithms and integrated into a CDSS, with a view to easier use in clinical practice [3]. The integration of the results of an expert consensus into a CDSS raises the question of whether the translated rules faithfully express those defined initially by their originators. This integration involves an intermediate step before computer coding: translation into seminatural language, i.e. the production of Boolean language (e.g. AND/OR, WITHOUT [...]) that enables natural language to be converted into a programming language. This essential but difficult step requires an understanding of the determinants of this translation [4]. Given the aging of the population and the high prevalence of polymedication among older adults, we decided to work on the integration of the criteria from REMEDI[e]S (Review of potentially inappropriate MEDIcation pr[e]scribing in Seniors), a prescription support tool for use with older adults, also known as the Laroche list, into CDSSs [5].

The primary objective of the present study was to translate the REMEDI[e]s tool's explicit criteria into seminatural language, in order to implement these criteria as alert rules and then enable their computer coding in a CDSS.

Methods

The study was conducted at Lille University Hospital (Lille, France) by a group of clinical pharmacists with experience of using CDSSs in collaboration with the REMEDI[e]s development team. We used the original version of the REMEDI[e]s explicit criteria, which were validated in Roux et al.'s Delphi consensus survey in 2021 [5]. All the REMEDI[e]s criteria ($n = 104$) were translated into seminatural language by clinical pharmacists with experience of CDSSs. The translations were validated by the REMEDI[e]s tool's developers, to ensure that each criterion's original definition had not been distorted by translation into seminatural language. This work is presented as a table (Table S1, Appendix 1) comprising each REMEDI[e]s criterion, the causal relationship, the action to be taken, and the seminatural language translation.

Three multidisciplinary consensus meetings (bringing together 3 experts in CDSS programming rules and 3 experts who contributed to the consensus on the REMEDI[e]s explicit criteria) were required to discuss the construction of each seminatural language rule and the choice of coding. The project's objective was defined in the first meeting, and the translations were validated in the following two meetings.

Lastly, in order to quantify the proportion of rules that could be created for each type of data integrated into the CDSSs at each hospital, we built a summary table (Table 2). Each line gave the patient's data (weight), the prescription data (the anatomical therapeutic chemical [ATC] code or the French *unité commune de dispensation* code [UCD]), the dose level, the administration frequency, the duration of administration, and the administration route, data on the patient's medical history (the International Statistical Classification of Diseases and Related Health Problems 10th/11th Revision [ICD-10/ICD-11]) codes, clinical notes on the ongoing hospital stay, the primary diagnosis from the ongoing hospital stay, the laboratory data (the Logical Observation Identifiers Names & Codes [LOINC], and bacterial culture results) and physiological data (arterial blood pressure and gastrointestinal transit).

Results

The multidisciplinary consensus meetings resulted in the elaboration of a summary table (Table 1) and a detailed table (Supplementary Table S1, specifying the drugs' ATC codes and the action to be taken). We were able to translate the 104 criteria into seminatural language. Since the purpose of the REMEDI[e]s list is to revise potentially inappropriate prescriptions in older adults, we decided to translate ''older adult'' into language seminatural as ''[age $\geq$ 75 years OR ($\geq$ 65 years AND > 2 chronic diseases)]'', as defined by the REMEDI[e]s tool's designers. The set of ''chronic diseases'' would be translated into seminatural language by ''previous and/or concomitant medical conditions or clinical and laboratory variables that explicitly translate into previous and/or concomitant medical conditions''.

Other criteria were specified by consensus. For example, ''except if acute event < 12 months'' was added to the seminatural language translation of rule D-4 ''concomitant use of 2 or more antiplatelet drugs''. Several variables cited in the explicit criteria had therefore to be specified. Concerning drug classes, we specified all diuretic drugs in criterion D-1, all angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in criteria D-2/O-3/O-4/O-6/I-9/I-10/I-11, all antihypertensive agents in criteria D-3/O-2, all antiplatelet drugs (antiaggregants) in criterion D-4, all antalgics in criterion D-6, all psychotropic drugs in criterion D-7, all statins and beta-blockers in criteria O-4/B-R 18, all nitrate derivatives in criterion O-5, calcium antagonists in criterion O-5, all antidepressants in criterion O-7/I-16, all inhaled beta-2 agonist and inhaled anticholinergics in criterion O-9, all opioids in criteria O-14/I-15, all corticosteroids in criterion O-15, and all antiepileptics, antipsychotics, benzodiazepines, or antidepressants in criterion I-15.

Other criteria did not have a very precise seminatural language definition. Concerning the patient's medical history, the general terms covering ''resistant arterial hypertension'' (rule O-2), ''major depression'' (rule CC-8/CC-9) and ''cognitive disorders'' (rule CC-8/CC-9) were not specified. Furthermore, the microalbuminuria threshold value in rule O-6 ''diabetes with microalbuminuria'' was not specified; each centre using a CDSS was able to adjust the threshold value as a function of its own laboratory data.

It should be noted that any change in the initial REMEDI[e]s criteria had to be justified and validated.

Table 2 summarizes the percentage of rules whose creation requires the ''drug'' variable. We decided to quantify these rules after excluding the definition ''[age $\geq$ 75 years OR ($\geq$ 65 years AND > 2 chronic diseases)]'', which requires knowledge of the patient's age and the ICD-10/-11 classification in all cases.

Discussion

The present study is the first to have translated the 104 REMEDI[e]s explicit criteria into seminatural language. One of the study's strengths relates to the close collaboration between the experts having developing the REMEDI[e]s explicit criteria and experts in CDSS programming rules; this ensured the exactitude of the seminatural language translations and limited (mis)interpretations. The 104 seminatural language translations could serve as the basis for various software applications and, once integrated into a CDSS, might be of value to healthcare establishments.

CDSSs are increasingly used in clinical practice, where they help healthcare professionals to make informed, effective decisions about their patients' drug treatments. By providing alerts and recommendations in real time, CDSSs improve the quality of care, identify the best treatment options and accelerate decision-making by finding the clinical information more quickly [6—9]. The REMEDI[e]s list is acknowledged to be France's leading reference list of potentially inappropriate drugs in older adults; it resulted from a Delphi-method expert consensus [5]. Use of this list broadly reduces complication rates and improves quality of life among older adults [10—12]. Integration of the REMEDI[e]s criteria into a CDSS might therefore help to standardize clinical care and enable healthcare professionals to leverage the tool's advantage when managing patients. The STOPP/START reference list of potentially inappropriate drugs in the older adults is one of the most frequently used tools in this field and has already been translated for integration into CDSSs [13—15].

A recent study evaluated the frequency with which a team of pharmacologists accepted the STOPP/START alerts generated by a CDSS; the acceptance rate ranged from 2.5% to 75.8% [3]. The most frequent alert was the suggested discontinuation of a drug that lacked an indication. The variability in the acceptance rates for alerts derived from explicit criteria highlight the value of integrating lists of potentially inappropriate drugs into a CDSS and thus optimizing the system's performance.

Our study's single-centre design was a limitation: all the translation work was performed by staff at Lille University Hospital. However, the staff have significant expertise and several years of experience in the field of CDSSs, as evidenced by a number of publications. The REMEDI[e]s

Table 1 A summary table of the REMEDI[e]S criteria's translations into seminatural language.

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
Duplication			
D-1	Concomitant use of 2 or more diuretics in arterial hypertension	Increased risk of functional renal failure and serious hydroelectrolytic disorders (dysnatraemia, dyskalaemia)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND hypertension AND ≥ 2 diuretics
D-2	Concomitant use of 2 or more inhibitors of the renin-angiotensin system (≥ 2 ACEI, ≥ 2 ARB, ACEI/ARB)	Increased risk of renal failure and hyperkalaemia, postural hypotension and syncope, with no proven beneficial effect on the reduction of cardiovascular mortality	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (≥ 2 ACEIs*) OR (≥ 2 sartans) OR (ACEIs AND sartan)
D-3	Concomitant use of 4 or more antihypertensive drugs	Risk of fluid and electrolyte disorders and functional renal failure Increased risk of postural hypotension and falls	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ≥ 4 antihypertensive agents
D-4	Concomitant use of 2 or more antiplatelet drugs	Increased risk of bleeding	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ≥ 2 platelet antiaggregants WITHOUT acute event < 12 months
D-5	Concomitant use of 2 or more NSAIDs (nonsteroidal anti-inflammatory)	Increased risk of gastrointestinal ulcer and haemorrhage, functional renal failure and hyperkalaemia, and increased risk of infection	[Age ≥ 75 years OR (≥ 65 years and > 2 chronic diseases)] AND ≥ 2 NSAIDs
D-6	Concomitant use of 2 or more different analgesics of the same step (excluding the association of two galenic forms of the same molecule, for example: delayed and immediate release form of morphine)	Potentiation of adverse effects without increasing efficiency	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND [(≥ 2 level 1 analgesics) OR (≥ 2 level 2 analgesics) OR (≥ 2 level 3 analgesics)]
D-7	Concomitant use of 2 or more psychotropic drugs of the same therapeutic class (≥ 2 benzodiazepines, ≥ 2 antidepressants, ≥ 2 antipsychotics)	Potentiation of adverse effects (cognitive disorders, confusion, problems of alertness, falls) without effectiveness increase	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND [(≥ 2 benzodiazepines) OR (≥ 2 antidepressants) OR (≥ 2 antipsychotic agents)]
Omission			
O-1	Atrial fibrillation		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND atrial fibrillation WITHOUT [anticoagulant OR aspirin < 300 mg]
O-2	Resistant arterial hypertension (> 150/90 mmHg)		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND persistent arterial hypertension WITHOUT antihypertensive agent
O-3	Chronic systolic heart failure		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND systolic heart failure WITHOUT [(ACEIs OR sartan) AND beta-blocker]

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
O-4	Acute coronary post-syndrome in secondary prevention		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND acute coronary post-syndrome in secondary prevention < 12 months WITHOUT [platelet antiaggregant AND beta-blocker AND (ACEIs OR sartan) AND statin]
O-5	Chronic coronary syndrome		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND chronic coronary syndrome WITHOUT [platelet antiaggregant AND (beta-blocker OR calcium antagonist OR nitrate derivative) AND statin]
O-6	Diabetes with microalbuminuria		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND diabetic patient AND microalbuminuria WITHOUT (ACEIs OR sartans)
O-7	Major depression		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND depression WITHOUT antidepressant
O-8	Primary open-angle glaucoma		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND open-angle glaucoma WITHOUT eye drops
O-9	Chronic obstructive pulmonary disease		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND COPD WITHOUT (inhaled beta-2 agonists OR inhaled anticholinergic)
O-10	Confirmed osteoporosis (Bone Mineral Density T-scores more ≤ −2.5) and/or history of fragility fractures		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND Osteoporosis WITHOUT (Ca/Ca-VitD/Vit D supplementation OR bisphosphonate OR raloxifene OR denosumab OR teriparatide)
O-11	Influenza		Age ≥ 65 years WITHOUT influenza vaccination
O-12	Pneumococcus		Age ≥ 65 years WITHOUT [residence in an institution AND pneumococcal vaccination]
O-13	Zona		(Age ≥ between 65 AND < 75 years) WITHOUT herpes zoster vaccination
O-14	Opioid treatment		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND opioid WITHOUT laxative
O-15	Long-term corticoids (> 3 consecutive months with a dosage ≥ 7.5 mg/day prednisone equivalent)		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (Prescription of corticosteroids > 3 months AND corticosteroid dose > 7.5 mg prednisone equivalent) WITHOUT [Ca AND vitD]
O-16	Weekly methotrexate treatment		[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND methotrexate > 1 per week WITHOUT (folinic/folic acid on the following day OR the day after the following day)
			[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND methotrexate > 1 per week AND folic acid on the same day

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
Risk/benefit			
B/R-1	First generation antihistamines	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND first-generation antihistamine
B/R-2	Antiarrhythmics (Class Ia)	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND class Ia antiarrhythmic drug
B/R-3	Analgesics (step 1)	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND nefopam
B/R-4	Antiemetics (excludes use in palliative care and post-chemotherapy)	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND anti-emetic WITHOUT (context of palliative care OR context of chemotherapy)
B/R-5	Gastrointestinal antispasmodics	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND gastrointestinal antispasmodic
B/R-6	Tricyclic antidepressants	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND imipramine antidepressant
B/R-7	Antiparkinsonian agents	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND antiparkinsonian drug
B/R-8	Phenothiazine antipsychotics	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND phenothiazide antipsychotic
B/R-9	Antivertigo	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND meclizine
B/R-10	Anxiolytics	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND anxiolytic
B/R-11	Hypnotics	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND hypnotic
B/R-12	Antitussives	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND antitussive agent
B/R-13	Urinary antispasmodics	Anticholinergic effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND urinary tract antispasmodic
B/R-14	Antianginal agents — Nicorandil	Risk of mucocutaneous ulcerations. Increased risk of orthostatic hypotension in associations with other antihypertensive drugs	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND Nicorandil
B/R-15	Centrally acting antihypertensives — Clonidine — Methyldopa — Moxonidine — Filmenidine	Increased risk of orthostatic hypotension, bradycardia, syncope and falls. Risk of sedation, depressive syndrome and constipation	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (clonidine OR methyldopa OR moxonidine OR rilmenidine)
B/R-16	Peripherally acting antihypertensives (alpha-1 blockers) — Doxazosin — Prazosine — Urapidil	Increased risk of orthostatic hypotension and falls, dizziness, sleep disturbances and urinary incontinence	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (doxazosine OR prazosine OR urapidil)

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
B/R-17	Immediate release calcium channel blockers — Nicardipine	Increased risk of orthostatic hypotension and reflex tachycardia with immediate-release forms. Increased risk of cardiovascular complications (myocardial ischemia)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND immediate release nicardipine
B/R-18	Statins in primary prevention of cardiovascular events	Lack of conclusive evidence of the efficacy of statins in reducing all-cause mortality in individuals > 75 years at low cardiovascular risk in primary prevention Musculoskeletal adverse effects (myalgia, myopathies, rhabdomyolysis), risk of diabetes and hepatic injury	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND statins WITHOUT cardiovascular event
B/R-19	Antiplatelet agents for primary prevention of cardiovascular events — Aspirin (≤ 375 mg/day)	Increased risk of bleeding with uncertain efficacy in primary prevention of cardiovascular events in older adults ≥ 70 years	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND platelet antiaggregant WITHOUT cardiovascular event
B/R-20	Antiplatelet agents — Dipyridamole (excludes the injectable form for cardiovascular function testing)	Increased risk of vasodilation and orthostatic hypotension with risk of falls	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND dipyridamole
B/R-21	Antiplatelet agents — Prasugrel	Increased risk of bleeding in older adults ≥ 75 years and weight less than 60 kg	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND weight < 60 kg AND prasugrel
B/R-22	Antiplatelet agents — Ticlopidine	Severe haematological and hepatic toxicity	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ticlopidine
B/R-23	Phlebotonics — Diosmin — Ginkgo biloba — Rutoside — Troxerutin	Questionable efficacy	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (diosmine OR ginkgo biloba OR rutoside OR troxerutine)
B/R-24	NSAIDs — Indomethacin (excludes ophthalmic)	More common neuropsychic adverse effects for indomethacin compared to other NSAIDs Risk of gastrointestinal bleeding and ulcerations Increased risk of renal failure and high blood pressure	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND indomethacin per os
B/R-25	Skeletal muscle relaxants — Baclofen — Methocarbamol	Drowsiness and sedation with risk of falls and fractures	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (baclofen OR methocarbamole)
B/R-26	Long- and short-acting sulfonylureas — Glibenclamide — Gliclazide — Glimepiride — Glipizide	Risk of severe hypoglycaemia	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (Glibenclamide OR Gliclazide OR Glimepiride OR Glipizide)

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
B/R-27	Glinides — Repaglinide	Risk of severe hypoglycaemia and lack of evidence regarding the reduction of cardiovascular risk. No clinical studies in older adults ≥ 75 years in the treatment of type 2 diabetes	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND Repaglinide
B/R-28	Aluminium-based antacids (alone or in association) — Aluminium hydroxide — Aluminium phosphate	Questionable efficacy with risk of aluminium encephalopathy in cases of severe renal failure and aluminium-induced constipation Drug interaction if not administered in a timely manner with other drugs	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND aluminium-based antacids
B/R-29	Antidiarrhoea — Loperamide	Morphinic adverse effects (drowsiness, confusion, dizziness, faecal impaction). Increased risk of infection in case of infectious diarrhoea by slowing down transit	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND loperamide
B/R-30	H2-receptor antagonists — Cimetidine	Increased risk of confusion and drug interactions	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND cimetidine
B/R-31	Antiulcer — Sucralfate	Questionable efficacy with increased risk of bezoar and risk of aluminic encephalopathy in cases of severe renal failure and aluminium-induced constipation Drug interaction with other drugs if not administered in a timely manner	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND sucralfate
B/R-32	Laxative lubricants — Paraffin oil	Risk of inhalation and lipoid pneumopathy in older adults with swallowing problems Aggravation of anal incontinence and disorders of digestive absorption (reduced absorption of fat-soluble vitamins with prolonged use)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND paraffin oil
B/R-33	Stimulant laxatives — Bisacodyl — Docusate sodium — Anthracene laxatives (cascara, senna glycosides, aloe) — Sodium picosulfate	Colon irritation and abdominal pain Increased risk of hypokalaemia, especially in association with other hypokalaemic drugs	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (Bisacodyl OR Docusate sodium OR Anthracene laxatives OR Sodium picosulphate)
B/R-34	Fluoroquinolones	Increased risk in older adults of tendinopathies (common with associated corticosteroid therapy), hypoglycaemia or hyperglycaemia in diabetic individuals, neuro-psychiatric disorders (confusion), convulsions, QT interval prolongation, aortic aneurysm and aortic dissection Drug interactions (potentiation of vitamin K antagonists effects) and increased risk of antibiotic resistance	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND Fluoroquinolones WITHOUT (male urinary tract infection OR pyelonephritis caused by extended-spectrum β-lactamase-producing Enterobacteriaceae)

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
B/R-35	Long-acting anxiolytic benzodiazepines (half-life > 20 hours)	Increased risk of adverse effects due to longer half-life as metabolism decreases with age Central nervous system adverse effects (confusion, cognitive disorders, psychomotor disorders, behavioural disorders and altered day/night cycle) Risk of falls and fractures, loss of functional independence Risk of physical and psychological dependence in case of prolonged use	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND long-acting benzodiazepine anxiolytic (> 20 h)
B/R-36	Long-acting hypnotic benzodiazepines (half-life > 20 hours)	Increased risk of adverse effects due to longer half-life as metabolism decreases with age Central nervous system adverse effects (confusion, cognitive disorders, psychomotor disorders, behavioural disorders and altered day/night cycle) Risk of falls and fractures, loss of functional independence Risk of physical and psychological dependence in case of prolonged use	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND long-acting benzodiazepine hypnotic (> 20 h)
B/R-37	Dopaminergic agonists for treatment of essential tremors	No proven efficacy in essential tremor Increased risk of adverse effects: delirium, hallucinations, dizziness, orthostatic hypotension and digestive disorders	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND Dopamine agonists AND essential tremor
B/R-38	Cerebral vasodilators — Gingko biloba — Pentoxifylline — Piracetam — Moxisylyte	Questionable efficacy; risk of orthostatic hypotension, falls and syncope	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (Ginkgo biloba OR Pentoxifylline OR Piracetam OR Moxisylyte)
B/R-39	5-alpha-reductase inhibitors — Dutasteride — Finasteride	Questionable efficacy in the treatment of benign prostatic hyperplasia Significant risk of depressive disorders including suicide	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (dutasteride OR finasteride)
Inappropriate dose level			
DO-1	Colchicine > 1.5 mg/day on the first day of treatment for acute gout.	Risk of overdose with gastrointestinal disorders (diarrhoea, nausea, vomiting, abdominal pain), hypotension, haematological disorders (pancytopenia), polypnea, nephrotoxicity and multivisceral failure potentially fatal Risk of drug interactions [cf. criterion I-22]	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (colchicine > 1.5 mg/day on D1)

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
DO-2	Digoxin > 0.125 mg/day or digoxin serum concentration > 1.2 μg/L	Increased sensitivity to digoxin in older adults (drug with a narrow therapeutic range) Risk of intoxication in individuals with severe renal failure Signs of overdose: digestive disorders (vomiting, diarrhoea), conduction and heart rhythm disorders, psychiatric disorders (confusion, hallucinations, delirium) and colour vision abnormalities	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (digoxin > 0.125 mg OR blood digoxin > 1.2 μ/L)
DO-3	Tramadol > 200 mg/day	Prolonged elimination half-life in individuals > 75 years. Central nervous system adverse effects (confusion, dizziness with risk of falls), digestive disorders (nausea) Serotoninergic properties with risk of serotonin syndrome if association with other serotoninergic drugs [cf. criterion I-16]	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND tramadol > 200 mg/d
DO-4	Short or intermediate half-life benzodiazepines or nonbenzodiazepine hypnotics (Z-drugs) > half the dose given in young adults Lorazepam > 3 mg/day, oxazepam > 30 mg/day, alprazolam > 2 mg/day, clotiazepam > 5 mg/day, loprazolam > 0.5 mg/day, lormetazepam > 0.5 mg/day, zolpidem > 5 mg/day, zopiclone > 3.75 mg/day, estazolam > 1 mg/day	No evidence of superior efficacy when the dose is above half that prescribed to young adults with increased risk of adverse effects (confusion, cognitive disorders, psychomotor disorders, behavioural disorders and altered day/night cycle). Risk of falls and fractures, loss of functional independence Risk of physical and psychological dependence in case of prolonged use	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (lorazepam > 3 mg/day OR oxazepam > 30 mg/day OR alprazolam > 2 mg/day OR clotiazepam > 5 mg/day OR loprazolam > 0.5 mg/day OR lormetazepam > 0.5 mg/day OR zolpidem > 5 mg/day OR zopiclone > 3.75 mg/day OR estazolam > 1 mg/day)
Inappropriate duration			
DU-1	Benzodiazepines > 12 weeks (anxiolytic use)	Increased risk of adverse effects due to longer half-life as metabolism decreases with age Adverse effects on the central nervous system (confusion, cognitive disorders, psychomotor disorders, behavioural disorders and altered day/night cycle) Risk of falls and fractures, loss of functional independence Risk of physical and psychological dependence in case of prolonged use	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND benzodiazepine anxiolytics for more than 12 weeks

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
DU-2	Benzodiazepines and nonbenzodiazepine hypnotics (Z-drugs) > 4 weeks (hypnotic use)	Cf. criterion DU-1	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (benzodiazepine hypnotics > 4 weeks OR related hypnotics > 4 weeks)
DU-3	Colchicine for prophylaxis of acute gout > 6 months	Unfavourable benefit/risk ratio during prolonged use Risk of drug interactions [cf. criterion I-22] and overdose with potentially fatal consequences [cf. criterion DO-1]	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND colchicine > 6 months
DU-4	Cotrimoxazole > 10 days (excludes treatment in the context of transplantation, prevention of infections in HIV-infected individuals)	Haematologic adverse effects more common in older adults ≥ 65 years Risk of hyperkalaemia and renal failure, and drug-drug interactions (vitamin K antagonists, hypoglycaemic sulfonylureas, etc.)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND cotrimoxazole every day for more than 10 days WITHOUT (transplant recipient or HIV-positive person)
DU-5	Nitrofurantoin for curative treatment > 7 days	Pulmonary and hepatic toxicities (including some of immuno-allergic origin) more frequent in older adults > 65 years; risk of peripheral neuropathies Adverse effects especially with prolonged treatment (continuous or intermittent)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND nitrofurantoin AND (man OR prescribed > 7 days OR GFR < 45 mL/min) WITHOUT positive urine culture
DU-6	Proton pump inhibitors (PPIs) > 8 weeks	Risk of adverse effects with long-term use such as pneumopathies, *Clostridium difficile* pseudomembranous colitis, hypocalcaemia with risk of osteoporosis and fractures, hyponatraemia, hypomagnesemia, iron and vitamin B12 deficiency	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND IPP > 8 weeks WITHOUT (NSAIDs OR platelet antiaggregant OR anticoagulant)
Clinical conditions			
CC-1	Orthostatic hypotension And Alpha-1 blockers for urinary incontinence (includes benign prostatic hyperplasia) Conventional and atypical antipsychotics Nitrates Drugs with anticholinergic properties	Increased risk of orthostatic hypotension with risk of falls, especially in individuals prone to orthostatic hypotension and treated with antihypertensive drugs	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND orthostatic hypotension AND (Alpha-1 blocker for urological indications OR conventional antipsychotic OR second-generation antipsychotic OR nitrate derivative OR anticholinergic)
CC-2	Heart failure And Nondihydropyridine calcium channel blockers	Risk of worsening heart failure by negative inotropic effect (contraindication if ejection fraction < 35%; monitoring necessary if ejection fraction > 35%)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND heart failure AND (diltiazem OR verapamil)

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
CC-3	Heart failure And NSAIDs	Risk of chronic heart failure decompensation	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND NSAIDs AND heart failure
CC-4	Heart failure And Dronedarone	Risk of cardiac decompensation in individuals with severe heart failure Risk of heart failure, stroke and cardiovascular death in individuals with permanent atrial fibrillation (> 6 months)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND heart failure AND dronedarone
CC-5	Constipation chronic And Drugs with anticholinergic properties	Risk of increased constipation and intestinal occlusion	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND constipation AND anticholinergic
CC-6	Constipation chronic And Antihypertensives Centrally acting antihypertensives: Calcium channels blockers:	Risk of increased constipation and intestinal occlusion	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND constipation (AND centrally acting antihypertensive OR calcium inhibitor)
CC-7	Peptic ulcers And NSAIDs	Increased risk of peptic ulcers especially in individuals at risk (history of peptic ulcer or corticosteroid treatment) Increased risk of bleeding from existing peptic ulcers in individuals receiving antiplatelet or anticoagulant therapy	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND gastroduodenal ulcer AND NSAIDs
CC-8	Disorders cognitive And Benzodiazepines and nonbenzodiazepines (Z-drugs)	Risk of worsening cognitive disorders and/or occurrence of confusion, risk of falls	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND cognitive disorders AND (Benzodiazepine OR related drug)
CC-9	Disorders cognitive And Drugs with anticholinergic properties	Risk of worsening cognitive disorders and/or occurrence of confusion, risk of falls	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND cognitive disorders AND Drug with anticholinergic properties
CC-10	Disorders cognitive And Conventional antipsychotics Atypical antipsychotics	Risk of worsening cognitive disorders and/or occurrence of confusion, risk of falls Sedation, gait disorders with risk of falls and head injuries Increased risk of stroke and risk of death	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND cognitive disorders AND conventional/second-generation antipsychotic
CC-11	Deficiency renal chronic And NSAIDs	Risk of worsening chronic renal failure Reminder: contraindication in cases of severe renal insufficiency	[Age ≥ 75 years or (≥ 65 years AND > 2 chronic diseases)] AND chronic kidney failure AND NSAIDs

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
CC-12	Chronic urinary retention (includes benign prostatic hyperplasia) and drugs with anticholinergic properties	Risk of worsening urinary retention (definite contraindication for use of drugs with anticholinergics properties in case of urinary retention)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND urine retention AND Drug with anticholinergic properties
CC-13	Closed-angle glaucoma and drugs with anticholinergic properties	Risk of worsening closed-angle glaucoma (definite contraindication for use of drugs with anticholinergic properties in case of closed-angle glaucoma)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND closed-angle glaucoma AND Drug with anticholinergic properties
Drug—drug interactions			
I-1	Drug with bradycardic properties (beta-blocker, digoxin, diltiazem, verapamil) + acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine)	Risk of conduction disorder, syncope and excessive bradycardia (additive effects)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND acetylcholinesterase inhibitors AND Drugs with bradycardic properties
I-2	Digoxin + loop diuretic or thiazide diuretic	Increased risk of digoxin toxicity due to hypokalaemia (conduction and excitability disorders, digestive disorders). Increased sensitivity to digoxin in older adults	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND [digoxin AND (loop diuretic OR thiazide diuretic)]
I-3	Oral anticoagulant (vitamin K antagonists (AVK), factor Xa inhibitors or direct thrombin inhibitors) + antiplatelet agents (including low dose aspirin: 50 mg to 375 mg/day)	Increased risk of bleeding	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (AVK OR inhibitor factor Xa OR direct thrombin inhibitor) AND platelet antiaggregant
I-4	Oral anticoagulant (vitamin K antagonists, factor Xa inhibitors or direct thrombin inhibitors) + NSAIDs	Increased risk of bleeding	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND NSAIDs AND anticoagulant oral
I-5	Vitamin K antagonists + antibiotics [macrolides, fluoroquinolones, cyclines, cotrimoxazole, cephalosporins (cefamandole, ceftriaxone, cefazolin, clindamycin)]	Increased risk of bleeding by increase in the effect of the vitamin K antagonist (modification of the intestinal flora leading to a modification of the synthesis of vitamin K) Higher risk with certain classes of antibiotics	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND AVK AND (macrolides OR fluoroquinolones OR cyclines OR cotrimoxazole OR cephalosporines OR clindamycin)
I-6	Antiplatelet agents (includes low dose aspirin: doses of 50 mg to 375 mg/day) + NSAIDs	Increased risk of ulceration, bleeding and kidney failure	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND NSAIDs AND platelet antiaggregant

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
I-7	NSAIDs (includes aspirin > 375 mg/day) + corticosteroids	Increased risk of ulceration and gastrointestinal bleeding, especially in older adults	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND NSAIDs AND corticosteroids
I-8	Statins (simvastatin, pravastatin, atorvastatin) + macrolides (azithromycin, erythromycin, clarithromycin, roxithromycin)	Increased risk of rhabdomyolysis (concentration-dependent effect) due to decreased statin metabolism	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND statin (simvastatin or atorvastatin or atorvastatin) AND macrolide (azithromycin or erythromycin or clarithromycin or roxithromycin)
I-9	ACEI + potassium salts ACEI + potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) ARB + potassium salts ARB + potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) Potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) + potassium salts	Increased risk of hyperkalaemia	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ([(ACEIs OR ARA2) AND (potassium salts or potassium-sparing diuretics)] OR [potassium-sparing diuretics AND potassium salts])
I-10	Cotrimoxazole + ACEI Cotrimoxazole + ARB Cotrimoxazole + potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) Cotrimoxazole + potassium salts	Increased risk of hyperkalaemia	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND cotrimoxazole AND (ACEI OR sartans OR potassium salts OR potassium-sparing diuretic)
I-11	ACEI or ARB + NSAIDs (includes aspirin > 375 mg/day)	Risk of hyperkalaemia, acute renal failure in individuals at risk (dehydration, diuretic therapy, impaired renal function) Reduction of the antihypertensive effect	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (ACEIs or ARA2) AND NSAIDs
I-12	Diuretics + NSAIDs (includes aspirin > 375 mg/day)	Risk of acute renal failure and cardiac failure Reduction of the antihypertensive effect	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND diuretic AND NSAIDs
I-13	Concomitant use of 2 or more hyponatraemic drugs[a] (diuretics, TCA, SSRI (selective serotonin reuptake inhibitors), SNRI (Serotonin and norepinephrine reuptake inhibitors), mirtazapine, carbamazepine, oxacarbazepine)	Increased risk of hyponatraemia with or without associated SIADH Increased risk of confusion and falls in older adults	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ≥ 2 hyponatraemia drugs
I-14	Alpha-1 blockers (alfuzosin, doxazosin, silodosin, tamsulosin, terazosin) + drugs with anticholinergic properties (criteria B/R-1 to B/R-14, I-18)	Antagonism of action with increased risk of urinary retention when the anticholinergic drug is added Risk of orthostatic hypotension	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND (Alpha-1 blockers in urological indications AND anticholinergic)

Table 1 (*Continued*)

References	Criteria REMEDIES	Causes/effects	Translation of the rules into seminatural language
I-15	Concomitant use of 3 or more central nervous system depressant drugs (among antiepileptics, antipsychotics, benzodiazepines, antidepressants, opioids)	Increased central depression and risk of confusion Impaired alertness, memory and balance with risk of falls	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ≥ 3 central nervous system depressants
I-16	Concomitant use of 2 or more drugs with serotonergic properties[a] (SSRI, SNRI, TCA, MAOI, mirtazapine, mianserin, tramadol, lithium)	Addition of the serotonergic effect Risk of occurrence or increase of a serotonin syndrome (diarrhoea, tachycardia, sweating, trembling, confusion to coma in the most severe cases)	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ≥ 2 drugs with serotoninergic properties
I-17	Anticholinesterase drug (galantamine, rivastigmine, donepezil, neostigmine) + drug with anticholinergic properties	Antagonism of action	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND anticholinesterase drugs AND anticholinergic drug
I-18	Concomitant use of 2 or more drugs with anticholinergic properties	Increased anticholinergic adverse effects	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND ≥ 2 anticholinergic drugs
I-19	Colchicine + macrolides (except spiramycin) or pristinamycin	Increased adverse effects of colchicine (inhibition of its metabolism) with risk of overdose (diarrhoea, vomiting, abdominal pain), hypotension, haematological disorders (pancytopenia), polypnea, nephrotoxicity multivisceral failure potentially fatal	[Age ≥ 75 years OR (≥ 65 years AND > 2 chronic diseases)] AND Colchicine AND (systemic macrolide OR pristinamycin)

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; NSAIDs: nonsteroidal anti-inflammatory; REMEDI[e]S: Review of potentially inappropriate MEDIcation pr[e]scribing in Seniors.

[a] Non-exhaustive list, targeting most drugs frequently used in older adults.

Table 2 Data to be analyzed by the CDSS in the creation of rules based on the REMEDI[e]s explicit criteria.

	% (number) of rules requiring the variable ($n = 104$)
Only the drugs are required	56% (58)
List of drugs + other information	44% (46)
Patient data	
Weight	0.1% (1)
Medical history/indications	
ICD-10/-11	27% (28)
Clinical notes on the ongoing hospital stay	32% (33)
Diagnosis for the ongoing hospital stay	29% (30)
Prescription data	
Dose level	6% (6)
Duration	7% (7)
Administration frequency	4% (4)
Administration route	5% (5)
Laboratory data	
LOINC	4% (4)
Bacterial cultures (identification of the bacteria, antibiotic susceptibility profile)	0.1% (1)
Physiological data	
Blood pressure	2% (2)
Gastrointestinal transit	2% (2)

CDSS: clinical decision support systems; ICD10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; ICD-11: International Statistical Classification of Diseases and Related Health Problems 11th Revision; LOINC: Logical Observation Identifiers Names & Codes; REMEDI[e]S: Review of potentially inappropriate MEDIcation pr[e]scribing in Seniors.

developers' involvement made the results more robust. It should be borne in mind that the REMEDI[e]s criteria were not designed for seminatural language translation and CDSS integration; some of the criteria were therefore not explicit enough initially and had to be specified during the translation process.

It would be interesting to develop terminologies that facilitate coherent seminatural language translations as soon as a reference list of potentially inappropriate prescriptions is drawn up [15,16]. Moreover, another limitation relates to the fact that the coding system sometimes prevents a distinction between several situations. Thus, the World Health Organization's ATC drug classification has certain limitations for rule creation. In fact, some ATC codes do not distinguish between different administration routes for a given drug class; hence, another specific drug class code or information about the administration route is required. One example is criterion B/R-24, related to a poor risk-benefit ratio and/or debatable effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) and indomethacin per os (other than eye drops). Lastly, the differences in drug availability from one country to another limit the ability to generalize our results (particularly to non-European countries) [17]. These limitations have already been discussed with regard to the translation of the STOPP/START criteria into algorithmic coding [13,15].

Interpretation of Table 2 (summarizing the CDSS parameters needed to generate the alerts) is complicated by the fact that combinations of data are sometimes needed for application of the rule. It should be noted that use of the REMEDI[e]s list alone (i.e. information on the drug taken) enables the generation of 56% of the alerts (vs. 18% for the STOPP/START criteria) [15]. Depending on the CDSS's abilities, certain seminatural language translations could be modified. For example, the preexisting or concomitant conditions ''orthostatic hypotension'', ''constipation'', ''gastroduodenal ulcer'' and ''urine retention'' in criteria CC-1, CC-5, CC-6, CC-7 and CC-12 could be identified by an ICD-10 code or an ATC code for corrective treatment. However, the CDSS will have to simultaneously detect the patient's age, the ICD-10/-11 codes and/or the clinical and laboratory variables that explicitly translate into an existing or concomitant condition if it is to comply with the definition of an older adult: ''[age $\geq$ 75 years OR ($\geq$ 65 years AND > 2 chronic diseases)]''.

Further integration into clinical practice will require CDSSs to be recognized as true sentinels that complement the pharmacist's recommendation and the physician's prescription. However, there is a risk of over-alerting when a CDSS generates alerts that are irrelevant for the patient in question. In fact, two large clinical trials (OPERAM and SENATOR) and a prospective study highlighted a low physician acceptance rate for STOPP/START alerts, with one of the potential reasons being the lack of relevance of some alerts [7,18,19]. Over-alerting can lead to a loss of value or even a reduction in the healthcare professional's level of vigilance when an alert is viewed [20]. As a consequence, the healthcare professional can miss important alerts that might have a significant impact on the patient. To minimize over-alerting, the CDSS must be designed to provide only relevant alerts that are essential for each specific treatment situation [21]. Thus, certain alerts from the

REMEDI[e]s criteria will be more appropriate for identifying a high-risk iatrogenic drug situation, whereas others will be more appropriate for optimizing a medication review. This approach might lead to a distinction between rules that correct a risky situation and those that prevent such a situation. More broadly, the relevance may vary from one hospital department to another and so must be taken into account: an acute medical ward will not have the same need for alerts as a long-term care ward. In any case, it is important to note that a CDSS's benchmarks and alerts will not replace the physician's and pharmacist's expert judgment; each case must be evaluated individually by taking account of the patient's specific features, such as the clinical status, comorbidities, functional status, adherence, and prognosis [11]. CDSSs have already demonstrated their ability to train healthcare professionals; however, further studies will be required to establish whether the alert acceptation rate is higher among inexperienced prescribers (medical students) on the wards [22]. Lastly, after an evaluation of the relevance and use of each REMEDI[e]s criterion in a CDSS, other points will have to be explored: the acceptance rate, human factors, and cost savings.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.therap.2024.09.002.

Disclosure of interest

The authors declare that they have no competing interest.

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