The updated PIM-Taiwan criteria: a list of potentially inappropriate medications in older people

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Abstract

Background: Explicit criteria for potentially inappropriate medications (PIMs) developed for other countries are difficult to apply to a specific territory. This study aimed to update the PIM-Taiwan criteria from a qualitative review of several published PIM criteria, followed by consensus among regional experts in Taiwan.

Methods: After a review of the literature, we selected four sets of published PIM criteria to construct preliminary core PIMs. The Beers criteria, Fit fOR The Aged (FORTA), and Japan criteria were used for PIMs, without consideration of chronic diseases. The Beers criteria, Screening Tool of Older Persons' Prescriptions (STOPP) criteria, and Japan criteria were used for PIMs with respect to chronic diseases. We asked experts ($n = 24$) to rate their agreement with each statement, including in the final PIM criteria, after two rounds of modified Delphi methods. The intraclass coefficient (ICC) was used to examine the reliability of the modified Delphi method.

Results: Overall, two categories of PIMs were established: 131 individual drugs and 9 drugs with combinations that should generally be avoided; and 9 chronic diseases with their corresponding PIMs that have drug–disease interactions. The ICC estimates for PIMs to be avoided generally were 0.634 and 0.557 (round 1 and 2) and those for PIMs with respect to chronic diseases were 0.866 and 0.775 (round 1 and 2) of the Delphi method, respectively.

Conclusions: The 2018 version of PIM-Taiwan criteria was established and several modifications were made to keep the criteria updated and relevant. Clinicians can use them to reduce polypharmacy and PIMs among older patients.

Keywords: modified Delphi method, older people, potentially inappropriate medications

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Introduction

National Health Insurance in Taiwan is well known worldwide and has a high coverage rate.[1] Therefore, the average years of survival among Taiwanese individuals is increasing under this affordable and well-developed health care system. When people live longer, they frequently have a higher chance of having chronic diseases. In current clinical practice, under the assumption of one guideline that is applied to all adults,[2] multiple medications are more likely to be prescribed for multimorbid patients, because each guideline might recommend an average of three medications.[3,4] As the number of medications increases, the incidence of adverse drug reactions (ADRs) and drug–drug and drug–disease interactions increases significantly.[5] ADRs are associated with falls, geriatric syndrome, higher rates of hospitalization, and mortality.[6,7] In previous studies, some ADRs were regarded as preventable when medications with high risks of ADRs can be avoided before they are prescribed.

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Drugs with a risk of ADRs outweighing clinical benefits, uncertain therapeutic effects, or with safer alternatives for older people are defined as "potentially inappropriate medications' (PIMs).[8] Under this concept, explicit criteria are established to discourage the use of PIMs in older people. The first established PIM criteria was the Beers criteria in the United States in 1991.[8] The initial arrangement of this list was not a system-oriented arrangement, and the PIMs were selected from locally available drugs and regarded as inappropriate according to experts opinions. However, it has been updated[9] and applied to clinical practice and many clinical studies to find the associations between PIMs and outcomes over the past two decades.[10] However, the prescription preference of physicians and the drug market varies in different regions of the world. Therefore, regional PIM criteria are preferred, and they have also been developed in many countries including Germany,[11] France,[12] Ireland,[13] Norway,[14] Italy,[15] Thailand,[16] Japan,[17] and Canada.[18]

Establishing a new set of criteria is time-consuming, particularly during the literature review process, and relatively few studies have enrolled older people with multiple comorbidities in clinical trials. Since the publication of the Beers criteria in 1991, most regional PIM criteria have been derived from expert's opinions using the modified Delphi method.[19] Based on regionally available drugs, the consensus among regional experts was obtained using the modified Delphi method. The PIM-Taiwan criteria have been established and have proven their applicability in several cross-sectional studies among older Taiwanese adults.[20–22] In comparison with the Beers criteria and PRISCUS criteria, PIM-Taiwan can detect a similar number of PIMs across different populations in Taiwan. PIM users had higher health resource utilization and higher costs of medications[20,21] than non-PIM users.

As technology advanced and new results from clinical studies emerged, many new medications were developed after 2010, and some of the statements in the PIM criteria were considered irrelevant or inaccurate. In addition, some older drugs are not available in the market. Therefore, the aim of this study was to establish a new version of the PIM-Taiwan criteria using a two-round modified Delphi method, and intraclass correlations were used to investigate the correlation and agreement among experts' opinions.

Methods

Establishment of a preliminary list

The initial literature review was conducted on PubMed from studies published from 1 January 2011 to 1 January 2017. We selected this time limit for literature inclusion because our PIM-Taiwan criteria were published in 2012. Because we could not include some sets of criteria that were published 1 year before the PIM-Taiwan publication year (2012), we searched for studies dated after 2011. The search included the terms (potentially inappropriate medication list [MeSH] OR inappropriate prescribing [All Fields] OR inappropriate prescribing/classification [All Fields] OR inappropriate prescription [All Fields]). The MeSH term 'potentially inappropriate medications' was introduced in 2016. Prior to this time, the term 'inappropriate prescribing' was used.

As an initial step for the development of PIM criteria in Taiwan, we identified nine sets[9,11,13,15,17,23–26] of explicit criteria published in the English language. After criteria were omitted that were developed based on other published criteria, we selected four sets of criteria to develop a preliminary list (Figure 1). A research team was convened, including three geriatricians, one psychiatrist, and two clinical pharmacists, to create a list of preliminary PIMs from the four published criteria. For the preliminary list of PIMs that should be generally avoided, the Beers criteria, Japan criteria, and FORTA criteria were used as references. For PIMs with respect to comorbidity, the Beers criteria, Japan criteria, and Screening Tool of Older Persons' Prescriptions (STOPP) criteria were used as references. Medications/medication classes that appeared in at least two out of three sets of the criteria were selected and reviewed by the research team. The research team reviewed the concerns regarding these PIMs and approved a preliminary list that consisted of 169 individual drugs and 9 drugs with combinations to be generally avoided and 9 statements for drug–disease interactions.

The availability of medications in Taiwan listed in the preliminary PIM list was confirmed using the medication database from the National Health Insurance Administration. We identified generic names and the Anatomical Therapeutic Chemical (ATC) Classification System code for each

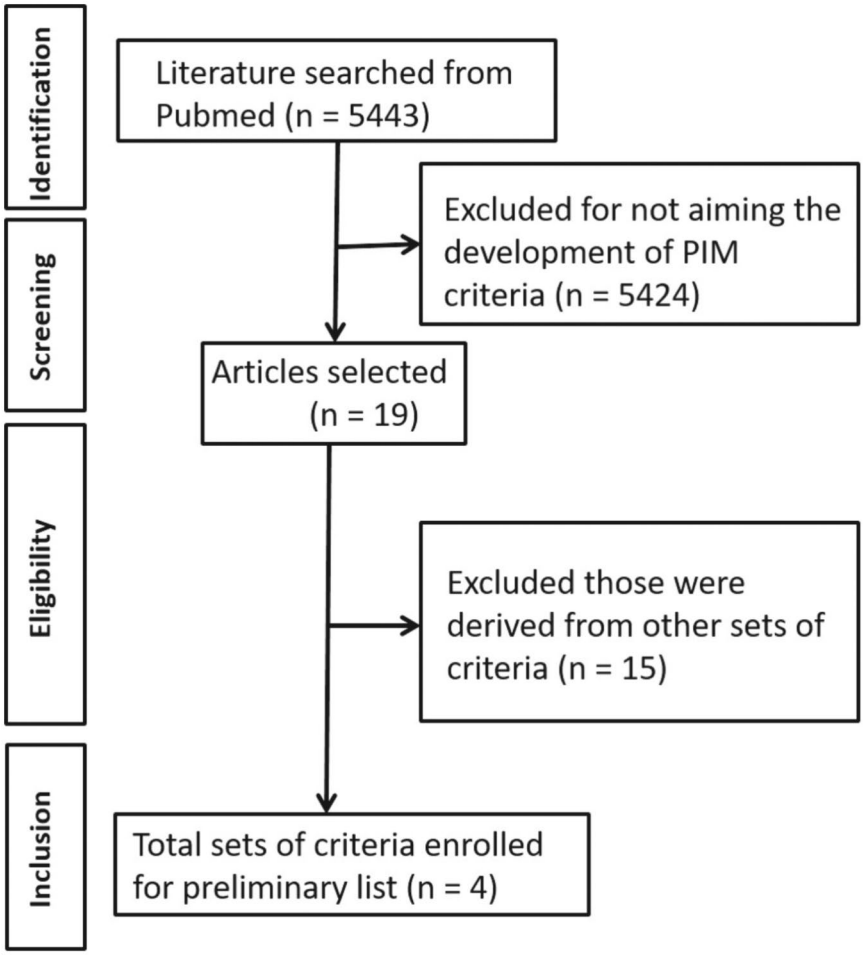

Figure 1. Flow diagram of the systemic literature review and selection of explicit criteria.

medication. When a set of medication classes, rather than an individual medication, was considered potentially inappropriate, we identified all available medications in Taiwan belonging to this set of medication classes. For anticholinergic drugs, we reviewed the literature to define the strong anticholinergic drugs that were given a score of at least two on the 'Anticholinergic Risk Scale'.[9,27]

Modified Delphi method

A group of 24 experts from different specialties (geriatricians, neurologists, psychiatrists, cardiologists, pulmonologists, gastroenterologists, urologists, and clinical pharmacists) was invited to develop a consensus using the modified Delphi methods from the preliminary PIM list. Briefly, this method is a form of communication among these experts with a structured questionnaire to reach a consensus decision. All nongeriatric experts were selected because they are experienced and skilled in the principles of prescribing for older people and have reputations in their specialties in Taiwan. Hard copies of the questionnaire were mailed to all of the experts. A brief introduction of the modified Delphi method and scoring methodology was also given. Then, the experts were asked to rank each statement according to its degree of inappropriateness using a 5 point Likert scale that ranged from 5 points (strongly agree) to 1 point (strongly disagree). In addition, the experts could add suggestions for PIMs that were not listed originally or remove PIMs in the preliminary list. The first round of the questionnaires was scored by each expert by October 2017. PIMs with a mean Likert scale $\geqslant$3.5 were scored again by November 2017. During round two, we also gave the mean score

for each statement, and all experts could find the opinion of other experts in round one. We also welcomed the suggestions of new statements or alternative therapies from the experts. The PIM list was finalized from medications/medication classes with mean Likert scale scores ≥ 3.5 after two rounds of rating. We welcomed the suggestions of new statements or alternative therapies from the experts, and the alternative therapies or suggestions for each PIM to be generally avoided were finalized by four clinical pharmacists. Finally, the research team confirmed that all PIMs were available in Taiwan, and that all of the concerns and alternative therapies/suggestions were optimized.

Theory and calculation

The resulting data generated by the hard copies of the survey were imported into Microsoft Excel (Microsoft Office 2013) for analysis. Descriptive statistics were used to measure the consistency of each measurement. The intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals were calculated using Stata statistical package version 13 (Stata, College Station, TX, USA) based on a mean-rating ($k = 24$), consistency, and a two-way mixed-effect model.

According to the 'Human Subjects Research Act' in Taiwan, this study did not involve obtaining, investigating, analyzing, or using human specimens or an individual person's biological behavior, physiological, psychological, genetic, or medical information. Therefore, this study was not human subject research. In the legislation of the Research Ethics Committee of National Taiwan University Hospital, the study did not need ethical approval as it was not human subject research. The objectives of the Delphi method were presented to all experts, their agreement and availability to participate were obtained (consisted of replying positively by email to the invitation sent by the research team). The information that this study generated was used for consensual quality criteria only and can be publicly accessible and there is no reasonable expectation of privacy.

Results

The preliminary list consisted of 169 individual drugs and 9 drugs with combinations, for example, 'promethazine, combinations' (ATC code R05FA02) to be avoided generally and 9 statements for drug–disease interaction. A total of 29 individual drugs were not available in 2018. PIMs in the first round ($n = 9$) with mean Likert scale scores <3.5 were not entered into the second round. The response rate of the hard copies of the questionnaire was 100% in two rounds of the Delphi method. After two rounds of the modified Delphi method, the final PIM-Taiwan criteria included 131 individual drugs, 9 drugs with combinations to be avoided generally (Table 1), and 9 statements for drug–disease interaction. When an entire medication class was considered to be PIMs, all individual drugs available in the class are listed in Table 1. We designated the symbol marker† for drugs that were already listed in the 2012 PIM-Taiwan criteria. Alternative therapies or suggestions for PIMs were created to prevent the general use of PIMs. When there was no optimal alternative medication for certain PIMs, we recommended other nonpharmacological therapies. For example, antipsychotics for behavioral problems of dementia or delirium should be avoided among older adults because the mortality rate is higher for antipsychotic users. Therefore, nonpharmacological options (e.g. behavioral interventions, such as psychosocial interventions, reality orientation, and physical activity) are suggested first for the behavioral problems of dementia or delirium.[28] Otherwise, PIMs should be used only for a short duration for those with appropriate indications. Table 2 summarizes drug–disease interactions, which included individual medications or medication classes that should be avoided in patients with corresponding chronic diseases. The entire medication class should be considered inappropriate if patients have a corresponding chronic disease. Table 3 lists 131 individual drugs in 10 medication classes overall. The ATC codes, medication/medication classes, and reasons for inclusion are provided. The statements and drugs have been removed since the 2012 version of PIM-Taiwan were enumerated (Table 4). The entire medication class of muscle relaxants was removed from PIM-Taiwan.

For drug–disease interactions, the entire criterion was removed, including blood clotting disorders or anticoagulant therapy, chronic constipation, glaucoma, sleep apnea syndrome, and urinary incontinence. Statements were removed for benzodiazepines for patients with chronic obstructive pulmonary disease and benzodiazepines for patients with cognitive impairment or dementia.

Table 1. 2018 version for potentially inappropriate medication use in persons aged ⩾65 years of age (PIM-Taiwan) independent of diagnoses or chronic diseases.

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
Cardiovascular system	Alderostone antagonists	Spironolactone	C03DA01	Risk of hyperkalemia.	Use other diuretics or regularly monitor serum potassium.
	Antiarrhythmic	Amiodarone	C01BD01	With greater toxicities than other antiarrhythmics used in atrial fibrillation.	Use other rhythm control medications for atrial fibrillation.
	Central alpha blockers	Clonidine†	C02AC01	High risk of adverse central nervous system effects; may cause orthostatic hypotension and bradycardia.	Use other first-line antihypertensive as suggested by guidelines.
	Digitalis glycoside	Digoxin >0.125 mg/d†	C01AA05	Should not be used for atrial fibrillation because it may be associated with higher mortality. When it has been used for heart failure, higher dosages were associated with higher mortality.	Use medications for rhythm control, except amiodarone for atrial fibrillation.
	Peripheral alpha-1 blockers	Prazosin	C02CA01	High risk of orthostatic hypotension; not first-line treatment for hypertension.	Use other first-line antihypertensive as suggested by guidelines.
		Doxazosin	C02CA04		
		Terazosin	G04CA03		
Endocrine system	Androgens	Methyltestosterone	G03BA02	Potentially increased risk of cardiac problems; contraindicated in men with malignancy of prostate.	Avoid use unless absolutely indicated.
		Testosterone	G03BA03		
	Estrogens (including combination)	Estradiol	G03CA03	Carcinogenic potential (breast and endometrium); lack of cardiovascular or cognitive protective effects in older women.	Vaginal estrogens for treatment of vaginal dryness are safe, but those with history of breast cancer are advised to discuss the risk-benefits ratio of low-dose vaginal estrogen therapy with their health provider.
		Estriol	G03CA04		
		Estrone	G03CA07		
		Estradiol, combinations	G03CA53		
		Conjugated estrogens	G03CA57		
		Norethisterone and estrogen	G03FA01		
		Hydroxyprogesterone and estrogen	G03FA02		
		Progesterone and estrogen	G03FA04		
		Norgestrel and estrogen	G03FA10		

(Continued)

Table 1. (Continued)

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
		Medroxyprogesterone and estrogen	G03FA12		
	Sulfonylureas, long-duration	Glyburide (glibenclamide)	A10BB01	Long half-life; can cause prolonged hypoglycemia.	Use other oral hypoglycemic agents.
		Chlorpropamide†	A10BB02		
	Thiazolidinediones	Pioglitazone	A10BG03	Can lead to osteoporosis and fractures in women; exacerbation of heart failure.	Use other oral hypoglycemic agents when patients have heart failure or osteoporosis.
Gastrointestinal system	H2-receptor antagonists	Cimetidine†	A02BA01	Central nervous system adverse effects with potential to induce or worsen delirium.	Proton-pump inhibitors (avoid >8 weeks unless for special circumstances).
		Ranitidine	A02BA02		
		Famotidine	A02BA03		
		Nizatidine	A02BA04		
	Propulsives	Metoclopramide	A03FA01	Can cause extrapyramidal effects.	Domperidone, mosapride.
	Synthetic anticholinergic agents in combination with psycholeptics	Clidinium and chlordiazepoxide*	A03CA02	High anticholinergic effects that may lead to risk of confusion, urinary retention, constipation, dry mouth, etc.	Avoid long-term use.
Genitourinary system	Drugs for urinary frequency and incontinence	Oxybutynin†	G04BD04	High anticholinergic effects that may lead to risk of confusion, urinary retention, constipation, dry mouth, etc.	Use other drugs with less anticholinergic activity.
		Tolterodine	G04BD07c		
Nervous system	Antidepressants, selective serotonin reuptake inhibitors (SSRIs)	Paroxetine	N06AB05	High anticholinergic effects that may lead to sedation, urinary retention, and orthostatic hypotension. Increased risk of skin and mucosa bleeding and hyponatremia.	Use other antidepressants, except TCAs.
	Antidepressants, in combination	Melitracen† and psycholeptics	N06CA02	High anticholinergic effects that may lead to sedation, urinary retention, and orthostatic hypotension.	Use other antidepressants, except paroxetine.
	Antidepressants, tetracyclic	Maprotiline	N06AA21		
	Antidepressants, tricyclic	Imipramine†	N06AA02		

(Continued)

Table 1. (Continued)

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
		Clomipramine†	N06AA04		
		Amitriptyline†	N06AA09		
		Doxepin†	N06AA12		
	Antiparkinsonian agents	Trihexyphenidyl (benzhexol)	N04AA01	High anticholinergic effects that may lead to confusion, urinary retention, constipation, dry mouth, etc.	Use other antiparkinsonian drugs.
		Biperiden	N04AA02		
	Antipsychotics, first-generation (conventional)	Chlorpromazine†	N05AA01	Increased risk of cerebrovascular accident.	Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g. behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.
		Levomepromazine†	N05AA02		
		Fluphenazine	N05AB02		
		Perphenazine	N05AB03		
		Trifluoperazine	N05AB06		
		Thioridazine†	N05AC02		
		Haloperidol	N05AD01		
		Flupentixol	N05AF01		
		Chlorprothixene	N05AF03		
		Pimozide	N05AG02		
		Loxapine†	N05AH01		
		Sulpiride	N05AL01		
	Antipsychotics, second-generation (atypical)	Ziprasidone	N05AE04	Increased risk of cerebrovascular accident.	Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g. behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.
		Lurasidone	N05AE05		
		Clozapine†	N05AH02		

(Continued)

Table 1. (Continued)

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
		Olanzapine	N05AH03	(stroke) and greater rate of cognitive decline and mortality in persons with dementia.	
		Amisulpride	N05AL05		
		Risperidone	N05AX08		
		Zotepine	N05AX11		
		Aripiprazole	N05AX12		
		Paliperidone	N05AX13		
	Benzodiazepines	Clonazepam†	N03AE01	Increased risk of cognitive impairment, confusion, falls, fractures, and motor vehicle accidents.	Avoid as possible; low-dose and short-term use as needed.
		Diazepam†	N03BA01		
		Medazepam	N03BA03		
		Oxazepam	N05BA04		
		Lorazepam	N05BA06		
		Bromazepam	N05BA08		
		Clobazam†	N05BA09	Increased risk of cognitive impairment, confusion, falls, fractures, and motor vehicle accidents.	
		Prazepam	N05BA11		
		Alprazolam	N05BA12		
		Nordazepam†	N05BA16		
		Fludiazepam†	N05BA17		
		Oxazolam†	N05BA		
		Flurazepam†	N05CD01		
		Nitrazepam†	N05CD02		
		Flunitrazepam†	N05CD03		
		Estazolam	N05CD04		

(Continued)

Table 1. (Continued)

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
		Triazolam†	N05CD05		
		Midazolam	N05CD08		
		Brotizolam	N05CD09		
	Nonbenzodiazepine hypnotics	Zopiclone	N025CF01		
		Zolpidem	N025CF02		
		Zaleplon	N025CF03		
		Eszopiclone	N025CF04		
Pain medications	Non-COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs)	Indomethacin†	M01AB01	Increased risk of gastrointestinal bleeding or peptic ulcer disease; concurrent use of proton-pump inhibitor or misoprostol reduces but does not fully prevent the risk. Increased risk of acute kidney injury.	Use acetaminophen or COX-2 selective NSAIDs; avoid long-term use.
		Sulindac	M01AB02		
		Tolmetin	M01AB03		
		Diclofenac	M01AB05		
		Alclofenac	M01AB06		
		Etodolac	M01AB08		
		Acemetacin	M01AB11		
		Ketorolac†	M01AB15		
		Aceclofenac	M01AB16		
		Piroxicam†	M01AC01		
		Tenoxicam	M01AC02		
		Meloxicam	M01AC06		
		Ibuprofen	M01AE01		

(Continued)

Table 1. (Continued)

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
		Naproxen	M01AE02		
		Ketoprofen	M01AE03		
		Fenoprofen	M01AE04		
		Fenbufen	M01AE05		
		Flurbiprofen	M01AE09		
		Tiaprofenic acid	M01AE11		
		Mefenamic acid	M01AG01		
		Flufenamic acid	M01AG03		
		Meclofenamic acid	M01AG04		
		Nabumetone	M01AX01		
		Niflumic acid	M01AX02		
		Benzydamine	M01AX07		
		Nimesulide	M01AX17		
Respiratory system	First-generation antihistamines	Brompheniramine, combinations	R01BA52	High anticholinergic effects that may lead to confusion, urinary retention, constipation, dry mouth, etc.	Second-generation antihistamine.
		Triprolidine, combinations	R01BA02		
		Promethazine, combinations	R05FA02		
		Dexchlorpheniramine, combinations	R05X		
		Diphenhydramine†	R06AA02		
		Dimenhydrinate	R06AA02		
		Clemastine†	R06AA04		
		Diphenylpyraline†	R06AA07		
		Carbinoxamine†	R06AA08		
		Doxylamine†	R06AA09		
		Diphenhydramine, combinations	R06AA52		

(Continued)

Table 1. (Continued)

Category	Subtype	Drugs	ATC code	Concern	Alternatives/suggestions
		Diphenylpyraline, combinations	R06AA57		
		Brompheniramine†	R06AB01		
		Dexchlorpheniramine†	R06AB02		
		Chlorpheniramine†	R06AB04		
		Promethazine†	R06AD02		
		Mequitazine†	R06AD07		
		Buclizine†	R06AE01		
		Cyclizine†	R06AE03		
		Chlorcyclizine†	R06AE04		
		Meclizine (meclozine)†	R06AE05		
		Oxatomide†	R06AE06		
		Buclizine, combinations	R06AE51		
		Meclizine, combinations	R06AE55		
		Homochlorcyclizine HCl (homoginin)†	R06AE91		
		Cyproheptadine†	R06AX02		
		Phenindamine†	R06AX04		
		Triprolidine†	R06AX07		
		Mebhydrolin†	R06AX15		
		Ketotifen†	R06AX17		
		Hydroxyzine**	N05BB01		

*Chlordiazepoxide is classified as a benzodiazepine, and it is available in Taiwan by combining clidinium, anticholinergics or antacid as a single pill for gastrospasm or gastritis.
**Hydroxyzine is classified as a first-generation antihistamine, but it can be used for sedation and anxiolysis.
†Identical medications listed in the 2012 version of PIM-Taiwan criteria.
NSAID, nonsteroidal anti-inflammatory drug; PIM, potentially inappropriate medication; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Table 2. 2018 version for potentially inappropriate medication use in persons aged ⩾65 years of age (PIM-Taiwan): drug–condition interactions that may cause the exacerbation of chronic diseases.

System	Condition	Medication classification	Concern
Circulatory system	Heart failure	• Nonsteroidal anti-inflammatory drugs (non-COX-2 selective NSAIDs) (Table 3.1)	• Potential to promote fluid retention and exacerbate heart failure.
		• Nonsteroidal anti-inflammatory drugs (COX-2 inhibitors) (Table 3.1.1)	
		• Nondihydropyridine calcium channel blockers (Table 3.2)	
		• Thiazolidinediones (Table 3.3)	
	Syncope	• Acetylcholinesterase Inhibitors (Table 3.4)	• Increases risk of orthostatic hypotension or bradycardia.
		• Peripheral alpha-1 blockers (Table 3.5)	
Nervous system	Delirium, dementia, or cognitive impairment	• Strongly anticholinergic drugs (Table 3.6)	• Avoid in older adults with or at high risk of delirium because of the potential to induce or worsen delirium. • Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g. behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.
		• Antipsychotics (Table 3.7)	
	History of falls or fractures	• Antipsychotics (Table 3.7)	• May cause ataxia, impaired psychomotor function, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. • If one of the drugs must be used, consider reducing the use of other CNS-active medications that increase risk of falls and fractures (i.e. anticonvulsants, opioid receptor agonists, antipsychotics, antidepressants, benzodiazepine receptor agonists, other sedatives and hypnotics) and implement other strategies to reduce fall risk.
		• Benzodiazepines (Table 3.8)	
		• Nonbenzodiazepine hypnotics (Table 3.9)	
	Parkinson's disease	• Antipsychotics (except quetiapine and clozapine) (Table 3.7)	• Dopamine-receptor antagonists with the potential to worsen Parkinsonian symptoms. Quetiapine, aripiprazole, clozapine appear to be less likely to precipitate the worsening of Parkinson's disease.
		• Antiemetics (Table 3.6)	
Digestive system	History of gastric or duodenal ulcers	• Aspirin (>325 mg/d)	• May exacerbate existing ulcers or cause new or additional ulcers.

(Continued)

Table 2. (Continued)

System	Condition	Medication classification	Concern
		• Nonsteroidal anti-inflammatory drugs (non-COX-2 selective NSAIDs) (Table 3.1)	
Genitourinary	Chronic kidney disease (creatinine clearance <30 ml/min)	• Nonsteroidal anti-inflammatory drugs (non-COX-2 selective NSAIDs and COX-2 inhibitors, oral and parenteral) (Table 3.1)	• May increase risk of acute kidney injury and further decline of renal function.
	Lower urinary tract symptoms, benign prostatic hyperplasia	• Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (Table 3.6)	• May decrease urinary flow and cause urinary retention.
Respiratory system	Bronchial asthma, chronic obstructive pulmonary disease	• Nonselective beta-blockers (Table 3.10)	• May worsen respiratory symptoms.

CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drug; PIM, potentially inappropriate medication.

ICC estimates for PIMs to be avoided generally were 0.634 (95% confidence interval 0.540–0.716, $p < 0.001$) and 0.557 (95% confidence interval 0.444–0.657, $p < 0.001$) in rounds one and two of the Delphi method, respectively (Table 5). The ICC estimates for PIMs considering chronic disease were 0.866 (95% confidence interval 0.760–0.939, $p < 0.001$) and 0.775 (95% confidence interval 0.599–0.898, $p < 0.001$) in rounds one and two of the Delphi method, respectively. This result indicated that there was moderate or good reliability in experts' measurements for each PIM statement.

Discussion

Explicit criteria with a listing of potentially inappropriate criteria have been established since 1991. These criteria have been applied to discourage the use of high-risk drugs among older people and have been used as indicators for prescription quality. The first version of the PIM-Taiwan criteria was published in 2012. Our methodology has been used as a reference to develop regional PIM lists because the literature review processes were dynamic and complex. After the PIM-Taiwan criteria were published, more than half of the regional PIM criteria were established using prior PIM lists.

Without adding new areas to our PIM criteria, the 2018 version of the PIM criteria only has two categories of PIMs, including PIMs that are generally avoided (Table 1) and those considered potentially inappropriate in certain chronic diseases (Table 2). After the PIM-Taiwan criteria were updated, many medication classes and drugs that are newly available in Taiwan have been added to the 2018 version. In contrast, some medications and drug–disease interaction statements were removed (Table 4). The user-friendly characteristics of the statements were retained, including alternative therapies or suggestions for PIMs in Table 1, and the concern and the ATC code for each PIM.

The experts who participated in the establishment of the most frequently published PIM criteria were geriatricians, psychiatrists, and clinical pharmacists. In this study, we invited many experts from other specialties including gastroenterology, cardiology, pulmonary medicine, neurology, and urology, to reflect the multidisciplinary perspectives. With a multidisciplinary approach, the rating of

Table 3. Individual medication list for medication classes in Table 2 for drug–condition interactions that may cause the exacerbation of chronic diseases.

Medication classification	Drugs	ATC code	Medication classification	Drugs	ATC code
3.1 Nonsteroidal anti-inflammatory drugs (non-COX-2 selective NSAIDs)	Indomethacin	M01AB01	3.3 Thiazolidinediones	Pioglitazone	A10BG03
	Sulindac	M01AB02		Rosiglitazone	A10BG02
	Tolmetin	M01AB03			
	Diclofenac	M01AB05	3.4 Acetylcholinesterase Inhibitors	Donepezil	N06DA02
	Alclofenac	M01AB06		Rivastigmine	N06DA03
	Etodolac	M01AB08		Galantamine	N06DA04
	Acemetacin	M01AB11			
	Ketorolac	M01AB15	3.5 Peripheral alpha-1 blockers	Doxazosin	C02CA04
	Aceclofenac	M01AB16		Prazosin	C02CA01
	Piroxicam	M01AC01		Terazosin	G04CA03
	Tenoxicam	M01AC02			
	Meloxicam	M01AC06	3.6 Strongly anticholinergic drugs (antimuscarinics for urinary incontinence)	Flavoxate	G04BD02
	Ibuprofen	M01AE01		Oxybutynin	G04BD04
	Naproxen	M01AE02		Solifenacin	G04BD08
	Ketoprofen	M01AE03		Tolterodine	G04BD07
	Fenoprofen	M01AE04		Trospium	G04BD09
	Fenbufen	M01AE05			
	Flurbiprofen	M01AE09	3.6 Strongly anticholinergic drugs (antihistamines)	Brompheniramine	R06AB01
	Tiaprofenic acid	M01AE11		Carbinoxamine	R06AA08
	Mefenamic acid	M01AG01		Chlorpheniramine	R06AB04

(Continued)

Table 3. (Continued)

Medication classification	Drugs	ATC code	Medication classification	Drugs	ATC code
	Flufenamic acid	M01AG03		Clemastine	R06AA04
	Meclofenamic acid	M01AG04		Cyproheptadine	R06AX02
	Nabumetone	M01AX01		Dexchlorpheniramine	R06AB02
	Niflumic acid	M01AX02		Dimenhydrinate	R06AA02
	Benzydamine	M01AX07		Diphenhydramine (oral)	R06AA02
	Nimesulide	M01AX17		Doxylamine	R06AA09
				Hydroxyzine	N05BB01
3.1 Nonsteroidal anti-inflammatory drugs (COX-2 selective NSAIDs)	Celecoxib	M01AH01		Meclizine	R06AE05
	Etoricoxib	M01AH05		Triprolidine	R06AX07
3.2 Nondihydropyridine Calcium Channel Blockers	Diltiazem	C08DB01	3.6 Strongly anticholinergic drugs (antiparkinsonian agents)	Trihexyphenidyl (benzhexol)	N04AA01
	Verapamil	C08DA01		Biperiden	N04AA02
3.6 Strongly anticholinergic drugs (skeletal muscle relaxants)	Cyclobenzaprine	M03BX08	3.7 Antipsychotics, chronic and as needed use antipsychotics, first-generation (conventional)	Chlorpromazine	N05AA01
	Orphenadrine	M03BC01		Levomepromazine	N05AA02
				Fluphenazine	N05AB02
3.6 Strongly anticholinergic drugs (antidepressants)	Amitriptyline	N06AA09		Perphenazine	N05AB03
	Clomipramine	N06AA04		Trifluoperazine	N05AB06
	Doxepin (>6 mg)	N06AA12		Thioridazine	N05AC02
	Imipramine	N06AA02		Haloperidol	N05AD01
	Paroxetine	N06AB05		Flupentixol	N05AF01

(Continued)

Table 3. (Continued)

Medication classification	Drugs	ATC code	Medication classification	Drugs	ATC code
				Chlorprothixene	N05AF03
3.6 Strongly anticholinergic drugs (antipsychotics)	Chlorpromazine	N05AA01		Pimozide	N05AG02
	Clozapine	N05AH02		Loxapine	N05AH01
	Loxapine	N05AH01		Sulpiride	N05AL01
	Olanzapine	N05AH03	3.7 Antipsychotics, chronic and as needed use antipsychotics, second-generation (atypical)	Ziprasidone	N05AE04
	Perphenazine	N05AB03		Lurasidone	N05AE05
	Thioridazine	N05AC02		Clozapine	N05AH02
	Trifluoperazine	N05AB06		Olanzapine	N05AH03
				Quetiapine	N05AH04
3.6 Strongly anticholinergic drugs (antiarrhythmic)	Disopyramide	C01BA03		Amisulpride	N05AL05
				Risperidone	N05AX08
3.6 Strongly anticholinergic drugs (antispasmodics)	Atropine (excludes ophthalmic)	A03BA01		Zotepine	N05AX11
	Belladonna alkaloids	A03BA04		Aripiprazole	N05AX12
	Clidinium-chlordiazepoxide	A03CA02		Paliperidone	N05AX13
	Dicyclomine	A03AA07			
	Hyoscyamine	A03BA03	3.8 Nonselective beta-blocker	Alprenolol	C07AA01
	Propantheline	A03AB05		Carteolol	C07AA15
	Scopolamine (excludes ophthalmic)	A04AD01		Pindolol	C07AA03

(Continued)

Table 3. (Continued)

Medication classification	Drugs	ATC code	Medication classification	Drugs	ATC code
				Sotalol	C07AA07
3.6 Strongly anticholinergic drugs (antiemetics)	Prochlorperazine	N05AB04			
	Promethazine	R06AD02	3.9 Nonbenzodiazepine hypnotics	Zopiclone	N025CF01
				Zolpidem	N025CF02
				Zaleplon	N025CF03
				Eszopiclone	N025CF04
3.10 Benzodiazepines	Clonazepam	N03AE01	3.10 Benzodiazepines	Nordazepam	N05BA16
	Diazepam	N05BA01		Fludiazepam	N05BA17
	Chlordiazepoxide	N05BA02		Oxazolam	N05BA
	Medazepam	N05BA03		Flurazepam	N05CD01
	Oxazepam	N05BA04		Nitrazepam	N05CD02
	Lorazepam	N05BA06		Flunitrazepam	N05CD03
	Bromazepam	N05BA08		Estazolam	N05CD04
	Clobazam	N05BA09		Triazolam	N05CD05
	Prazepam	N05BA11		Midazolam	N05CD08
	Alprazolam	N05BA12		Brotizolam	N05CD09

NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Medications or criteria removed since the 2012 PIM-Taiwan criteria.

Independent of diseases	Considering diseases
• Belladonna alkaloid (A03BA/A03BB)	• Blood clotting disorders or receiving anticoagulant therapy, entire criterion
• Hyoscyamine products (A03BA03)	• Chronic constipation, entire criterion
• Ticlopidine (B01AC05)	• Glaucoma, entire criterion
• Methyldopa (C02AB01)	• Sleep apnea syndrome, entire criterion
• Reserpine (C02AA02)	• Urinary incontinence, entire criterion
• Phenylbutazone (M01AA01)	• Chronic obstructive pulmonary disease, benzodiazepine
• **Muscle relaxants**	• Cognitive impairment, dementia- benzodiazepine
• Baclofen (M03BX01)	
• Carisoprodol (M03BA02)	
• Chlormezanone (M03BB02)	
• Chlorphenesin carbamate (M03)	
• Chlorzoxazone (M03BB03)	
• Cyclobenzaprine (M03BX08)	
• Dantrolene (M03CA01)	
• Methocarbamol (M03BA03)	
• Orphenadrine (M03BC01)	
• Phenprobamate (M03BA01)	
• Pridinol (M03BX03)	
• Tizanidine (M03BX02)	
• Tolperisone (M03BX04)	
• Pethidine (N02AB02)	
• Propoxyphene (N02AC04)	
• Potassium clorazepate (N05BA05)	
• Meprobamate (N05BC01)	
• Amobarbital (N05CA02)	
• Pentobarbital (N05CA01)	
• Secobarbital (N05CA06)	
• Dosulepin (N06AA16)*	
• Alimemazine (R06AD01)*	
• Azatadine (R06AX09)*	

(Continued)

Table 4. (Continued)

Independent of diseases	Considering diseases
• Chlorphenoxamine (R06AA06)*	
• Mepyramine (R06AC01)*	
• Pheniramine (R06AB05)*	
• Tripelennamine (R06AC04)*	

PIM, potentially inappropriate medication, 2012 PIM-Taiwan criteria.[29]

Table 5. Summary of interrater reliability statistics for medications considered to be potentially inappropriate.

	Round 1				Round 2			
	Intraclass correlation coefficient*				Intraclass correlation coefficient*			
	Value	95% CI	*p* value	*F* test	Value	95% CI	*p* value	*F* test
PIM to be avoided generally	0.634	0.540–0.716	<0.001	2.73	0.557	0.444–0.657	<0.001	2.26
PIM considering chronic diseases	0.866	0.760–0.939	<0.001	7.45	0.775	0.599–0.898	<0.001	4.45

*Intraclass correlation coefficients using mean-rating ($k = 24$), consistency, two-way mixed effects model ($0.75 > ICC > 0.5$ describes moderate reliability, $0.9 > ICC > 0.75$ describes good reliability).
CI, confidence interval; PIM, potentially inappropriate medication.

some PIMs in the preliminary list can be more heterogeneous, particularly for medications commonly prescribed in certain specialties. In Table 1, the quetiapine and insulin sliding scale was not considered to be potentially inappropriate. Quetiapine has a less negative influence on mortality than do other antipsychotics. In addition, the majority of its adverse drug events were preventable. Although we did not regard it as a PIM in the PIM criteria, physicians still need to monitor its adverse events and avoid long-term use. For the sole use of sliding scale insulin, we could not conclude from current systemic reviews that using other strategies can reduce hyperglycemia and prevent hypoglycemia. Therefore, we did not include this statement as PIM. In Table 2, all experts agreed that these medication classes were potentially inappropriate in their corresponding chronic comorbidities.

After we published our strategy to establish a new country- or region-specific PIM criteria,[29] several sets of criteria were established using a similar methodology. If we use all the newly published sets of criteria to establish our preliminary lists, we find that some of the PIMs are duplicated, because they may be derived from other criteria, such as the Beers criteria. Therefore, we only selected those established based on the results of a literature review and a subsequently modified Delphi method. As a result of this strategy, in Table 1, two classes of medications (barbiturates and muscle relaxants) that were regarded as PIMs in the first version of our criteria were removed. In Table 2, five chronic diseases (blood clotting disorders or anticoagulant therapy, chronic constipation, glaucoma, sleep apnea syndrome, and urinary incontinence) were removed, because these diseases were not restricted to older adults. These disease–medication interactions should be considered among the general population without regard to age.

Polypharmacy has been shown to be associated with adverse outcomes, high healthcare costs, and poor quality of life. The avoidance of potentially inappropriate medication is an important strategy

to prevent adverse drug events and to deprescribe for older adults. In the systemic review, deprescribing seems to be an effective strategy to reduce mortality in nonrandomized studies. However, when studies aim to investigate the effect of implicit and explicit tools on the outcome of reducing PIMs, the benefit of interventions was not clear. When using implicit criteria, pharmacists or other clinicians need more knowledge and clinical experiences to identify target medications for deprescribing. In addition, clinicians may identify different targets for deprescribing without a clear reference. In contrast, the use of explicit criteria is straightforward and simple. Therefore, PIM criteria can be an important tool to reduce PIM-related adverse events. After our PIM-Taiwan criteria are updated, more PIMs could be identified.[22] However, the number of individual drugs and statements increased when PIM lists were updated, and it would be a barrier for clinicians to apply these tools efficiently in clinical practice. With the assistance of e-prescribing or computerized physician order entry systems, the positive effect of reduced PIMs has been demonstrated in several studies.[30]

The first disadvantage of this tool was that PIMs were derived from existing criteria, and new findings from recent clinical trials were not fully reviewed. Our criteria only listed drugs to be avoided and not those that should be initiated among older adults. Second, for ease of application in clinical practice, we did not use the complex classification system adopted by the 2015 version of the Beers criteria including PIMs to be used with caution, drug–drug interactions, and dose consideration with varying levels of kidney function in older adults. Third, all medications listed in these criteria were available in the medication database from the National Health Insurance Administration in Taiwan. Therefore, the criteria should be modified before applying them in other countries.

Conclusion

In conclusion, a 2018 version of the PIM-Taiwan criteria was developed through a systemic method that could be replicated by other groups. Several important modifications were made to maintain the relevance and usefulness of the criteria. Its user-friendly characteristics will help clinicians to reduce polypharmacy and PIMs among older patients.

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References

1. Cheng TM. Reflections on the 20th anniversary of Taiwan's single-payer national health insurance system. *Health Aff (Millwood)* 2015; 34: 502–510.
2. Wald DS, Law M, Morris JK, *et al*. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009; 122: 290–300.
3. Kantor ED, Rehm CD, Haas JS, *et al*. Trends in prescription drug use among adults in the United States from 1999–2012. *JAMA* 2015; 314: 1818–1831.
4. Wang YJ, Chiang SC, Lee PC, *et al*. Is excessive polypharmacy a transient or persistent phenomenon? A nationwide cohort study in Taiwan. *Front Pharmacol* 2018; 9: 120.
5. Rodrigues MC and Oliveira C. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. *Rev Lat Am Enfermagem* 2016; 24: e2800.
6. Leelakanok N, Holcombe AL, Lund BC, *et al*. Association between polypharmacy and death: a systematic review and meta-analysis. *J Am Pharm Assoc* (2003) 2017; 57: 729–738 e710.
7. Oscanoa TJ, Lizaraso F and Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur J Clin Pharmacol* 2017; 73: 759–770.
8. Beers MH, Ouslander JG, Rollingher I, *et al*. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991; 151: 1825–1832.

9. By the American Geriatrics Society Beers Criteria Update Expert Panel. American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015; 63: 2227–2246.
10. Bala SS, Narayan SW and Nishtala PS. Potentially inappropriate medications in community-dwelling older adults undertaken as a comprehensive geriatric risk assessment. *Eur J Clin Pharmacol* 2018; 74: 645–653.
11. Kuhn-Thiel AM, Weiss C, Wehling M, *et al*. Consensus validation of the FORTA (Fit fOR The Aged) list: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. *Drugs Aging* 2014; 31: 131–140.
12. Laroche ML, Charmes JP and Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. *Eur J Clin Pharmacol* 2007; 63: 725–731.
13. O'Mahony D, O'Sullivan D, Byrne S, *et al*. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015; 44: 213–218.
14. Nyborg G, Straand J, Klovning A, *et al*. The Norwegian general practice—nursing home criteria (NORGEP-NH) for potentially inappropriate medication use: a web-based Delphi study. *Scand J Prim Health Care* 2015; 33: 134–141.
15. Maio V, Del Canale S, Abouzaid S, *et al*. Using explicit criteria to evaluate the quality of prescribing in elderly Italian outpatients: a cohort study. *J Clin Pharm Ther* 2010; 35: 219–229.
16. Winit-Watjana W, Sakulrat P and Kespichayawattana J. Criteria for high-risk medication use in Thai older patients. *Arch Gerontol Geriatr* 2008; 47: 35–51.
17. Kojima T, Mizukami K, Tomita N, *et al*. Screening tool for older persons' appropriate prescriptions for Japanese: report of the Japan Geriatrics Society Working Group on 'Guidelines for medical treatment and its safety in the elderly'. *Geriatr Gerontol Int* 2016; 16: 983–1001.
18. Rancourt C, Moisan J, Baillargeon L, *et al*. Potentially inappropriate prescriptions for older patients in long-term care. *BMC Geriatr* 2004; 4: 9.
19. Motter FR, Fritzen JS, Hilmer SN, *et al*. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. Eur J Clin Pharmacol. *Epub ahead of print* 27 March 2018. DOI: 10.1007/s00228-018-2446-0.
20. Chang CB, Lai HY, Yang SY, *et al*. Patient- and clinic visit-related factors associated with potentially inappropriate medication use among older home healthcare service recipients. *PLoS One* 2014; 9: e94350.
21. Chang CB, Yang SY, Lai HY, *et al*. Application of three different sets of explicit criteria for assessing inappropriate prescribing in older patients: a nationwide prevalence study of ambulatory care visits in Taiwan. *BMJ Open* 2015; 5: e008214.
22. Chang CB, Lai HY, Hwang SJ, *et al*. The application of updating PIM-Taiwan criteria in clinic-visiting older patients with polypharmacy. *Ther Adv Drug Saf* 2018; 9: 699–709.
23. Holt S, Schmiedl S and Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int* 2010; 107: 543–551.
24. Basger BJ, Chen TF and Moles RJ. Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA appropriateness method. *BMJ Open* 2012; 2. pii: e001431.
25. Mann E, Bohmdorfer B, Fruhwald T, *et al*. Potentially inappropriate medication in geriatric patients: the Austrian consensus panel list. *Wien Klin Wochenschr* 2012; 124: 160–169.
26. Renom-Guiteras A, Meyer G and Thurmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. *Eur J Clin Pharmacol* 2015; 71: 861–875.
27. Rudolph JL, Salow MJ, Angelini MC, *et al*. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008; 168: 508–513.
28. Tible OP, Riese F, Savaskan E, *et al*. Best practice in the management of behavioural and psychological symptoms of dementia. *Ther Adv Neurol Disord* 2017; 10: 297–309.
29. Chang CB, Yang SY, Lai HY, *et al*. Using published criteria to develop a list of potentially inappropriate medications for elderly patients in Taiwan. *Pharmacoepidemiol Drug Saf* 2012; 21: 1269–1279.
30. Scott IA, Pillans PI, Barras M, *et al*. Using EMR-enabled computerized decision support systems to reduce prescribing of potentially inappropriate medications: a narrative review. *Ther Adv Drug Saf* 2018; 9: 559–573.