Original Article

Potentially Inadequate Medications in the Elderly: PRISCUS 2.0

First Update of the PRISCUS List

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Summary

Background: The term potentially inadequate medication (PIM) is used to describe substances that may be unsuitable for use in the elderly and should be avoided. The PRISCUS list, published in 2010, was the first catalog of PIM designed for the German drug market to become adopted in practice. While 24% of German patients aged ≥ 65 years were prescribed at least one PIM per year in 2009, the proportion in 2019 was only 14.5%.

Methods: In a three-round Delphi process, experts from clinical practice and research evaluated whether selected substances are PIM for the elderly. The participants were provided with dedicated literature including systematic reviews carried out for the particular purposes of this project.

Results: Fifty-nine persons took part in the Delphi process and, in addition, contributed comments and therapeutic alternatives. Altogether, 187 substances were classed as PIM. One hundred thirty-three of the substances now listed were not in the original PRISCUS list: these include some oral antidiabetics, all of the selective COX-2 inhibitors, and moderately long acting benzodiazepines such as oxazepam. For some other substances, e.g., proton pump inhibitors (PPI), the advisability of treatment for more than 8 weeks was considered as potentially inappropriate, as was the use of ibuprofen in doses >1200 mg/day and for more than 1 week without PPI. Risperidone for more than 6 weeks is also PIM.

Conclusion: The new, greatly extended PRISCUS list must now be validated in epidemiological and prospective studies and its practicability in routine daily use must be verified.

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Pharmacotherapy in the elderly has recently been addressed in national guidelines (1, 2). Along with attention to numerous factors such as patient preferences, compliance, and interactions, drug safety in old age can also be enhanced by avoidance of potentially inadequate medications (PIM). Many medications cause more—and sometimes different—side effects in the elderly than in younger patients, so the benefit–risk ratio may change. The substances primarily concerned are those that bring about dizziness or a rapid decrease in blood pressure, impair cognition, or increase the danger of falls (3, 4).

The PRISCUS list (Latin *priscus*: old, venerable) for the German drug market was published in 2010 (5) and has since found its way into textbooks and prescription software. Numerous studies have shown the association between the intake of PIM on the PRISCUS list and adverse drug events (ADE), in particular an elevated risk of hospital admission (6–8).

One challenge in evaluating the safety and tolerability of drugs in old age is the frequent lack of data from clinical research (9). For this reason, PIM lists are compiled by experts, usually in a Delphi process (5).

Nevertheless, it is advisable to substantiate an expert survey with the best available evidence. For an update of the PRISCUS list, additional systematic reviews should therefore be performed and existing reviews should be processed and presented to experts as the basis for maximally evidence-based decisions. The PRISCUS list is also in urgent need of updating because of the changes in the drugs market since 2010.

TABLE 1

GRADE summary of findings: PPI compared with no treatment in elderly patients

Outcomes	Expected absolute effects*1 [95% CI]		Relative effect [95% CI]	Number of participants (studies)	Certainty of evidence (GRADE)
	Risk without treatment	Risk with PPI			
GERD symptoms (e24) measured in terms of: frequency Observation period: mean 5 years				44 (1 observational study)	Very low*2
• **Comment:** PPI may reduce GERD symptoms in the elderly (MD 10.6 times less common per month), but the evidence is uncertain.					
Mortality (e25) measured in terms of: events Observation period: 1 year	10 410 per 100 000	15 295 per 100 000 [10 705; 26 251]	HR 1.51 [1.03; 2.77]	491 (1 observational study)	Low*3, *4, *5
Hospitalization – not reported			–	–	
Quality of life – not reported			–	–	
Clostridium difficile diarrhea (e26, e27)	233 per 1000	291 per 1000 [152; 485]	OR 1.35 [0.59; 3.10]	281 cases, 279 controls (2 observational studies)	Low*6, *7
Hip joint fracture after > 4 years of PPI treatment (e28) measured in terms of: events Exposure time: 1 year	40 per 1000	62 per 1000 [0; 0]	OR 1.59 [1.39; 1.80]	13 556 cases, 135 386 controls (1 observational study)	Moderate*5, *8
• **Comment:** Absolute numbers were not reported and were calculated by study staff. The OR was determined for multiple covariates.					
Pneumonia – not reported			–	–	
Dementia (e29, e30)	7789 per 100 000	14 267 per 100 000 [10 845; 18 572)	RR 1.97 [1.44; 2.70]	2666 (2 observational studies)	Low*9
• **Comment:** Three studies were excluded from the meta-analysis because absolute numbers were not reported. One study found an elevated risk of dementia from PPI use (e31; HR 1.44; 95 % CI [1.36; 1.52]). One study found no difference between PPI users and non-users (e32; only p-value reported [p = 0.66]). One study found a lower risk of dementia in PPI users (e33; HR 0.78; 95% CI [0.66; 0.9]).					
Hospitalization owing to acute kidney injury (e34)	2 per 1000	4 per 1000 [4; 5]	HR 2.45 [2.21; 2.71]	58 1184 (1 observational study)	Low*5

*1The risk in the intervention group and the 95% confidence interval are based on the assumed risk in the control group and the relative effect of the intervention (and the and the 95% confidence interval)
*2Before and after study with no control group; *3cohort study with incomplete follow-up; *4 only hospitalized patients; *5only one study;
*6contradictory results in two studies; *7large 95% confidence interval, including a considerable positive benefit/risk ratio; *8case–control study;
*9high risk of bias in individual studies

GRADE Working Group levels of evidence
High certainty: Considerable confidence that the true effect is similar to the estimated effect.
Moderate certainty: Moderate confidence in the effect estimator: the true effect is probably close to the estimated effect, but the possibility exists that it differs markedly.
Low certainty: Confidence in the effect estimator is limited: the true effect may be markedly different from the estimated effect.
Very low certainty: Confidence in the effect estimator is very low: the true effect is probably markedly different from the estimated effect.

CI, Confidence interval; GERD, gastro-esophageal reflux disease; HR, hazard ratio; MD, mean difference; OR, odds ratio; PPI, proton pump inhibitors; RR, relative risk

Method

In order to facilitate preparation of a list of substances and substance classes for evaluation, the literature was searched for international PIM lists published since 2010 and a systematic literature review was conducted *(eBox 1a)*. To narrow down the substances for assessment, prescription data from the statutory health insurance funds in Germany and Austria were analyzed, as a joint PRISCUS 2.0 list was to be compiled for use in both countries.

Moreover, substances were prioritized for analysis in systematic reviews on the basis of prescription frequency. We were also able to take advantage of existing reviews from the PRIMA-eDS study (an EU project; for details see www.prima-eds.eu) (9–13). Additionally, an exploratory survey was carried out to establish whether, for the remaining substances, information from other sources was sufficient for assessment by the participants (pre-Delphi; *eBox 1b*). The processing of the reviews' findings was oriented on the standards for clinical practice guidelines (14–16). A detailed description can be found in *eBox 1*. Furthermore, the experts had access to a collection of literature with complete texts and abstracts from publications cited in Micromedex (17), for example, and the other publications used *(eBox 1c)*.

The substances were evaluated on a consensus basis over a three-round Delphi process (18, 19). For this purpose, persons with expertise in geriatric pharmacotherapy were identified (professional bodies, the Drug

Commission of the German Medical Association, participants in the compilation of the original PRISCUS list [5] and the Austrian PIM list [e1]) and invited to take part. The participants evaluated the substances on a five-point Likert scale, from from 1 = potentially inappropriate (= PIM) to 5 (definitely not a PIM) *(eBox 2a)*. The rating method is explained in *eBox 2b*.

In addition to their ratings on the Likert scale, the participants were asked, if possible, to give the following information:

- Dose or time limit(s) from which the substance is a PIM
- More appropriate alternatives
- Monitoring of the effects if the substance is used
- Contraindicating comedication and comorbidities
- Any other comments

The participants also had the opportunity to suggest other substances for evaluation.

The results of the first Delphi round were provided to the participants as feedback *(eBox 2c)*. Substances that were not rated unambiguously in the first round and those for which discrepancies emerged between expert evaluation and systematic reviews had to be evaluated anew in the second round. Based on the participants' comments, some substances were evaluated in different doses and durations of use. In addition to the two Delphi rounds originally scheduled, a third round focused on one topic was added, because of inconsistencies between the evaluations and the participants' comments with regard to the non-steroidal anti-inflammatory drugs (NSAID).

The results were available for (professional) public comment on the project website for 4 weeks in March 2021. Finally, all comments were summarized and incorporated into the complete version of PRISCUS 2.0.

Results

We identified 24 articles that listed PIM in the elderly (5, e1–e23) and eight relevant systematic reviews on ADE in older patients (20–27). Evaluation of the international PIM lists, the prescription data of the German National Association of Statutory Health Insurance Fund (GKV), and the substances available for use in Austria resulted in identification of a total of 250 substances and substance classes to be considered for addition to the update of the PRISCUS list. No further substances were revealed by scrutiny of the identified systematic reviews.

Thirteen systematic reviews were carried out to provide evidence backing up the suggested additions for the update of the PRISCUS list. An overview of these reviews and their roles in the project can be found in *eTable 1*. Altogether, 21 GRADE summary of findings (SOF) and evidence profile tables for the results of the new and identified reviews were compiled. An example of the selected presentation can be found in *Table 1*.

Of 101 persons contacted with regard to the Delphi process, 70 signed a declaration that they would participate. Fifty-five persons took part in the first round, 52 in the second round, and eight in the third round. Overall 59 persons took part in at least one Delphi round, representing a broad spectrum of medical specialties (including general medicine, geriatrics, clinical pharmacy, psychiatry, internal medicine, palliative medicine, clinical pharmacology, and cardiology). The distribution of the participants across the three rounds of the Delphi process is visualized in the *eFigure*.

The three-round Delphi process began in March 2020. Of the 250 substances/substance classes evaluated in the first round, 158 were rated as PIM and 23 as non-PIM. On the basis of the expert comments, 13 substances were differentiated in terms of time/dose limits, two according to indication, one substance was added to the list, and two substances were reconsidered in their own right rather than as part of their class. Thus a total of 87 substances were put forward for assessment in the second Delphi round, 29 of which were classified as PIM and 13 as non-PIM. There was still no unambiguous rating for 45 substances. In a third Delphi round, none of the four substances evaluated were unambiguously classified as PIM or non-PIM. Over the course of the Delphi process, therefore, 187 substances were rated as PIM, 36 as non-PIM, and the classification of 49 substances was ambiguous, i.e., they may be PIM (*eTable 4*). The Delphi process is portrayed in the *eFigure*.

In addition to the median, mean, and 95% confidence interval, the detailed version of PRISCUS 2.0 contains the following details on each substance:

- Possible alternatives
- Information about monitoring
- Comedication/comorbidities to be avoided
- Reason for classification as PIM
- Discussion points

Substances that are no longer marketed in Germany or are not eligible for prescription are listed separately. This version is available on the project website (www.priscus2-0.de). PRISCUS 2.0 contains 177 substances/substance classes *(Table 2, eTable 2)*.

Six substances in the original PRISCUS list were not suggested for inclusion in PRISCUS 2.0, either because they were no longer marketed (e.g., zaleplon) or because, going by the GKV prescription data, their prescription to patients aged 65 years or over had decreased to a very low level (e.g., triprolidine). Nitrofurantoin, in contrast to the original list, was no longer classified as a definite PIM. A total of 133 substances were newly classified as PIM; nine of these, however, are currently not on the market (e.g., rilmenidine) or not eligible for prescription (e.g., reboxetine).

Discussion

PRISCUS 2.0, with 177 substances listed, is more than twice as long as the original PRISCUS list. In several cases (e.g., neuroleptics and NSAID), the individual

TABLE 2

PRISCUS 2.0, short version

Substance/class	Possible alternatives depending on indication (expert opinion)
Drugs for acid-related diseases	
Antacids containing magnesium **> 4 weeks**	Antacids containing alginate PPI < 8 weeks
Compounds containing aluminum	Antacids containing alginate PPI < 8 weeks
Cimetidine, ranitidine*[1]	PPI < 8 weeks When indicated, famotidine
Proton pump inhibitors **> 8 weeks**	PPI < 8 weeks When indicated, famotidine
Drugs for functional gastrointestinal disorders	
Mebeverine	E.g., psyllium, non-pharmacological
Metoclopramide, domperidone	E.g., setrons, herbal preparations
Alizapride	
Antiemetics and drugs for nausea	
Dimenhydrinate	E.g., setrons, herbal preparations
Scopolamine	E.g., corticosteroids, setrons
Drugs for constipation	
Liquid paraffin	E.g., macrogol, psyllium
Sennosides **> 1 week**	E.g., sennosides < 1 week, macrogol
Sodium picosulfate **> 1 week**	E.g., sodium picosulfate < 1 week, macrogol
Antipropulsives	
Loperamide **> 3 d, > 12 mg/d**	E.g., loperamide < 3 d, < 12 mg/d, racecadotril
Antidiabetic drugs	
Glibenclamide, gliquidone, gliclazide, glimepiride	E.g., metformin, DPP-4 inhibitors
Acarbose	E.g., metformin, DPP-4 inhibitors
Pioglitazone	E.g., metformin, DPP-4 inhibitors
Antithrombotic drugs	
Ticlopidine, prasugrel	E.g., clopidogrel, ASA
Cardiac treatment	
Digoxin and derivatives	E.g., beta-blockers, digitoxin
Lidocaine	E.g., beta-blockers, when indicated amiodarone
Propafenone **as long-term medication**	E.g., beta-blockers, when indicated amiodarone
Flecainide	Beta-blockers, when indicated amiodarone
Dronedarone	E.g., beta-blockers, when indicated amiodarone
Antihypertensives	
Methyldopa, clonidine, moxonidine	E.g., ACE inhibitors, other antihypertensives
Doxazosin	E.g., ACE inhibitors, other antihypertensives
Terazosin **as antihypertensive**	ACE inhibitors, other antihypertensives
Dihydralazine, hydralazine*[2]	E.g., ACE inhibitors, other antihypertensives
Minoxidil	E.g., ACE inhibitors, other antihypertensives
Potassium-sparing drugs	
Spironolactone **> 25 mg/d**	E.g., spironolactone ≤ 25 mg/d
Peripheral vasodilators	
Pentoxifylline	E.g., memantine, ASA, memory/walking training
Naftidrofuryl, cilostazol	E.g., walking training, ASA
Beta-adrenoceptor antagonists	
Pindolol, propranolol, sotalol	Others (selective beta-blockers)
Calcium-channel blockers	
Non-slow-release nifedipine	E.g., long-acting calcium antagonists
Drugs acting on the renin–angiotensin system	
Aliskiren	ACE inhibitors, sartans
Sexual hormones and modulators of the genital system	
Testosterone	
Oral estrogens	Vaginal estrogens, black cohosh
Urologics	
Flavoxate	E.g., pelvic floor training, bladder training
Oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin, fesoterodine, desfesoterodine	Non-pharmacological
Mirabegron	Non-pharmacological
Hypophyseal and hypothalamic hormones and analogs	
Desmopressin	Tamsulosin, vaginal estrogens
Antibiotics for systemic use	
Fluoroquinolones	Depending on antibiogram
Endocrine treatment	
Medroxyprogesterone	Tamoxifen, fulvestrant, vaginal estrogens
Non-steroidal anti-inflammatory and antirheumatic drugs	
Phenylbutazone	E.g., topical agents, paracetamol
Indomethacin, diclofenac, acemetacin, proglumetacin, aceclofenac	E.g., topical agents, paracetamol
Piroxicam, meloxicam	E.g., topical agents, paracetamol
Ibuprofen **> 3 × 400 mg/d, > 1 week or > 3 × 400 mg/d, with PPI > 8 weeks**	E.g., ibuprofen ≤ 3 × 400 mg/d, ≤ 1 week, with PPI ≤ 8 weeks
Naproxen **> 2 × 250 mg/d, > 1 week or > 2 × 250 mg/d, with PPI > 8 weeks**	E.g., naproxen ≤ 2 × 250 mg/d, ≤ 1 week, with PPI ≤ 8 weeks
Ketoprofen, dexketoprofen	E.g., topical agents, paracetamol
Etofenamate	E.g., topical agents, paracetamol
Coxibs	E.g., topical agents, paracetamol
Nabumetone	E.g., topical agents, paracetamol
Muscle relaxants	
Methocarbamol, orphenadrine (citrate), baclofen, tizanidine	E.g., Paracetamol, tilidine
Pridinol	
Tolperisone	Paracetamol, metamizole

Other drugs for disorders of the musculoskeletal system	
Quinine	E.g., stretching exercises, magnesium < 4 weeks
Analgesics	
Dihydrocodeine, codeine **as analgesic**	
Pethidine, tapentadol, tramadol	E.g., tilidine, other opioids
Methadone, levomethadone	Other opioids
Acetylsalicylic acid **as analgesic**	E.g., paracetamol
Phenazone, propyphenazone	E.g., paracetamol
Ergotamine	Triptans, paracetamol
Antiepileptics	
Phenobarbital, primidone, phenytoin, carbamazepine	E.g., lamotrigine, valproate
Drugs for Parkinson's disease	
Trihexyphenidyl, biperiden, procyclidine, bornaprine	E.g., levodopa, ropinirole
Amantadine	E.g., levodopa, ropinirole
Pramipexole, piribedil	E.g., levodopa, ropinirole
Dopaminergic ergot alkaloids (e.g., pergolide)	E.g., levodopa, ropinirole
Monoaminoxidase-B inhibitors (e.g., selegiline)	E.g., levodopa, ropinirole
Tolcapone	Entacapone, when indicated opicapone
Antipsychotics	
Levomepromazine, perazine, thioridazine, chlorprothixene, zuclopenthixol, prothipendyl	E.g., risperidone < 6 weeks
Fluphenazine, perphenazine, haloperidol, benperidol, bromperidol, flupentixol, fluspirilene, pimozide	E.g., risperidone < 6 weeks
Melperone **> 100 mg/d, > 6 weeks**	E.g., melperone < 100 mg/d, < 6 weeks
Pipamperone **> 120 mg/d, > 6 weeks**	E.g., pipamperone < 120 mg/d, < 6 weeks
Ziprasidone, clozapine, olanzapine, sulpiride, amisulpride, tiapride, aripiprazole, sertindole, paliperidone, cariprazine	E.g., risperidone < 6 weeks
Quetiapine **> 100 mg/d, > 6 weeks**	E.g., quetiapine < 100 mg/d, < 6 weeks
Risperidone **> 6 weeks**	E.g., risperidone < 6 weeks
Anxiolytics, hypnotics, and sedatives	
Hydroxyzine	E.g., melatonin, mirtazapine
Long-acting benzodiazepines (e.g., diazepam)	E.g., melatonin, mirtazapine
Lorazepam	E.g., melatonin, mirtazapine, valerian
Moderately long-acting benzodiazepines (e.g., oxazepam)	E.g., melatonin, mirtazapine, valerian
Short-acting benzodiazepines (e.g., triazolam)	E.g., melatonin, mirtazapine, valerian
Chloral hydrate	E.g., melatonin, mirtazapine, valerian
Zopiclone, zolpidem	E.g., melatonin, mirtazapine, valerian
Clomethiazole	E.g., melatonin, mirtazapine
Doxylamine	E.g., melatonin, mirtazapine, valerian
Promethazine	E.g., melatonin, mirtazapine, valerian
Antidepressants	
Tricyclics (e.g., amitriptyline), nortriptyline[*3]	E.g., citalopram, mirtazapine
Opipramol	E.g., citalopram, mirtazapine
Doxepin	E.g., citalopram, mirtazapine
Maprotiline, mianserin	E.g., citalopram, mirtazapine
Fluoxetine, paroxetine, fluvoxamine	E.g., citalopram, mirtazapine
Sertraline **> 100 mg/d**	E.g., sertraline < 100 mg/d
Tranylcypromine, moclobemide	E.g., citalopram, mirtazapine
St John's wort	E.g., citalopram, mirtazapine
Bupropion	E.g., citalopram, mirtazapine
Tianeptine	E.g., citalopram, mirtazapine
Agomelatine	E.g., citalopram, mirtazapine
Psychostimulants	
Methylphenidate	
Pyritinol	E.g., memantine
Piracetam	E.g., memantine
Anti-dementia drugs	
Ginkgo leaf	E.g., memantine
Nicergoline	E.g., memantine
Nimodipine	E.g., memantine, amlodipine
Drugs for vertigo	
Betahistine	See long version
Cinnarizine[*4], flunarizine	See long version
Drugs for obstructive respiratory tract diseases	
Sympathomimetics for systemic use, no inhalation (e.g., salbumatol)	Inhaled sympathomimetics
Theophylline, aminophylline	Inhaled salbutamol LABA, LAMA, ICS
Cough and cold remedies	
Codeine, dihydrocodeine **as antitussive**	E.g., phytopharmaceuticals, DMP
Antihistamines for systemic use	
First generation	
Diphenhydramine, clemastine, dimetindene, cyproheptadine, ketotifen	E.g., cetirizine, topical agents
Second generation	
Ebastine, rupatadine	E.g., cetirizine, loratadine

ACE, Angiotensin-converting enzyme; ASA, acetylsalicylic acid; DMP, dextromethorphan; DPP-4, dipeptidyl peptidase-4; ICS, inhaled corticosteroids; LABA, long-acting beta-2 sympathomimetics; LAMA long-acting muscarine antagonists; PPI, Proton pump inhibitors

[*1] License suspended since January 2021 owing to nitrosamine contamination

[*2] In Germany: only as a compound with atenolol and chlorthalidone

[*3] According to comments, nortriptyline is tolerated better than other tricyclics; therefore, it was evaluated in its own right in the second round of the Delphi process

[*4] In Germany: only as a compound with dimenhydrinate

substances are listed separately rather than the substance class as a whole, in order to take account of possible differences among the substances. For some indications, such as diabetes mellitus, there was previously only one single substance listed; now numerous others have been added, not only for diabetes but also in the categories of beta-blockers, muscle relaxants, and drugs for use against Parkinson's disease.

The need to update lists of PIM regularly because recommendations for the use of certain substances change over time can be illustrated by the example of the direct oral anticoagulants (DOAC). We conducted a systematic review specifically to clarify the safety of DOAC in the elderly. Although DOAC were not evaluated at all for the first PRISCUS list, they were classified as PIM in the EU(7) list published in 2015 (e2). In the PRISCUS 2.0 process, however, they were rated as non-PIM, with the exception of dabigatran, which was categorized as a possible PIM. In the current version of the Beers list, dabigatran and rivaroxaban are mentioned as substances that should be used with caution in the elderly (e3).

In comparison with the LUTS-FORTA list (e18), it is striking that the alpha-blockers used in urology are rated in PRISCUS 2.0 as unclear (e.g., terazosin) or as non-PIM (tamsulosin), whereas LUTS-FORTA classifies them as "use with caution" (C) or "avoid" (D). A systematic review of the safety of alpha-blockers in the elderly carried out specifically for PRISCUS 2.0 did not lead to any of them being classified as PIM (28). While oral antidiabetics such as glibenclamide, glimepiride, and acarbose were categorized as PIM, the FORTA list differentiates them: glibenclamide is classified as D, glimepiride and acarbose as C. This difference is reflected somewhat in the much lower mean rating for glibenclamide than for the other substances.

Taken together, these examples clearly illustrate the discrepancies among different lists of PIM. On the one hand, this is due to the changes in available evidence over time and the different publication times of the individual lists. On the other hand, it must be remembered that the classifications of the substances considered depend on the ratings assigned by the experts involved in the process. Differences in classification of individual substances between PIM lists may be attributable to the compositions of the groups of experts recruited.

When compiling PIM lists, other lists are often used as data sources (29). In this respect, our systematic research and the development of an adapted GRADE procedure (16) represent a considerable step forward in methodology. FORTA classifies DPP-4 inhibitors as A (absolutely suitable), whereas the systematic review conducted for PRISCUS 2.0 revealed evidence of a possible elevation in mortality risk and a slightly increased risk of hypoglycemia compared with the standard treatment; however, DPP-4 were definitely superior to the sulfonylureas (30). Nevertheless, overall this class of substances was not categorized as PIM.

Since the publication of the PRISCUS list in 2010, lists of PIM have been compiled in many other countries (29). A number of studies have shown that intake of PIM is associated with adverse effects (6–8). Although there is not yet any evidence to show that discontinuation of PIM leads to reduction of morbidity and mortality (31), some analyses show a decline in the prescription of PIM in Germany (32).

Limitations

Restricting the list of substances suggested for PRISCUS 2.0 to those found in the GKV prescription data means that substances which can be obtained without prescription or are not eligible for prescription were not considered sufficiently. One example is the antihistamine triprolidine.

It remains the case that elderly persons are often excluded from clinical trials, leading to paucity of data (33). For reasons of time and resources, we were able to conduct systematic reviews only for certain substances, so that data on the remainder were limited to the findings of non-systematic research. In contrast to the original intention, some of the systematic reviews were completed only in time for the second round of the Delphi process.

The third Delphi round, focusing on NSAID, featured fewer participants than the previous rounds. It is possible that the results of the third round would have been different if a higher number of experts had taken part. In view of the participants' comments on which the third Delphi round was based, however, this is unlikely.

PIM lists specify substances that may not be suitable for use in the elderly. Prescription of a PIM may still be necessary in an individual patient, however, so the presence of a substance on a PIM list is not equivalent to a universally valid negative rating or prohibition. Individual assessment of each patient's clinical situation and the resulting choice of appropriate medication is and will remain a central task for the treating physicians. Whether a given drug is suitable or otherwise for the person concerned can be decided only in the knowledge of the particular patient's clinical situation, of which PRISCUS 2.0 takes no account. Although on the one hand this represents a crucial limitation, it means that PRISCUS 2.0 can also be used by persons with restricted access (or none at all) to clinical data, e.g., pharmacists, community carers, and relatives, to identify drugs that may not be appropriate. At various points in the medication process, therefore, it is possible to analyze—and potentially optimize—the patient's pharmaceutical treatment in consultation and cooperation with the physicians involved. Furthermore, the PRISCUS list is useful for pharmacoepidemiological analyses in situations where clinical data are sparse (32, 34).

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Conflict of interest statement
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► **Supplemenary material**

eReferences, eTables, eFigure, eBoxes:
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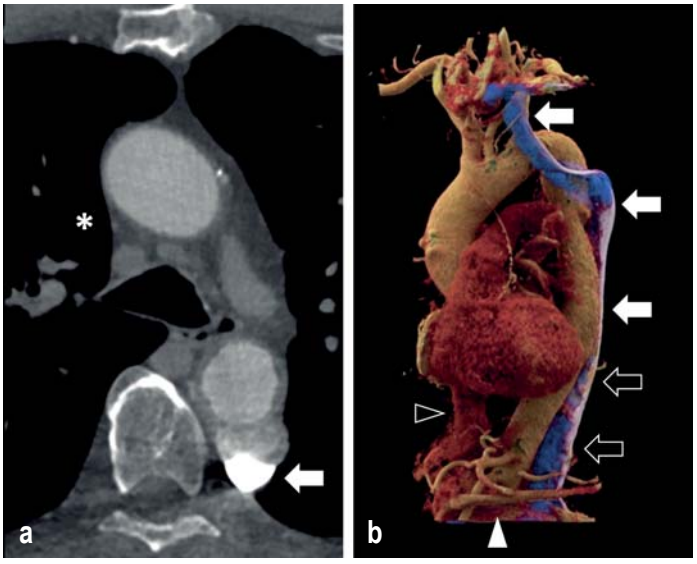
CLINICAL SNAPSHOT

Isolated Persistent Left Superior Vena Cava with Continuation Into the Hemiazygos Vein and Left Renal Vein



Elective computed tomography in an 85-year-old man (*Figure a;* mixed arterial/venous contrast phase) revealed an absent right superior vena cava (SVC; asterisk) and an isolated persistent left SVC (IPLSVC; arrows). Volumetric reconstruction *(Figure b)* demonstrates venous outflow via the IPLSVC (arrows), with continuation over the hemiazygos vein (open arrows) into the dilated left renal vein (arrowhead) and the normal right inferior vena cava (open arrowhead). The embryologically paired superior cardinal veins normally form the SVC on the right and the coronary sinus on the left. Left-sided SVC is the most common venous anomaly in the chest (prevalence, 0.3–0.5%, usually as a double SVC) and, from a clinical perspective, may complicate left-sided venous access to the heart, for example, when pacing electrodes or Swan-Ganzcatheters. In 80–90% of cases, the left SVC drains via the coronary sinus into the right atrium. The IPLSVC draining via the left renal vein detected incidentally in this case is a rarity.

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Supplementary material to:

Potentially Inadequate Medications in the Elderly: PRISCUS 2.0

First Update of the PRISCUS List

by Nina-Kristin Mann, Tim Mathes, Andreas Sönnichsen, Dawid Pieper, Elisabeth Klager, Mahmoud Moussa, and Petra A. Thürmann

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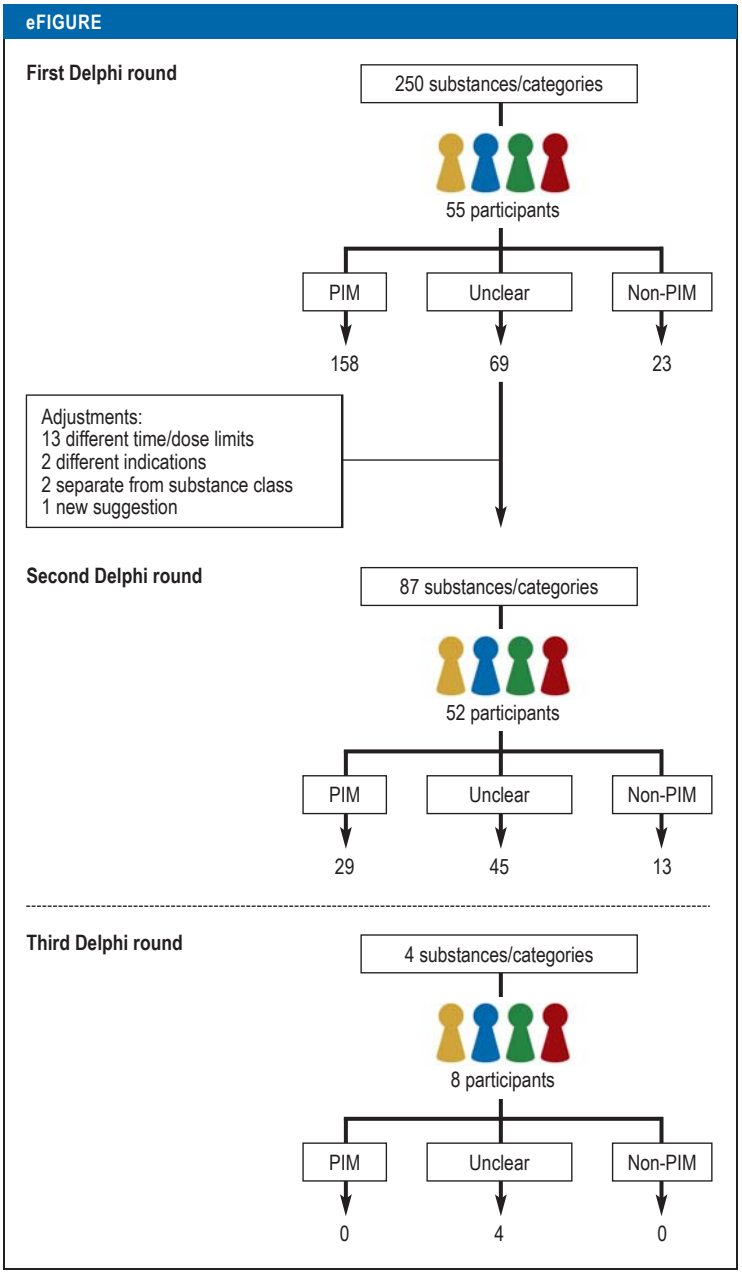
eFIGURE



Delphi process
PIM, Potentially inappropriate medication

eTABLE 1

Overview of new and identified systematic reviews and GRADE tables

Review on	First round?	Second round?	GRADE table?	No. of GRADE tables	Place of entry in expert material
From: PIM Austria—project report					
PPI	No	Yes	Second round	1	A02BC PPI
Benzodiazepines	No	No	No		
• **Comment:** Irrelevant in second round due to lack of discrepancy between review and expert assessment					
Alpha blockers	No	Yes	Second round	1	G04CA alpha-adrenoceptor antagonists
• **Comment:** Not entered for individual substances					
Ginkgo biloba	No	No	No		
• **Comment:** Irrelevant in second round due to lack of discrepancy between review and expert assessment					
Anticholinergic urologics and beta-3-adrenoceptor agonists	No	No	No		
• **Comment:** Irrelevant in second round due to lack of discrepancy between review and expert assessment					
Imidazoline receptor agonists	No	No	No		
• **Comment:** Irrelevant in second round due to lack of discrepancy between review and expert assessment					
Tramadol	No	Yes	Second round	1	N02AX02 Tramadol
Sulfonylureas	No	No	No		
• **Comment:** Irrelevant in second round due to lack of discrepancy between review and expert assessment					
Z substances	No	No	No		
• **Comment:** Irrelevant in second round due to lack of discrepancy between review and expert assessment					
Pregabalin	No	Yes	Second round	1	N03AX16 pregabalin
Aldosterone antagonists	No	Yes	Second round	1	C03DA aldosterone antagonists
• **Comment:** Not entered for individual substances being evaluated					
From: generic review on aging					
Anabolic steroids after hip fracture	Yes	No	First round	1	G03BA03 testosterone
Second-generation antipsychotics: severe side effects	Yes	Yes	First round Second round	1	N05A antipsychotics
Second-generation antipsychotics: mortality					
• **Comment:** Not entered for individual substances being evaluated					
Antibiotics in urinary tract infections	Yes	Yes	First round Second round	1	J01 antibiotics for systemic use
• **Comment:** Not entered for individual substances being evaluated					
Laxatives and iatrogenic falls	Yes	Yes	First round Second round	1	A06A medications to treat constipation
• **Comment:** Not entered for individual substances being evaluated					
Antihistamines and falls/fractures	Yes	Yes	First round Second round	1	R06A antihistamines for systemic use
• **Comment:** Not entered for individual substances being evaluated					

Atypical antipsychotics BPSD	Yes (risperidone)	Yes (risperidone)	First round Second round	1	N05AX08 risperidone
Antidepressants in patients aged ≥ 65 years	Yes (duloxetine)	Yes (duloxetine)	First round Second round	1	N06AX21 duloxetine
From: PRIMA-eDS and update/new research					
DOAC	Yes (text form)	No	No		B01AA vitamin-K antagonists
• **Comment:** Not entered for individual substances being evaluated					
DPP-4	Yes (text form)	Yes	Second round	2	A10BH DPP-4 inhibitors
• **Comment:** Two GRADE PDFs, one for each control					
From: PRIMA-eDS					
Beta-blockers	Yes	Yes	First round Second round	2	C07A beta-blockers
• **Comment:** Not entered for individual substances being evaluated Two GRADE PDFs, one for each control					
Metformin	Yes	No	First round	5	A10BA02 metformin
• **Comment:** Five GRADE PDFs, one for each control					
			Total	21	

BPSD, Behavioral and psychological symptoms of dementia; DOAC, direct oral anticoagulants; DPP-4, dipeptidylpeptidase-4; PPI, proton pump inhibitors

eTABLE 2

Substances classified as PIM (supplement to Table 2): number of ratings, mean, and confidence interval

Substance/class n = number of ratings	Mean [95% CI]
Drugs for acidity-related diseases	
Antacids containing magnesium **> 4 weeks** (n = 34)	2.29 [2.00; 2.59]
Compounds containing aluminum (n = 43)	2.60 [2.26; 2.95]
Cimetidine (n = 43)	1.98 [1.72; 2.23]
Ranitidine*1 (n = 44)	2.66 [2.35; 2.97]
Proton pump inhibitors **> 8 weeks** (n = 43)	2.47 [2.16; 2.77]
Drugs for functional gastrointestinal disorders	
Mebeverine (n = 36)	2.56 [2.24; 2.87]
Metoclopramide (n = 46)	2.20 [1.90; 2.49]
Domperidone (n = 47)	2.23 [1.95; 2.52]
Alizapride (n = 33)	2.30 [1.97; 2.64]
Antiemetics and drugs for nausea	
Dimenhydrinate (n = 49)	1.73 [1.44; 2.03]
Scopolamine (n = 48)	1.65 [1.42; 1.87]
Drugs for constipation	
Liquid paraffin (n = 45)	2.31 [1.93; 2.69]
Sennosides **> 1 week** (n = 42)	1.95 [1.74; 2.17]
Sodium picosulfate **> 1 week** (n = 41)	2.27 [2.01; 2.52]
Motility inhibitors	
Loperamide **> 3 d > 12 mg/d** (n = 42)	2.02 [1.81; 2.24]
Antidiabetic drugs	
Glibenclamide (n = 46)	2.00 [1.69; 2.31]
Gliquidone (n = 35)	2.29 [1.91; 2.66]
Gliclazide (n = 37)	2.27 [1.95; 2.59]
Glimepiride (n = 43)	2.26 [1.95; 2.56]
Acarbose (n = 45)	2.64 [2.32; 2.97]
Pioglitazone (n = 43)	2.05 [1.73; 2.36]
Antithrombotic drugs	
Ticlopidine (n = 41)	2.32 [2.01; 2.63]
Prasugrel (n = 42)	2.64 [2.31; 2.98]
Cardiac treatment	
Digoxin and derivatives (n = 42)	1.95 [1.69; 2.22]
Lidocaine (n = 45)	2.51 [2.21; 2.82]
Propafenone **as long-term medication** (n = 43)	2.53 [2.24; 2.83]
Flecainide (n = 40)	2.38 [2.09; 2.66]
Dronedarone (n = 38)	1.95 [1.63; 2.26]
Antihypertensives	
Methyldopa (n = 44)	1.93 [1.59; 2.28]
Clonidine (n = 45)	1.93 [1.69; 2.18]
Moxonidine (n = 40)	2.03 [1.76; 2.29]
Doxazosin (n = 45)	2.27 [1.98; 2.56]
Terazosin **as antihypertensive** (n = 40)	2.30 [2.00; 2.60]
Dihydralazine (n = 21)	2.24 [1.86; 2.62]
Hydralazine*2 (n = 38)	2.03 [1.76; 2.30]
Minoxidil (n = 41)	2.29 [2.04; 2.55]
Potassium-sparing drugs	
Spironolactone **> 25 mg/d** (n = 43)	2.51 [2.23; 2.79]
Peripheral vasodilators	
Pentoxifylline (n = 44)	1.73 [1.48; 1.98]
Naftidrofuryl (n = 42)	1.71 [1.46; 1.97]
Cilostazol (n = 34)	2.26 [1.92; 2.61]
Beta-adrenoceptor antagonists	
Pindolol (n = 36)	2.42 [2.07; 2.76]
Propranolol (n = 46)	2.70 [2.47; 2.92]
Sotalol (n = 43)	2.42 [2.09; 2.74]
Calcium-channel blockers	
Non-slow-release nifedipine (n = 42)	1.88 [1.59; 2.17]
Drugs acting on the renin–angiotensin system	
Aliskiren (n = 41)	2.66 [2.33; 2.99]
Sexual hormones and modulators of the genital system	
Testosterone (n = 42)	2.24 [1.91; 2.57]
Oral estrogens (n = 41)	2.17 [1.83; 2.51]
Urologics	
Flavoxate (n = 38)	2.03 [1.80; 2.25]
Oxybutynin (n = 44)	1.84 [1.61; 2.08]
Propiverine (n = 34)	1.74 [1.54; 1.93]
Tolterodine (n = 39)	2.03 [1.74; 2.31]
Solifenacin (n = 37)	2.08 [1.80; 2.36]
Trospium (n = 44)	2.36 [2.10; 2.63]
Darifenacin (n = 39)	2.00 [1.71; 2.29]
Fesoterodine, desfesoterodine (n = 40)	2.05 [1.77; 2.33]
Mirabegron (n = 37)	2.62 [2.29; 2.95]
Hypophyseal and hypothalamic hormones and analogs	
Desmopressin (n = 39)	2.51 [2.17; 2.86]
Antibiotics for systemic use	
Fluoroquinolones (n = 45)	2.27 [1.98; 2.55]
Endocrine treatment	
Medroxyprogesterone (n = 38)	2.42 [2.14; 2.70]
Non-steroidal anti-inflammatory and antirheumatic drugs	
Phenylbutazone (n = 45)	1.38 [1.18; 1.57]
Indomethacin (n = 44)	1.48 [1.26; 1.70]
Diclofenac (n = 45)	1.96 [1.73; 2.18]
Acemetacin (n = 41)	1.68 [1.42; 1.94]
Proglumetacin (n = 37)	1.49 [1.22; 1.75]
Aceclofenac (n = 36)	1.58 [1.34; 1.83]
Piroxicam (n = 47)	1.62 [1.38; 1.85]
Meloxicam (n = 44)	1.68 [1.45; 1.92]
Ibuprofen*3 **> 3 × 400 mg/d, > 1 week or > 3 × 400 mg/d, with PPI > 8 weeks** (n = 48)	2.60 [2.30; 2.91]
Naproxen*3 **> 2 × 250 mg/d, > 1 week or > 2 × 250 mg/d, with PPI > 8 weeks** (n = 43)	2.58 [2.26; 2.90]

Ketoprofen, dexketoprofen (n = 40)	1.80 [1.51; 2.09]
Etofenamate (n = 34)	1.82 [1.56; 2.09]
Coxibs (n = 42)	2.07 [1.83; 2.31]
Nabumetone (n = 31)	2.19 [1.77; 2.62]
Muscle relaxants	
Methocarbamol (n = 34)	2.00 [1.64; 2.36]
Orphenadrine (citrate) (n = 40)	1.78 [1.50; 2.05]
Baclofen (n = 47)	2.19 [1.91; 2.48]
Tizanidine (n = 37)	1.89 [1.59; 2.19]
Pridinol (n = 26)	2.00 [1.64; 2.36]
Tolperisone (n = 32)	2.16 [1.85; 2.46]
Other drugs for disorders of the musculoskeletal system	
Quinine (n = 43)	1.77 [1.52; 2.02]
Analgesics	
Dihydrocodeine, codeine **as analgesic** (n = 40)	2.45 [2.10; 2.80]
Pethidine (n = 46)	1.91 [1.66; 2.17]
Tramadol (n = 46)	2.65 [2.33; 2.97]
Tapentadol (n = 37)	2.59 [2.30; 2.89]
Methadone, levomethadone (n = 40)	2.30 [2.00; 2.60]
Acetylsalicylic acid **as analgesic** (n = 47)	2.45 [2.12; 2.77]
Phenazone (n = 35)	1.89 [1.65; 2.12]
Propyphenazone (n = 36)	2.19 [1.87; 2.52]
Ergotamine (n = 44)	1.59 [1.41; 1.77]
Antiepileptics	
Phenobarbital (n = 40)	1.53 [1.35; 1.70]
Primidone (n = 39)	2.23 [1.95; 2.51]
Phenytoin (n = 40)	2.43 [2.13; 2.72]
Carbamazepine (n = 46)	2.39 [2.13; 2.65]
Drugs for Parkinson's disease	
Trihexyphenidyl (n = 33)	1.73 [1.47; 1.98]
Biperiden (n = 38)	2.26 [1.94; 2.58]
Procyclidine (n = 34)	1.91 [1.59; 2.24]
Bornaprine (n = 33)	2.06 [1.73; 2.39]
Amantadine (n = 41)	2.49 [2.16; 2.82]
Pramipexole (n = 41)	2.66 [2.37; 2.95]
Piribedil (n = 30)	2.43 [2.14; 2.72]
Dopaminergic ergot alkaloids (e.g., pergolide) (n = 40)	2.05 [1.81; 2.29]
Monoaminoxidase-B inhibitors (e.g., selegiline) (n = 35)	2.46 [2.12; 2.79]
Tolcapone (n = 33)	2.48 [2.25; 2.72]
Antipsychotics	
Levomepromazine (n = 44)	1.57 [1.33; 1.81]
Fluphenazine (n = 35)	1.54 [1.33; 1.75]
Perphenazine (n = 39)	1.79 [1.52; 2.06]
Perazine (n = 31)	2.13 [1.78; 2.48]
Thioridazine (n = 39)	1.59 [1.32; 1.85]
Haloperidol (n = 45)	2.16 [1.86; 2.46]
Melperone **> 100 mg/d, > 6 weeks** (n = 36)	1.92 [1.73; 2.10]
Pipamperone **> 120 mg/d, > 6 weeks** (n = 36)	2.06 [1.80; 2.31]
Bromperidol (n = 33)	1.82 [1.58; 2.06]
Benperidol (n = 31)	1.84 [1.57; 2.11]
Sertindole (n = 35)	1.77 [1.49; 2.05]
Ziprasidone (n = 37)	2.08 [1.78; 2.38]
Flupentixol (n = 41)	1.90 [1.67; 2.13]
Chlorprothixene (n = 41)	1.71 [1.45; 1.96]
Zuclopenthixol (n = 40)	1.73 [1.53; 1.92]
Fluspirilene (n = 33)	1.79 [1.47; 2.10]
Pimozide (n = 35)	1.49 [1.29; 1.68]
Clozapine (n = 42)	2.12 [1.84; 2.40]
Olanzapine (n = 43)	2.28 [1.99; 2.57]
Quetiapine **> 100 mg/d, > 6 weeks** (n = 43)	2.23 [1.97; 2.50]
Sulpiride (n = 40)	2.30 [2.01; 2.59]
Tiapride (n = 37)	2.30 [2.03; 2.57]
Amisulpride (n = 38)	2.24 [1.96; 2.52]
Prothipendyl (n = 39)	2.13 [1.82; 2.44]
Risperidone **> 6 weeks** (n = 45)	2.69 [2.38; 2.99]
Aripiprazole (n = 39)	2.41 [2.10; 2.72]
Paliperidone (n = 32)	2.47 [2.10; 2.83]
Cariprazine (n = 27)	2.00 [1.73; 2.27]
Anxiolytics, hypnotics, and sedatives	
Hydroxyzine (n = 44)	1.70 [1.46; 1.95]
Long-acting benzodiazepines (e.g., diazepam) (n = 44)	1.45 [1.29; 1.62]
Lorazepam (n = 43)	2.26 [1.95; 2.56]
Moderately long-acting benzodiazepines (e.g., oxazepam) (n = 46)	2.13 [1.91; 2.35]
Short-acting benzodiazepines (e.g., triazolam) (n = 44)	2.20 [1.90; 2.51]
Chloral hydrate (n = 40)	1.78 [1.54; 2.01]
Zopiclone (n = 39)	2.23 [1.93; 2.53]
Zolpidem (n = 43)	2.35 [2.06; 2.64]
Clomethiazole (n = 40)	1.93 [1.62; 2.23]
Doxylamine (n = 40)	1.63 [1.42; 1.83]
Promethazine (n = 39)	1.92 [1.60; 2.25]
Antidepressants	
Tricyclics (e.g., amitriptyline) (n = 46)	1.65 [1.42; 1.88]
Opipramol (n = 41)	2.24 [1.98; 2.51]
Nortriptyline*[4] (n = 37)	2.22 [1.95; 2.48]
Doxepin (n = 41)	1.88 [1.57; 2.19]
Maprotiline (n = 42)	1.83 [1.61; 2.06]
Fluoxetine (n = 43)	2.23 [1.97; 2.50]
Paroxetine (n = 45)	2.29 [2.01; 2.57]
Sertraline **> 100 mg/d** (n = 40)	2.33 [2.06; 2.59]
Fluvoxamine (n = 41)	2.17 [1.91; 2.43]

Tranylcypromine (n = 37)	1.81 [1.51; 2.11]
Moclobemide (n = 42)	2.62 [2.31; 2.93]
St John's wort (n = 45)	2.53 [2.22; 2.84]
Mianserin (n = 38)	2.45 [2.14; 2.75]
Bupropion (n = 41)	2.59 [2.28; 2.89]
Tianeptine (n = 36)	2.56 [2.28; 2.83]
Agomelatine (n = 40)	2.45 [2.12; 2.78]
Psychostimulants	
Methylphenidate (n = 36)	1.78 [1.53; 2.02]
Pyritinol (n = 33)	1.94 [1.66; 2.22]
Piracetam (n = 42)	1.81 [1.58; 2.04]
Antidementives	
Ginkgo leaf (n = 41)	2.61 [2.23; 2.99]
Nicergoline (n = 40)	2.08 [1.83; 2.32]
Nimodipine (n = 34)	2.15 [1.89; 2.41]
Drugs for vertigo	
Betahistine (n = 39)	2.62 [2.27; 2.96]
Cinnarizine*5 (n = 40)	2.13 [1.81; 2.44]
Flunarizine (n = 34)	2.35 [2.06; 2.65]
Drugs for obstructive respiratory tract diseases	
Sympathomimetics for systemic use, no inhalation (e.g., salbumatol) (n = 44)	2.34 [2.10; 2.59]
Theophylline, aminophylline (n = 42)	1.83 [1.60; 2.07]
Cough and cold remedies	
Codeine, dihydrocodeine **as antitussive** (n = 42)	2.29 [2.03; 2.54]
Antihistamines for systemic use	
First generation	
Diphenhydramine (n = 43)	1.67 [1.45; 1.89]
Clemastine (n = 37)	1.78 [1.50; 2.07]
Dimetindene (n = 39)	1.87 [1.62; 2.12]
Cyproheptadine (n = 33)	1.67 [1.42; 1.91]
Ketotifen (n = 35)	2.31 [2.02; 2.61]
Second generation	
Ebastine (n = 34)	2.50 [2.25; 2.75]
Rupatadine (n = 24)	2.63 [2.30; 2.95]

CI, Confidence interval; PIM, potentially inappropriate medication; PPI, proton pump inhibitors
*1 License suspended since January 2021 owing to nitrosamine contamination
*2 In Germany: only as a compound with atenolol and chlorthalidone
*3 Additional evaluation in third round with time and dose limitation; data on confidence interval etc. for evaluation without time and dose limitation
*4 According to comments, nortriptyline is tolerated better than other tricyclics; therefore, it was evaluated in its own right in the second round of the Delphi process
*5 In Germany: only as a compound with dimenhydrinate

eTABLE 3

Substances classified as non-PIM

Substance/class	No. of ratings	Median	Mean	[95% CI]
Drugs for acidity-related diseases				
Magnesium hydroxide (as an example of antacids containing magnesium)	44	3	3.34	[3.09; 3.59]
Proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, rabeprazole)	46	4	3.74	[3.49; 3.99]
Sucralfate	43	4	3.44	[3.13; 3.75]
Drugs for constipation				
Macrogol	46	4	4.24	[4.00; 4.47]
Drugs for diarrhea and intestinal anti-inflammatories/anti-infectives				
Loperamide	44	4	3.30	[3.02; 3.57]
Antidiabetic drugs				
Insulins and analogs for injection, rapid-acting ("sliding scale insulins", (treatment **without** basal insulin/long-acting insulins)	43	4	3.47	[3.07; 3.86]
Metformin	47	4	4.00	[3.74; 4.26]
Dipeptidylpeptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin...)	45	4	3.67	[3.38; 3.95]
Glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide*)	39	3	3.44	[3.13; 3.74]
Sodium-glucose-cotransporter-2 (SGLT2) inhibitors (dapagliflozin, empagliflozin, canagliflozin*)	44	3.5	3.32	[3.03; 3.61]
Antithrombotic drugs				
Warfarin	36	4	3.83	[3.50; 4.16]
Phenprocoumon	45	4	3.80	[3.52; 4.08]
Acenocoumarol*	29	4	3.66	[3.27; 4.04]
Rivaroxaban	44	4	3.36	[3.06; 3.67]
Apixaban	44	4	3.89	[3.65; 4.12]
Edoxaban	46	4	3.63	[3.33; 3.93]
Cardiac treatment				
Propafenone **as "single shot"**	38	4	3.58	[3.33; 3.83]
Ivabradine	44	4	3.39	[3.08; 3.70]
Potassium-sparing drugs				
Spironolactone	46	4	3.63	[3.38; 3.88]
Eplerenone	40	4	3.58	[3.31; 3.84]
Calcium-channel blockers				
Moderately long-acting and long-acting calcium-channel blockers with predominantly vascular action (amlodipine, felodipine, isradipine, nisoldipine, nitrendipine, manidipine, lercanidipine)	42	4	3.98	[3.73; 4.22]
Drugs acting on the renin–angiotensin system				
Valsartan and **sacubitril**	45	4	3.71	[3.41; 4.01]
Urologics				
Tamsulosin	43	4	3.58	[3.36; 3.81]
Calcium homeostasis				
Teriparatide	38	4	3.42	[3.07; 3.78]
Drugs for treating bone diseases				
Denosumab	37	4	3.49	[3.12; 3.85]
Analgesics				
Metamizole	46	4	3.96	[3.74; 4.17]

Antiepileptics				
Gabapentin	41	4	3.39	[3.09; 3.69]
Levetiracetam **NEW**	40	4	3.43	[3.09; 3.76]
Antipsychotics				
Risperidone	45	4	3.53	[3.29; 3.78]
Antidepressants				
Citalopram, escitalopram	45	4	3.51	[3.27; 3.76]
Sertraline	41	4	3.54	[3.27; 3.80]
Mirtazapine	42	4	3.45	[3.15; 3.75]
Antidementives				
Memantine	42	4	3.36	[3.01; 3.70]
Drugs for obstructive respiratory tract diseases				
Inhaled anticholinergics (ipratropium bromide, tiotropium bromide, aclidinium bromide, glycopyrronium bromide, umeclidinium bromide)	43	4	3.65	[3.36; 3.94]
Antihistamines for systemic use				
Second generation				
Cetirizine, levocetirizine	43	4	3.44	[3.19; 3.70]
Loratadine, desloratadine	38	4	3.47	[3.19; 3.76]

*These substances are marketed only in Austria, not in Germany.
CI, Confidence interval; PIM, potentially inappropriate medication

eTABLE 4

Substances that were classified neither as PIM nor as non-PIM

Substance/class of substances	No. of evaluations	Median	Mean	[95% CI]
Drugs for acidity-related diseases				
Famotidine	43	3	2.81	[2.56; 3.07]
Drugs for functional gastrointestinal disorders				
Butylscopolamine	47	3	3.00	[2.71; 3.29]
Drugs for constipation				
Bisacodyl **> 10 mg/d, > 1 week**	41	2	2.71	[2.37; 3.05]
Sennosides	43	3	2.77	[2.46; 3.07]
Sodium picosulfate	42	3	3.14	[2.87; 3.41]
Prucalopride	33	3	3.03	[2.68; 3.38]
Antidiarrhea drugs and intestinal anti-inflammatories/anti-infectives				
Racecadotril	30	3	3.10	[2.72; 3.48]
Antithrombotic drugs				
Dabigatran etexilate	47	3	3.13	[2.78; 3.47]
Cardiac treatment				
Digitoxin	47	3	3.00	[2.66; 3.34]
Amiodarone	47	3	2.96	[2.64; 3.28]
Vernakalant	30	3	3.20	[2.84; 3.56]
Ranolazine	38	3	3.03	[2.66; 3.39]
Antihypertensives				
Urapidil	46	3	2.89	[2.55; 3.24]
Potassium-sparing drugs				
Eplerenone **> 25 mg/d**	39	3	2.77	[2.47; 3.07]
Amiloride or compounds containing triamterene	44	3	2.89	[2.59; 3.18]
Beta-adrenoceptor antagonists				
Atenolol	45	3	2.80	[2.51; 3.09]
Calcium-channel blockers				
Slow-release nifedipine	42	3	2.88	[2.60; 3.17]
Selective calcium-channel blockers with predominantly cardiac action (verapamil, diltiazem)	46	3	3.04	[2.81; 3.28]
Sexual hormones and modulators of the genital system				
Raloxifene	41	3	3.07	[2.81; 3.33]
Urologics				
Alfuzosin	43	3	3.12	[2.85; 3.38]
Terazosin	43	3	2.95	[2.68; 3.23]
Silodosin	39	3	3.03	[2.75; 3.30]
Antibiotics for systemic use				
Sulfamethoxazole and trimethoprim	48	3	2.79	[2.52; 3.06]
Nitrofurantoin	48	3	2.83	[2.53; 3.13]
Non-steroidal anti-inflammatory and antirheumatic drugs				
Ibuprofen **up to max. 3 × 400 mg/d, for max. 1 week**	7	4	3.43	[2.53; 4.33]
Ibuprofen **up to max. 3 × 400 mg/d, with PPI for max. 8 weeks**	5	4	3.60	[2.49; 4.71]
Naproxen **up to max. 2 × 250 mg/d, for max. 1 week**	6	4	3.67	[2.81; 4.52]
Naproxen **up to max. 2 × 250 mg/d, with PPI for max. 8 weeks**	7	4	3.43	[2.53; 4.33]

Drugs for gout				
Colchicine	45	3	2.76	[2.46; 3.05]
Analgesics				
Selective serotonin-5HT-1 receptor agonists/ triptans (sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, frovatriptan)	43	3	2.86	[2.57; 3.15]
Antiepileptics				
Topiramate	40	3	2.90	[2.66; 3.14]
Pregabalin	43	3	2.88	[2.55; 3.21]
Drugs for Parkinson's disease				
Ropinirole	40	3	2.80	[2.49; 3.11]
Rotigotine	36	3	2.75	[2.44; 3.06]
Entacapone	35	3	3.09	[2.82; 3.35]
Opicapone	34	3	2.91	[2.66; 3.16]
Antipsychotics				
Melperone	46	3	3.07	[2.76; 3.37]
Pipamperone	40	3	3.15	[2.83; 3.47]
Quetiapine	46	3	3.04	[2.75; 3.34
Lithium	43	3	3.05	[2.74; 3.35]
Antidepressants				
Trazodone	45	3	2.84	[2.59; 3.10]
Venlafaxine	44	3	3.00	[2.74; 3.26]
Milnacipran	28	3	2.96	[2.62; 3.31]
Duloxetine	43	3	2.98	[2.66; 3.30]
Drugs for obstructive respiratory tract diseases				
Ipratropium bromide	42	4	3.29	[2.97; 3.60]
Cough and cold remedies				
Noscapine	39	3	3.15	[2.85; 3.46]
Antihistamines for systemic use				
Second generation				
Mizolastine	28	3	2.71	[2.40; 3.03]
Fexofenadine	32	3	2.84	[2.53; 3.16]
Bilastine	29	3	2.83	[2.49; 3.17]

*These substances are marketed only in Austria, not in Germany.
PPI, Proton pump inhibitors

eBOX 1

Method

a) Compilation of the list of substances and substance classes to be evaluated

- Literature search (PubMed, hand search of articles identified) for international PIM lists published since 2010
- Systematic literature review to identify systematic reviews on adverse drug events (ADE) in elderly patients
- Analysis of the German statutory health insurance funds' prescription data from the year 2018 in patients aged ≥ 65 years
- The prescription data of the statutory health insurance funds in Austria

→ Definition of the substances and substance classes to be evaluated

b) Pre-Delphi

Because finite time and resources meant that systematic reviews could not be carried out for all substances, an exploratory pre-Delphi process was conducted with four experts (specialties: clinical pharmacology, clinical care research, and clinical pharmacy). This served to assess whether the information from Micromedex and, if required, other sources (e.g., the summary of product characteristics) would suffice for evaluation of the substances without systematic review. To this end, the following questions were posed:

- Is evaluation of this substance/class of substances feasible on the basis of data from Micromedex or the summary of product characteristics?
- Is evaluation of this substance/class of substances feasible on the basis of the fact that it is included in one or more international PIM lists?
- Is a literature review necessary for this substance/class of substances?

It emerged that an additional literature review was necessary for only four of the substances/categories examined: aluminum-containing antacids, sucralfate, butylscopolamine, and loratadine/desloratadine. Rapid reviews were planned for these substances/categories but could not be conducted owing to the resource-intensive systematic reviews. The latter were prioritized because of their higher evidential value.

c) Evidence generation and presentation of the information for the experts in the Delphi process

Sources of information for the suggested substances in the Delphi process

- Data extracted from international PIM lists with the reasons given there for classification as PIM
- Data extracted from Micromedex, or alternatively from the summary of product characteristics if there is no Micromedex entry for the substance concerned
- Further literature from the original PRISCUS project
- The modified version of the GRADE (15, 16) summary of findings (SOF) and evidence profile tables
- The anticholinergic burden according to Kiesel et al. (e35)
- Information on dosage and treatment duration in the elderly from the summary of product characteristics (included from the second Delphi round onwards, because many participants referred to this in their evaluation)
- Literature mentioned by the participants (from the second Delphi round onwards)

eBOX 2

Delphi process

a) Rating of the substances on the Likert scale

"This substance/class of substances constitutes potentially inappropriate medication (PIM) for elderly patients and therefore should be avoided in this population"

1 – I strongly agree (that this substance is a PIM)
2 – I agree (that this substance is a PIM)
3 – Neutral (I neither agree nor disagree that this substance is a PIM)
4 – I disagree (that this substance is a PIM)
5 – I strongly disagree (that this substance is a PIM)
0 – No response/abstention*

*Served to mark an abstention and was not included in statistical analysis.

b) Classification of substances as PIM/non-PIM or ambiguous

A substance was rated to be definitely a PIM if the 95% confidence interval (95% CI) of all evaluations was < 3 and definitely a non-PIM if the 95% CI of all evaluations was > 3. If the 95% CI included 3, the substance was considered to be ambiguously rated and thus a questionable PIM. The confidence intervals were calculated with Excel.

c) Feedback from the first Delphi round

Feedback for the participants in the second Delphi round

- List of suggestions
  - Median, mean, and 95% confidence interval from the first round
  - Summary of the participants' comments from the first round
- PDF with list of substances definitely rated as PIM
- PDF with list of substances definitely rated as non-PIM