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Potentially inappropriate medication in geriatric patients: the Austrian consensus panel list

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Potentiell inadäquate Medikation bei geriatrischen Patienten: Die Österreichische PIM-Liste

Zusammenfassung. *Hintergrund:* Bei geriatrischen Patienten stellen inadäquate Medikamentenverordnungen einen wichtigen Risikofaktor für unerwünschte Arzneimittelereignisse dar. Sie führen in diesem Zusammenhang zu einer Zunahme von Spitalszuweisungen, welche die Gesundheitskosten belasten. Die Entwicklung Konsensus-basierter Listen von Medikamenten, die bei geriatrischen Patienten im Allgemeinen vermieden werden sollten, wird als eine mögliche Strategie angesehen, um die Qualität der medikamentösen Behandlung zu steigern.

Ziel: Erstellung einer, den österreichischen Verschreibungsgewohnheiten und der Marktsituation angepassten, Konsensus-basierten Liste von Arzneimitteln, deren Verordnung potentiell inadäquat für geriatrische Patienten ist, und die deshalb vermieden werden sollten.

Methode: Als Evaluierungsmethode wurde ein zweistufiger Delphi Prozess gewählt, an dem acht Experten mit Erfahrung in der medikamentösen Therapie geriatrischer Patienten teilnahmen. In der ersten Runde bewerteten die Experten Medikamente einer vorgegebenen Liste anhand einer 5-stufigen Likert Skala von sicher potentiell unangemessen bis sicher nicht potentiell unangemessen. Alle Medikamente, für deren Bewertung die obere Grenze des 95 % Konfidenzintervalls unter 3,0 lag, wurden als potentiell unangemessen klassifiziert. Medikamente, deren 95 % KI den Wert 3,0 umschloss, wurden in der zweiten Runde wieder anhand einer 5-stufigen Likert Skala bewertet, ebenso wie die in der ersten Runde neu vorgeschlagenen Medikamente. Nach Analyse der Ergebnisse der zweiten Runde wurde die finale Liste erstellt.

Resultate: Von den vorgegebenen 102 Medikamenten wurden 61 Medikamente (59,2 %) bereits in der ersten Runde als potentiell unangemessen für ältere Menschen eingestuft. Sechs Medikamente, die in der zweiten Runde erneut evaluiert wurden, und sechs in der ersten Runde neu vorgeschlagene Medikamente wurden in der zweiten Runde als potentiell inadäquat klassifiziert. Die finale Liste enthält 73 Arzneimittel, die aufgrund eines ungünstigen Nutzen/Risiko Profils oder aufgrund fraglicher Wirksamkeit bei geriatrischen Patienten nicht verordnet werden sollten.

Schlussfolgerung: Die Österreichische PIM Liste kann für klinisch tätige Ärzte ein in der Praxis anwendbares Instrument darstellen, das zu einer Verbesserung der Qualität von Medikamentenverordnungen bei älteren Patienten beiträgt. Studien zur Validierung der PIM-Liste stehen in Österreich ebenso wie in anderen Ländern mit bereits veröffentlichten PIM-Listen noch aus.

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Summary. *Background:* The practice of inappropriate medication and drug prescription is a major risk factor for adverse drug reactions in geriatric patients and increases the individual, as well as overall, rates of hospital admissions, resulting in increased health care expenditures. A consensus-based list of drugs, generally to be avoided in geriatric patients, is a practical tool to possibly improve the quality of prescribing.

Objective: The aim was to develop a consensus-based list of potentially inappropriate medications (PIM) for geriatric patients in Austria. Local market characteristics and documented prescribing regimens were considered in detail.

Methods: A two-round Delphi process involving eight experts in the field of geriatric medicine was undertaken to create a list of potentially inappropriate medications. Using a 5-point Likert scale (from strong agreement to strong disagreement), mean ratings from the experts were evaluated for each drug selected in the first round. The participants were first asked to comment on the potential inappropriateness of a preliminary list of drugs, and to propose alternate substances missing in the previous questionnaire for a second rating process. All drugs whose upper limit of the 95% CI was less than 3.0 were classified as potentially inappropriate. Drugs with a 95% CI enclosing 3.0 entered a second rating by the experts, in addition to other substances suggested during the first questionnaire. Drugs in the second rating were evaluated in comparable fashion to the first one. The final list was synthesized from the results in both rounds.

Results: Out of a preliminary list of 102 drugs, 61 drugs (59.2%) were classified as potentially inappropriate for geriatric persons in the first Delphi- round. In the second rating, six drugs that were reevaluated, and six drugs proposed additionally, were rated as potentially inappropriate. The final list contains 73 drugs to be avoided in older patients because of an unfavorable benefit/risk profile and/or unproven effectiveness. The list also contains suggestions for therapeutic alternatives and information about pharmacological and pharmacokinetic characteristics of all drugs judged as potentially inappropriate.

Conclusion: The current Austrian list of potentially inappropriate medications may be a helpful tool for clinicians to increase the quality of prescribing in older patients. Like all explicit lists previously published, its validity needs to be proven in validation studies.

Key words: Pharmacotherapy, inappropriate prescribing, older patients, aged, Delphi method, Austria.

Background

A potentially inappropriate medication (PIM) is defined as a drug administered whose effectiveness has not been established and/or whose risk of adverse drug events (ADEs) exceeds the expected clinical benefit, especially if there is evidence of a pharmacological alternative with fewer side effects [1].

Inappropriate drug prescription is a relevant public health concern, especially for geriatric patients because this group of patients has a particularly high risk of experiencing ADEs. A "geriatric patient" is defined as a biologically older patient who is at a high risk of developing diseases, who tends to suffer from multimorbidity, and who is in particular need for rehabilitative, physical-psychological, and psychosocial management due to age-related functional impairment. The high risk is the result of age-related changes in pharmacokinetics influencing the absorption, distribution, metabolism, and elimination of drugs, and of changes in pharmacodynamics, which may cause modified receptor sensitivity or reduced functional reserves leading to altered drug efficiency. It may be challenging to predict ADE's in the old population, since older patients are usually not recruited to clinical drug trials. Additionally, older patients tend to present with multimorbidity and polypharmacy [2]. Tools to avoid ADE's in older patients, may therefore be helpful and their development of high priority to any medical society treating older multimorbid patients.

Several recently published papers confirm the high prevalence of inappropriate drug prescriptions in hospitalised patients [3, 4], nursing home patients [5, 6], and in community dwelling geriatric patients [7, 8]. Recent publications also show significant correlations between the prescribing of potentially inappropriate treatments and the incidence of adverse drug events [9–11], increased risk of hospitalisation [12, 13], emergency room admissions [13, 14], and increased costs to the healthcare system [15].

In contrast to polypharmacy and multimorbidity, which are predictors of PIM, age *per se* does not seem to be a risk factor for PIM [16]. Only when older patients with a vulnerable general condition are treated with multiple long-term drug regimes, the risk of an ADE increases significantly [17].

There are different approaches to minimise PIM in geriatric patients. One possible strategy is to avoid drugs with a high risk of clinically relevant side effects as proven by expert consensus. Beers and colleagues developed the first PIM criteria published in literature in 1991 especially for nursing home patients. In 1997 Fick and colleagues extended the Beers criteria to recommendations for all patients aged over 65 years (i.e. also for those at home) [18, 19]. In 1997, McLeod published a PIM list especially fit for Canadian prescription patterns. This list also included drug interactions and interactions between drugs and diseases additionally to known ADE's [20]. Laroche and colleagues published the first European PIM list in 2007 for France [21], and Holt in Germany released the first German list in 2010, known as the PRISCUS list [22]. Gallagher and colleagues chose a structured approach to inappropriate medication, also referring to undermedication, i.e. the non-prescription of medication despite evidence-based indications [23]. This list is already well known all over Europe as the STOPP/START criteria. It has been already investigated in a multinational approach, testing the list in 6 different European countries. However, the pharmacy market and prescription patterns still seem to differ widely in the European countries. It is therefore useful and man-

datory to reveal national drug prescription habits and to develop tools fit to reduce the overall as well as individual rate of PIMs on national basis. It was the aim of the authors of the present article to develop a consensus-based Austrian PIM list taking into account the particularities of the Austrian pharmaceutical market and the prescribing habits of Austrian physicians.

The start of the project coincided with the creation of the PIM list in Germany at the end of 2008.

Methods

Based on the previously used Delphi method for the creation of PIM lists [18–23], the authors chose a modified two-round Delphi process to achieve an Austrian consensus PIM list [24].

The decision making process included 5 steps: (1) recruitment of experts, (2) first Delphi round by sending out the first questionnaire, (3) analysis of the first round's results, and creation of the second questionnaire, identifying the drugs for which no clear decision could be made in the first round, and those drugs that were introduced as new proposals by the experts in the first round, (4) second Delphi round by sending out the second questionnaire, and (5) evaluation of the results of the second Delphi round and final analysis.

For kick off of the Austrian PIM process, the drug interview previously used by German experts [22] was sent to the Austrian experts for further evaluation.

The elaboration of this basic list had been part of the 2008/2009 drug therapy safety campaign of the German Federal Ministry of Health, and it was developed by Thürmann et al. based on a qualitative analysis of international PIM lists, including two from the US, one each from Canada and France, as well as on a selective and comprehensive literature research as part of the joint project PRISCUS (www.priscus.net/). It was the aim of this literature research to identify any publications covering known age-specific drug recommendations and drug-related problems of drugs commonly used in the older population. The evidence of an increased risk for ADEs and interactions associated with the application of certain drugs and drug classes in the older persons was investigated in particular. Based on the search criterion "age", a lower age limit of 65 years was used. A summary of the results of the literature review and qualitative analysis of the existing PIM lists can be reviewed at http://priscus.net/download/PRISCUS-Liste_PRISCUS-TP3_2011.pdf.

This list was adapted to the Austrian market situation, which led to a reduction from 131 to 102 drugs.

A total of 14 experts from all the regions of Austria were invited to participate in the Delphi process. Eight of them agreed to participate. Lack of time was the main reason for hesitation.

All of the participating experts are outstanding experts in the field of geriatrics in Austria. They do represent all medical disciplines particularly relevant to geriatric medicine, the majority working in geriatric departments in hospitals or in the geriatric consultation service. The team consisted of a general practitioner, a specialist in neurology, three specialists in internal medicine, a psychiatrist, and two clinical pharmacists working in hospital pharmacies.

In March 2009, the first round of the Delphi process was launched sending the basic questionnaire per e-mail. The 102 drugs were classified into 19 different drug groups according to the drug registry of the Austrian Ministry of Health: Analgesics/anti-inflammatory drugs, antianaemics, antiarrhythmics, antibiotics, anticholinergics, sedatives/hypnotics, anti-dementia drugs/vasodilators, anticoagulants/antiplatelet agents, antipsychotics, antidepressants, antiemetics, antihypertensives, diuretics, ergotamine derivatives, hormones, antidiabetics, laxatives, muscle relaxants, bronchodilators, and antiepileptics. This classification was undertaken to specifically underline the local needs and prescribing habits. The experts were then asked to evaluate the drugs with regard to the following aspects: inadequacy in older patients, medication alternatives, need for monitoring and dose adjustment, drug interactions and interactions between drugs and specific diseases, additional comments based on individual evaluation. The inappropriateness of a drug was assessed using a 5-point Likert scale [25]: "1": the drug is very likely potentially inappropriate, "2": the drug is potentially inappropriate, "3": undecided, "4": the drug is not potentially inappropriate, and "5": the drug is certainly not potentially inappropriate for the older population.

Mean scorings of all experts were plotted against each other and medications ranking in an upper limit of the 95% CI of <3.0 (according to the previously mentioned Likert ranking) were classified as PIM, drugs with a lower limit of the 95% CI of >3.0 were classified as non-PIM. Those drugs with a 95% CI around 3.0 in the first round and all proposed new drugs were evaluated in a second Delphi round.

After analysis of data in the second Delphi rating, the final list of potentially inappropriate drugs for older people was completed.

Results

Delphi survey

The initial questionnaire contained 102 drugs, 61 (59.2%) of which were considered potentially inadequate in the first Delphi round. A second round of questioning was necessary for 38 medications. An additional 30 drugs, mainly newer antidepressants, analgesics, meprobamate, allopurinol, mephenytoin, and antiparkinson drugs, were proposed by the experts themselves.

A total of 68 drugs were included in the second questionnaire. Nifedipine and tolterodine were re-submitted for review, since the first round did not provide differentiation between their extended release and non-extended release formulation, as stated by the experts. A total of 12 drugs of this 2nd round were classified as potentially inadequate for older people. Only 6 drugs that achieved unclear results in the first round - phenobarbital, haloperidol, digoxin, nifedipine (extended release), and tolterodine (non-extended-release) - were evaluated as potentially inadequate in the second Delphi round.

Final results

The Austrian expert group evaluated 73 drugs in terms of an unfavourable benefit/risk ratio as potentially inappropriate for older people. For some of these drugs, safer alternatives are available, and some of them do not have any proven effects in older patients.

Table 1 shows the drugs of the Austrian PIM list.

Discussion

Adverse drug events due to potentially inappropriate medication represent a major health risk for geriatric patients. An increase of emergency room consultations and hospitalisations are responsible for burden of costs within the

Table 1. Austrian list of potentially inappropriate medication for older patients

Drug (number of experts)	Mean (95% CI)	Justification for the unfavourable benefit/risk profile	Alternative medication
Anti-inflammatory drugs		Serious adverse drug reactions: gastrointestinal ulcers, bleeding, kidney and liver insufficiency, hypertension	In the analgetic indication: Paracetamol, metamizole, hydromorphone
Indomethacin [7]	1.21 (0.92–1.51)	Highest incidence of CNS side effects (e.g. delirium) of all NSAIDs	
Acemetacin [7]	1.36 (1.00–1.71)		
Naproxen [7]	1.36 (1.00–1.71)		
Diclofenac [7]	1.71 (1.01–2.42)		
Ibuprofen [6]	1.83 (0.90–2.77)		
Ketoprofen [7]	1.57 (0.99–2.15)		
Acetylsalicylic acid [7]	1.93 (1.17–2.68)	High rate of gastrointestinal side effects (bleeding) in/with long-term use	
Piroxicam [6]	1.17 (0.84–1.49)		
Meloxicam [7]	1.64 (1.09–2.20)		
Celecoxib [7]	2.07 (1.26–2.88)		
Opioids			
Pethidine [7]	1.93 (1.06–2.80)	The major metabolite normeperidine can cause convulsions, delirium, sedation, and respiratory depression	Hydromorphone
Buprenorphine [7]	2.0 (1.14–2.86)	CNS side effects: Sedation and delirium, gastrointestinal effects: nausea at the beginning and constipation with medium- and long-term administration, anticholinergic side effects	Hydromorphone
Tramadol [7]	1.64 (1.09–2.20)	Lowers seizure threshold, may lead to delirium, frequent unwanted side effects: Vomiting, vertigo, constipation	Paracetamol, metamizole, hydromorphone
Antiarrhythmics			
Flecainide [6]	1.17 (0.84–1.49)	Pro-arrhythmogenic effect, can lead to ventricular arrhythmias, ventricular fibrillation, and cardiac arrest	Indication cardioversion: Amiodarone, indication frequency control: Beta-blockers, verapamil, diltiazem, digitoxin
Propafenone [7]	1.00	Pro-arrhythmogenic effect can lead to AV block, intraventricular conduction delays, common neurotoxic and gastrointestinal side effects	Indication cardioversion: Amiodarone, indication frequency control: Beta-blockers, verapamil, diltiazem, digitoxin
Dronedarone [7]	2.43 (1.90–2.96)	Severe liver dysfunction up to liver failure, increased mortality in patients with heart failure, "reserve drug" for amiodarone or beta-blockers in KI, indication made by specialists	Indication cardioversion: Amiodarone, indication frequency control: Beta-blockers,
Digoxin [6]	2.25 (1.59–2.91)	Risk of overdose in renal insufficiency: Nausea, vomiting, drowsiness, visual disturbances, cardiac rhythm disturbances	Digitoxin
Sotalol [7]	1.86 (1.19–2.52)	Pro-arrhythmogenic effect, can lead to torsade de pointes or ventricular tachycardia/ ventricular fibrillation, QT interval prolongation, and accumulation in patients with renal insufficiency	Other beta-blockers (except atenolol, which has unfavourable data regarding the endpoint of stroke)
Antihistamines		Can cause delirium and anticholinergic side effects like dry mouth, urinary retention, and constipation, and can cause QT interval prolongation	
Hydroxyzine [6]	1.83 (0.90–2.77)		
Chlorpheniramine [6]	2.0 (1.12–2.88)		
Anticholinergics		Can cause delirium and cognitive impairment, can worsen glaucoma and lead to partial or complete gastrointestinal obstruction	
Tolterodine (non-extended release) [6]	2.17 (1.91–2.92)		Trospium chloride
Oxybutynin (non-extended release) [5]	1.40 (0.92–1.88)		Trospium chloride
Antiparkinson drugs			
Dopamine agonists		Higher potential for hallucinations and delirium	
Pergolide [6]	1.5 (0.96–2.04)	Risk for cardiac valve fibrosis	L-dopa
Cabergoline [6]	1.21 (0.7–2.35)	Risk for cardiac valve fibrosis	L-dopa

Drug (number of experts)	Mean (95% CI)	Justification for the unfavourable benefit/risk profile	Alternative medication
Ropinirole [6]	1.92 (1.51–2.32)		
Pramipexole [6]	1.91 (1.51–2.32)		
Rotigotine [5]	1.91 (1.46–2.35)		
Muscarinic antagonists		Anticholinergic side effects: Restlessness, delirium, urinary retention, and negative effect on cognitive functions	L-dopa
Biperiden [6]	1.83 (1.08–2.58)		
Bornaprine [6]	1.83 (1.08–2.58)		
Antiplatelet agents			
Ticlopidine [6]	1.33 (0.92–1.75)	Can lead to life-threatening haematological side effects, including neutropenia/agranulocytosis, thrombotic-thrombocytopenic purpura, and aplastic anaemia	Clopidogrel, acetylsalicylic acid
Antidepressants			
Tricyclic/tetracyclic antidepressants		Severe anticholinergic side effects: Urinary retention, cognitive impairment, and glaucoma, orthostatic hypotension and falls, arrhythmias (QT prolongation), dry mouth	SSRIs (see below), SNRIs, Mirtazapine
Amitriptyline [7]	1.21 (0.92–1.51)		
Doxepin [7]	1.43 (1.03–1.82)		
Clomipramine [7]	1.29 (0.92–1.65)		
Maprotiline [7]	1.29 (0.92–1.65)		
SSRIs			
Fluvoxamine [8]	1.71 (0.85–2.58)	Nausea, vomiting, drowsiness, dizziness, dry mouth, constipation, diarrhoea, weight loss/anorexia	Other SSRIs; SNRIs; mirtazapine
Antiemetics			
Dimenhydrinate [6]	1.75 (1.14–2.36)	Effectiveness not proven, anticholinergic side effects: Urinary retention, glaucoma, sedation	
Antihypertensives			
Clonidine [5]	2.0 (1.38–2.62)	Main side effects: Hypotension, bradycardia, worsening of cognitive function	
Methyldopa [5]	1.20 (0.81–1.59)	Can cause orthostatic hypotension, can cause sedation	
Nifedipine short-acting [6]	1.66 (0.85–2.47)	Can cause severe hypotension	Non-extended release formulation
Typical antipsychotics		Main side effects: anticholinergic (urinary retention, constipation, visual disturbances), cognitive impairment, noradrenergic (orthostatic hypotension), antihistaminergic (sedation), extrapyramidal symptoms including Parkinson-like symptoms, dystonia, akathisia, and tardive dyskinesia	So-called atypical neuroleptics
Haloperidol [7]	2.33 (1.84–2.82)		
Prothipendyl [8]	2.25 (1.54–2.96)		
Fluphenazine [5]	1.20 (0.81–1.59)		
Levomepromazine [6]	1.29 (0.92–1.65)		
Perphenazine [6]	1.57 (0.99–2.15)		
Atypical antipsychotics			
Olanzapine [7]	2.0 (1.4–2.6)	Extrapyramidal and anticholinergic side effects, sedation, and cognitive impairment especially with higher doses	
Clozapine [6]	2.5 (2.06–2.94)	Can cause agranulocytosis	
Ergotamine alkaloids including derivatives		Vasoconstriction can lead to angina pectoris, hypertension, glaucoma, liver and renal impairment, urinary retention, and cramping	Therapy waiver
Dihydroergocristine [6]	1.0		
Dihydroergotoxine [6]	1.0		
Antidiabetics			
Glibenclamide [7]	1.93 (1.31–2.55)	Long-acting sulphonylureas cause an increased risk of hypoglycaemia	Sulphonylureas with a shorter half-life
Laxatives			
Bisacodyl [7]	2.0 (1.26–2.74)		

Drug (number of experts)	Mean (95% CI)	Justification for the unfavourable benefit/risk profile	Alternative medication
Liquid paraffin [5]	1.20 (0.81–3.21)	Can lead to hypocalcaemia and hypokalaemia, can lead to lipid pneumonia in case of aspiration pneumonia	Lactulose, macrogol
Muscle relaxants		Common side effects: Delirium, falls, headache, sedation	
Baclofen [7]	1.86 (1.35–2.37)		
Tetrazepam [7]	1.43 (1.03–1.82)		
Sedatives, hypnotics		Can cause amnesia, ataxia, hypotension, prolonged sedation, falls, respiratory depression and - when taken regularly - cognitive impairment, CAUTION: paradoxical reactions	Z-substances
Long-acting benzodiazepines			
Chlordiazepoxide [7]	1.14 (0.86–1.42)		
Diazepam [7]	1.14 (0.86–1.42)		
Dipotassium clorazepate [7]	1.14 (0.86–1.42)		
Bromazepam [7]	1.57 (0.85–2.29)		
Prazepam [7]	1.43 (0.85–2.01)		
Clobazepam [7]	1.14 (0.86–1.42)		
Nitrazepam [6]	1.50 (1.06–1.94)		
Flunitrazepam [7]	1.14 (0.86–1.42)		
Short- and intermediate-acting benzodiazepines			
Lorazepam [7]	2.29 (1.58–2.99)		
Oxazepam [6]	2.33 (1.68–2.99)		
Triazolam [6]	2.0 (1.28–2.72)		
Brotizolam [6]	2.17 (1.65–2.69)		
Drugs for obstructive respiratory diseases			
Theophylline [7]	1.43 (0.85–2.01)	Can cause atrial fibrillation and atrial flutter and tachycardia, cardiac arrhythmia, seizures, insomnia and irritability, vomiting and diarrhoea; dose-dependent	Inhalational drugs including tiotropium, glucocorticoids and long-acting beta-sympathomimetic drugs
Vasodilators, substances promoting blood circulation		Increased risk of orthostatic hypotension and falls and/or efficacy not proven	Therapy waiver
Pentoxifylline [6]	1.83 (1.05–2.62)		
Naftidrofuryl [7]	1.43 (0.85–2.01)		
Nicergoline [8]	1.29 (0.76–1.81)		
Piracetam [8]	1.57 (1.03–2.12)		
Ginko biloba [7]	2.0 (1.04–2.96)		
Antiepileptics			Levetiracetam, lamotrigine, carbamazepine, valproic acid. (Depending on the type of epileptic syndrome)
Phenytoin [6]	2.0 (1.12–2.88)	CNS depression, including delirium, tremor, ataxia, nystagmus, anaemia, and osteomalacia	
Clonazepam [5]	1.80 (1.07–2.53)	CNS depression, including delirium, depression, amnesia, and ataxia	
Phenobarbital [6]	1.33 (0.81–1.85)	Increased risk of cognitive impairment, including sedation, somnolence, memory impairment, paradoxical reaction and irritability, dyskinesia and ataxia, and respiratory depression	

healthcare systems all over the world. According to a Dutch study, 46.5% of all hospital admissions caused by ADEs are potentially avoidable [26].

In the present study, the authors created an Austrian PIM list, including drugs frequently used in long-term treatment, with proven unfavourable benefit/risk ratio or lack of evidence of efficacy in older multimorbid patients. The selection of substances was based on evidence for a higher risk of adverse drug events and drug-to-drug interactions in geriatric patients. Drugs were grouped according to the drug registry of the Austrian Ministry of Health reflecting the local needs and prescription patterns in Austria. The usefulness of a local "Austrian PIM list" arises from the fact that marked differences in prescription be-

haviours and drug markets do exist within the European Union [27]. As for Austria, Schuler et al. have already proven a significant association between ADEs and PIM in Austrian hospitalised patients [28] and demonstrated the need for nationally accepted screening tools.

Eight experts from disciplines relevant to geriatric medicine participated in the two-round Delphi process. This method of structured group interviews, which has been known and advanced for 50 years, was chosen in accordance to the development of the pre- existing PIM lists, and in the quest for a concrete consensus as a result of the group survey. The chosen method of evaluation allows a distinct comparison of the Austrian results to PIM lists abroad. Apart from the scientific aspect of the new Austrian PIM list, it has an impact on daily routine work of Austrian doctors. The drugs listed in the present PIM- list should not be prescribed to geriatric patients, but if at least after a thorough evaluation of the benefit/risk ratio in an individual clinical situation, regardless of the underlying diseases and comorbidities, functional impairment, or patient care setting. The current survey summarises 73 potentially inappropriate drugs for geriatric patients, with non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, antipsychotics, benzodiazepines, and antiparkinson drugs being the most common PIM (see Table 1). Results of special interest will be discussed briefly.

NSAR and pain management in general

Based on the evidence that use of all NSAIDs is associated with an increased risk of gastrointestinal bleeding as well as an increased risk of cardiovascular events [29], the experts classified not only long-acting but also short-acting NSAIDs as PIM. However, risk seems to be higher during exposure to NSAIDs with a long-half life or slow-release formulation [30]. The experts recommend acting with caution when using NSAIDs on long-term basis. However, there may be specific clinical situations when the short-term use of NSAIDs may be useful and provides an acceptable individual and overall risk.

Acetylsalicylic acid was rated as PIM in the indication as an anti-inflammatory drug as the high dosage poses geriatric patients at high risk for gastrointestinal bleeding. This does not seem to hold true for dosages of 100 mg/day or lower, used in primary and secondary prevention of cardiovascular events and ischemic stroke.

Interestingly, the local experts did not evaluate acetaminophen as PIM. It is a frequently used alternative to NSAIDs in pain therapy in older patients. Thus, it may not be considered to be "that safe" a drug. Recent publications underline its narrow therapeutic index, and the risk of liver toxicity caused by an active metabolite leading to elevated transaminase levels and liver failure in cases of overdose [31]. Furthermore, significantly increased blood pressure was found in patients with coronary heart disease [32].

A recent publication outlines the difficulties of a safe but efficient analgesic treatment, demonstrating an increased risk of gastrointestinal bleeding and fractures not only for NSAIDs but also for opioids, an increased risk of cardiovascular events for coxibes and opioids, an increased risk of hospital admissions due to ADEs for opioids, as well as an increase in total mortality [33].

Psychotropic drugs

Tricyclic antidepressants were classified as PIM in the first round of the Delphi process due to their central and peripheral anticholinergic activity. This result is of utmost importance as it has been shown by the authors very recently that prescription rates of tricyclic antidepressants are still high in Austrian nursing home residents [34].

Typical antipsychotics included in the Austrian PIM list rating were generally considered inappropriate for geriatric patients already in the first Delphi round: Only exception was made for haloperidol. Haloperidol was evaluated as PIM only in the second round taking into account its still leading role in the treatment of delirium, topping atypical antipsychotics in clinical efficacy and safety profile [35].

The Austrian study on medication use in nursing home residents also showed a clear prescription preference for prothipendyl for insomnia in nursing home residents [34]. The Austrian experts, however, in accordance with recommendations recently published by Alexopoulos and colleagues suggest avoiding the use of antipsychotics for the treatment of insomnia because of their clinically significant side effects [36]. The recently published evidence-based recommendations by Bloom for the management of insomnia also claim against the use of antipsychotics in this indication, due to problems with "off-label" prescribing and an unfavourable benefit/risk relation [37].

Austrian experts evaluated long-acting as well as short- to intermediate-acting benzodiazepines as PIM. Major reasons for the rating were the increased risk of falls and the worsening of cognitive functions in geriatric patients on regular treatment [38]. The classification of short- to intermediate-acting benzodiazepines as PIM is mainly directed against careless long-term prescription. However, due to their effectiveness, short-term (!) usage in old age psychiatry may sometimes be inevitable.

Z-substances (GABA-A receptor agonist non-benzodiazepine hypnotics) are rated inconsistently in the literature, particularly with regard to their potential for causing dependency. The Austrian experts did not rate them as PIM in short-term usage.

Anti-Parkinson drugs

In the group of anti-Parkinson drugs, dopamine agonists were rated as PIM because of their side effect profiles. This is in line with current guidelines that recommend first-line monotherapy with L-dopa when initiating antiparkinson therapy in patients over 70 years of age or multimorbid patients [39]. Continuous use of pergolide and cabergoline, should be considered as second-line therapy option due to severe valvular fibrosis, even in younger patients.

Infectious diseases

As the primary focus of the PIM list was on drugs prescribed for long-term use, antibiotics were not taken into

account during the current rating. The altered immune status of geriatric patients often causes severe bacterial infections and implies high-dose antibiotic therapy. Particular caution should therefore be put on the onset of ADE symptoms and drug interactions: This holds true for aminoglycosides and vancomycin, which are cleared renally. As geriatric patients have a high susceptibility for renal elimination problems this medication may put patients on special risk for secondary Clostridium difficile induced colitis due to drug accumulation.

The administration of fluoroquinolones requires precaution due to an increased risk of central nervous side effects such as seizures and delirium [40].

General considerations

Unlike in the published STOPP criteria by Gallagher, the dose and duration of drug administration and redundant prescriptions of two or more drugs of the same drug class were not taken into account in the Austrian list [41]. The dosage and duration of a treatment must be thoroughly monitored at every age, and a note with regard to the futility of redundant prescriptions seems not to be especially noteworthy in a PIM list.

The experts are convinced that an Austrian PIM list does not interfere with physicians' individual decision making during prescription process, but can be a helpful tool for a most beneficial and clinically effective medication with the possibly lowest risk of ADEs. Furthermore, the current PIM list may help to identify ADEs, a lesson that may be tricky in older patients because of their atypical and non-specific symptom presentation such as falls or delirium. The inclusion of a drug in the PIM list is not put on a level with an absolute contraindication. Rather, clinicians should become aware of the risks and make a prescription decision only after a thorough assessment of the benefit/risk ratio.

It must be noted though that the validity of PIM lists is limited by particular conditions of individual patients that must be considered with regard to morbidity, comorbidities, and polypharmacy: a drug that has been rated as PIM in one patient may be adequate for another patient in his/her specific clinical situation. In contrast, drugs that were not classified as PIM may also cause clinically relevant ADEs. The authors, therefore, emphasise that the PIM list is in no way a substitute for individual medical assessment and clinical evaluation. Furthermore, the list does not claim completeness.

Drug interactions and interactions between drugs and specific diseases were not included in the PIM list by the Austrian experts since there is sufficient literature available with regard to these aspects.

The Austrian PIM list does not contain recommendations for the dosage of drugs. However, we want to refer to the open-access website www.dosing.de that offers information in regard to the dosage of certain drugs in patients with impaired renal function.

Limitations

The current expert statement may have limitations due to the small number of experts participating. However, the expert group was thoroughly selected, representing the most relevant geriatric disciplines of in- and outpatient settings all over Austria.

The Delphi technique can be questioned in terms of its methodology: To achieve a consensus from randomly assigned experts in the field may be seen as low priority decision-making. However, the selection of these experts also reflects the regional character of the Austrian PIM list. The experts are well known in the field of geriatric medicine in Austria as well as in the European Union. They are not only involved in the Austrian clinical geriatric workup but also carry out most of the local research activity ongoing in the field of geriatrics and gerontology. Despite the methodological limitations of the Delphi technique itself, it is an internationally recognised standardising procedure and has been successfully applied in numerous clinical studies. Independent ranking by the participants allows free decision making irrespective of other group members' opinions and for changes of mind that could be difficult in a face-to-face interview. During the current study, the participants remained anonymous, and the ratings of each expert were evaluated without knowing the ratings given by other participants.

The Austrian PIM list does not claim to be complete. Authors are aware of the fact that a PIM list generally requires review and updating as new drugs are coming to the market and upcoming publications will provide new information on safety aspects and clinical implications also in older patients.

The Austrian PIM list can be a valuable tool to help clinical physicians ensure safe and efficient prescriptions. However, the validation of the Austrian PIM list in hospital and ambulatory care settings is pending, as it's true for almost all PIM lists. Only the very recently published STOPP related PIM list could prove efficacy in terms of avoidable ADEs that cause or contribute to urgent hospitalisation in a prospective trial [42].

Future studies need to investigate the efficacy of the Austrian PIM list based on patient-focused outcome measures, such as ADEs, hospitalisation and utilisation of health care resources, and to assess the impact on health care expenditures.

Conflicts of interest

All of the authors declare that there are no conflicts of interest. No fees from pharmaceutical companies were received: Mann E, Fruehwald Th, Boehmdorfer B, Dueckelmann-Hofer Ch, Rabady S. Honoraria for lectures received: Dovjak P: Novartis, Servier and Nutricia, Iglseder B: Pfizer, EVER, Lundbeck, Sanofi-Aventis and Novartis, Fischer P: Astra Zeneca, Eli Lilly, Germania, Lundbeck, Novartis, Pfizer and Servier, Roller-Wirnsperger R: Nutricia, Nestle, Pfizer, Novartis, Amgen, Madaus, and Baxter.

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