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CLINICAL TRIAL

Potentially inappropriate medication in older psychiatric patients

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Abstract

Purpose Many psychotropic drugs are listed as potentially inappropriate medication (PIM) in the older population. Potentially inappropriate means that prescription of those drugs in older adults may cause significant harm. The objective of this study was to analyze the prevalence and sort of PIM prescribing in a naturalistic, real-world psychiatric setting.

Methods The retrospective analysis gathered data from a large pharmacovigilance study, conducted at 10 psychiatric hospitals. Data from inpatients aged ≥ 65 years were included for the analysis. The number and sort of PIM, as defined by the German PRISCUS list, were controlled by analyzing the patients' medication profile.

Results In total, 4760 patient cases (59.2% female) with a mean (mean ± standard deviation (SD)) age of 77.33 ± 7.77 years were included into the study. Altogether, 1615 cases (33.9%) received at least 1 PRISCUS-PIM per day (regular and as-needed medication included). The most frequently prescribed PRISCUS-PIM ($n = 2144$) were zopiclone > 3.75 mg/day ($n = 310$), lorazepam > 2 mg/day ($n = 269$), haloperidol > 2 mg/day ($n = 252$), and diazepam ($n = 182$). Cases with PRISCUS-PIM were younger (75.7 vs. 78.2 years, $p < 0.001$) and had a longer (26 vs. 22 days, $p < 0.001$) hospital length of stay. Replacing benzodiazepines and z-substances, haloperidol > 2 mg, tricyclic antidepressants, first generation antihistaminergic drugs, and clonidine by non-PIM could reduce 69.9% of PRISCUS-PIM-prescribing.

Conclusions The prevalence of PRISCUS-PIM is high in the hospitalized psychiatric setting. Rational deprescribing of inappropriate anticholinergics, benzodiazepines, and antipsychotics in the older population is a key component to reduce the risk of adverse drug reactions. More tolerable medications should be prescribed.

Keywords Psychiatry · Potentially inappropriate medication · PRISCUS list · Psychopharmacology · Older patients

Introduction

Due to demographic change, the health care system will face a growing number of older, often multimorbid patients ≥ 65 years. Multimorbidity is often associated with polypharmacy [1]. Therefore, older patients who take multiple drugs are high-risk patients of developing adverse drug reactions (ADRs) [2], as polypharmacy increases the risk of pharmacokinetic and pharmacodynamic drug-drug and drug-disease interactions [3–6].

Because of age-related changes in pharmacokinetics and pharmacodynamics [7, 8], older patients, particularly people with frailty syndrome [9–11], are more prone to develop ADRs. Especially in gerontopsychiatry, physicians should consider the increased sensitivity to antipsychotic, e.g., anticholinergic, drugs (e.g., clozapine) [12–16], leading to peripheral and central anticholinergic ADRs, such as cognitive impairment and delirium [17–19].

Many psychotropic drugs are listed as potentially inappropriate medication (PIM) in older people [20–23]. Potentially

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inappropriate medication means that prescribing of those drugs in older patients may cause significant harm [17, 24, 25]. Therefore, PIM should be avoided or replaced by more tolerable alternative drugs [22, 26–29] in the older population. According to this, several lists of PIM have been published [21, 23, 30–32].

Lists of PIM in older patients, such as the PRISCUS list [20], have been developed to improve safety and tolerability of pharmacotherapy in older patients. The German PRISCUS list [33, 34] contains 83 drugs, arranged in 18 drug classes, with a high prevalence of psychotropic drugs.

Different studies have shown that PIM were more commonly associated with ADRs or medication errors, lower quality of life, hospitalizations, and higher health care costs than non-PIM in older patients [25, 35–40]. Based on German health insurance data, Schubert and coworkers [41] detected the highest PIM prevalence for antidepressants (6.5%), antihypertensive medication (3.8%), and antiarrhythmic drugs (3.5%). The most commonly prescribed PRISCUS-PIM observed by Amann, using claims data from three statutory health insurances in Germany [42], were amitriptyline (2.6%), acetyldigoxin (2.4%), tetrazepam (2.0%), and oxazepam (2.0%).

In particular, PIM-prescribing is common in psychiatric patients and potentially fatal [43]. Wucherer [44] conducted home medication reviews in a large sample of community-dwelling primary care patients in Germany and found that 22% of patients who were screened positive for dementia received at least one PRISCUS-PIM. In a study by Hefner, more than half ($n = 89$; 53.0%) of older psychiatric patients (inpatients and day hospital care) took at least 1 PRISCUS-PIM, whereas lorazepam > 2 mg/day ($n = 31$), zopiclone > 3.75 mg/day ($n = 11$), diazepam ($n = 10$), haloperidole > 2 mg/d ($n = 8$), amitriptyline ($n = 7$), clozapine ($n = 7$), and zolpidem > 5 mg/day ($n = 7$) were the most frequently prescribed PRISCUS-PIM [45].

Risk factors for using a PRISCUS-PIM were, e.g., older age, depression, polypharmacy, and female gender [41–43, 46, 47]. Interventions designed to considerably optimize medication may reduce the risk of ADRs in older adults [48].

This study aimed to determine the prevalence and sort of PIM-prescribing in psychiatric inpatients in a naturalistic psychiatric setting.

Methods

Study design

Since 2017, the Federal Joint Committee (G-BA, project executing organization, Deutsches Zentrum für Luft- und Raumfahrt, DLR) is funding health care research projects that aim to optimize quality of care for statutory insured persons in Germany. In this regard, the innovative study "Optimization of pharmacological treatment in hospitalized psychiatric patients" (OSA-PSY, study number 01VSF16009) is sponsored by the DLR. The present retrospective, longitudinal study used data from this large pharmacovigilance project. The study (ethical approval reference number FF 116/2017) is conducted in 10 psychiatric hospitals (Vitos corporation) in Germany. Data from 27,396 cases of treatment (24,118 inpatients and 3278 patients receiving day hospital care), assessed between October 2017 and September 2018, were retrospectively screened. Because of the longitudinal study design, medication patient data were screened on every day of hospital stay.

The project was started in October 2017. Pharmacovigilance is the primary focus of the study OSA-PSY, aiming to optimize psychopharmacotherapy by different interventions. In the first episode of the 3-year study, status quo of psychopharmacological treatment will be assessed. Based on detected discrepancies between clinical treatment and evidence-based recommendations and guidelines and in collaboration with an expert panel, parameters to optimize psychopharmacotherapy will be discussed. Based on these parameters, interventions to optimize psychopharmacotherapy will be developed. Afterwards, in the second episode, clinical utility and effectiveness of the new tools will be determined, based amongst others on quality indicators that have been implemented in all psychiatric Vitos hospitals by different indicators, e.g., CGI, GAF, and PANSS-8.

The study analyzed patient data stored electronically in the hospital information system, which has a computerized order entry system to prescribe all the drugs that are dispensed to the patient, and also includes "as needed" medications. Therefore, the data describes the present prescribing behavior in a real-world psychiatric setting.

Data from inpatients or day hospital care patients in adult psychiatry with a psychiatric disorder were included for analysis. Data from 4760 older patients ≥ 65 years were available. No further exclusion criteria were applied.

Clinical assessment

Medical records were screened for clinical data. Patient characteristics like age, gender, diagnosis (ICD-10), and medication were collected for analysis. The number and sort of PRISCUS-PIM were extracted by analyzing the patients' medication profile. We included all drugs that fulfilled the criteria (dosage) of a potentially inappropriate medication for older patients, designated as PIM in the PRISCUS list [20].

Statistical analyses provided measures of central tendencies and dispersion for continuous data and number of observations and proportions for categorical variables. Differences between means, medians, and proportions were tested with Welch's oneway, Kruskal-Wallis's rank sum, and Pearson's chi-

squared tests, respectively. All statistical analyses were carried out in R (R Core Team. R; a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/. 2019).

Results

In total, 4760 patient cases (59.2% female) with a mean (mean ± SD) age of 77.33 ± 7.77 years were included in the study (Table 1). Patient characteristics, such as hospital treatment, duration of hospital stay, and principal diagnosis, are shown in Table 1.

Altogether, 1615 patient cases (33.9%) received at least 1 and up to 4 PRISCUS-PIM at the same day (regular and as-needed medication included). They received an average number of 0.24 ± 0.45 PIM per day during their hospital stay (Table 1).

The most frequently prescribed PRISCUS-PIM (n = 2144, Table 2) were zopiclone > 3.75 mg/day (n = 310), lorazepam > 2 mg/day (n = 269), haloperidol > 2 mg/day (n = 252), and diazepam (n = 182). Patient cases with

Table 1 Patient characteristics

Number of patients (n)		4760
Age (mean standard deviation (SD))		77.33 (7.77)
Gender (n (%))	Female	2819 (59.2)
	Male	1941 (40.8)
Hospital Treatment (n (%))	Inpatients	4543 (95.4)
	Day hospital care	217 (4.6)
Duration of hospital stay (median [interquartile range IQR]) (days)		23.00 (12.00, 35.00)
Mean (± SD) potentially inappropriate medication (PRISCUS list) (mean (SD))* per day during hospital stay		0.24 (0.45)
Maximum number of potentially inappropriate medication at the same time-point during hospital stay (PRISCUS list) (n total; %)	0	3145 (66.1)
	1	1262 (26.5)
	2	309 (6.5)
	3	40 (0.8)
	4	4 (0.1)
Patients with polypharmacy (≥ 5 drugs/day) (n (%))		3977 (83.6)
Primary diagnosis (ICD-10) (n, %)	F0 Organic, including symptomatic, mental disorders	1768 (37.1)
	F1 Mental and behavioral disorders due to psychoactive substance use	390 (8.2)
	F2 Schizophrenia, schizotypal, and delusional disorders	402 (8.4)
	F3 Mood (affective) disorders	1542 (32.4)
	F4 Neurotic, stress-related, and somatoform disorders	131 (2.8)
	F5 Behavioral syndromes associated with physiological disturbances and physical factors	0 (0.0)
	F6 Disorders of adult personality and behavior	10 (0.2)
	F7 Mental retardation	3 (0.1)
	F8 Disorders of psychological development	0 (0.0)
	F9 Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	0 (0.0)
	Unspecified mental disorder	
	G3 Other degenerative diseases of the nervous system	485 (10.2)
	Demyelinating diseases of the central nervous system	
	Other	29 (0.6)

* Longitudinal study: 0.24 means that patients received by mean 0.24 PIM per day during hospital stay

Table 2 Frequencies of potentially inappropriate medication (PIM), as defined by the PRISCUS list. Alternative drugs were stated in the PRISCUS list

PIM (+ upper dose limit, if available)	Cases, *n*	Drug class	PIM	Cases, *n*	Drug class
Zopiclone > 3.75 mg/day	310	Z-substances	Triazolam	8	Benzodiazepines
Lorazepam > 2 mg/day	269	Benzodiazepines	Hydroxyzine	7	Antihistamines
Haloperidol > 2 mg/day	252	Antipsychotics	Oxazepam > 60 mg/day	7	Benzodiazepines
Diazepam	182	Benzodiazepines	Clemastine	5	Antihistamines
Amitriptyline	141	Antidepressants	Doxylamine	5	Antihistamines
Clonidine	141	Antihypertensives	Maprotiline	4	Antidepressants
Olanzapine > 10 mg/day	118	Antipsychotics	Metildigoxine	4	Antiarrhythmics
Doxepine	92	Antidepressants	Digoxine	3	Antiarrhythmics
Dimenhydrinate	64	Antiemetics	Temazepam	3	Benzodiazepines
Zolpidem > 5 mg/day	64	Z-substances	Fluphenazine	2	Antipsychotics
Bromazepam	59	Benzodiazepines	Flurazepam	2	Benzodiazepines
Clozapine	58	Antipsychotics	Imipramine	2	Antidepressants
Etoricoxib	55	Analgetics (NSAID)	Indometacin	2	Analgetics (NSAID)
Dimetindene	51	Antihistamines	Meloxicam	2	Analgetics (NSAID)
Trimipramine	48	Antidepressants	Naftidrofuryl	2	Vasodilator
Doxazosine	30	Antihypertensives	Nicergoline	2	Vasodilator
Nitrofurantoin	30	Antibacterials	Prasugrel	2	Antithrombotic agents
Clomipramine	19	Antidepressants	Brotizolam > 0.125 mg/day	1	Benzodiazepines
baclofen	15	Muscle relaxants	Chloralhydrate	1	Antihistamines
Solifenacin	14	Antispasmodic drugs	Diphenhydramine	1	Antihistamines
Alprazolam	12	Benzodiazepines	Flunitrazepam	1	Benzodiazepines
Oxybutynin	12	Urologicals	Nitrazepam	1	Benzodiazepines
Sotalol	11	Beta-blocker	Pentoxifylline	1	Vasodilator
Tolterodine	11	Urologicals	Perphenazine	1	Antipsychotics
Flecainide	8	Antiarrhythmics	Terazosin	1	Urologicals
Lormetazepam > 0.5 mg/day	8	Benzodiazepines	Total	2144	

PRISCUS-PIM were younger (75.7 vs. 78.2 years, $p < 0.001$) and had a longer (26 vs. 22 days, $p < 0.001$) hospital length of stay (Table 3).

Figure 1 shows odds ratios calculated for the prescription of potentially inappropriate medication in relation to different factors, as length of hospital stay, number of comorbidities, and diagnoses. CGI at admission (clinical global impression score), length of stay, number of comorbidities, and F1-F3 diagnosis were positive influencing factors for the prescription of PRISCUS-PIM.

Table 3 Differences in patient characteristics of elderly patients who receive at least 1 potentially inappropriate medication (PIM), as defined by the PRISCUS list ($n = 1617$) and patients who receive no PIM ($n = 3143$)

			No PIM	Min. 1 PIM	*p* value
Number of patients (*n*)			3145 (66.1)	1615 (33.9)	
Number of PIM (*n* total; %)	1			1262 (26.5)	
	2			309 (6.5)	
	3			40 (0.8)	
	4			4 (0.1)	
Gender (*n*, %)		Male	1285 (40.9)	656 (40.6)	0.898
		Female	1860 (59.1)	959 (59.4)	
Age (years, mean (SD))			78.16 (7.65)	75.71 (7.74)	< 0.001
Duration of hospital stay (median [IQR]) (days)			22.00 (11.00, 33.00)	26.00 (15.00, 39.00)	< 0.001

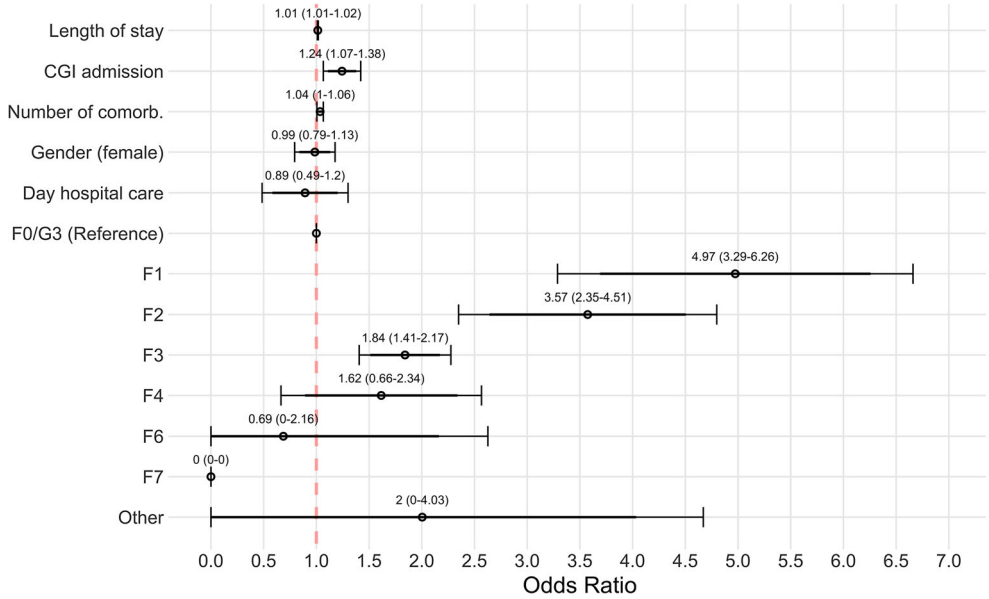

Fig. 1 Odds ratios calculated for the prescription of potentially inappropriate medication in relation to different factors

Discussion

The objective of this study was to analyze the prevalence and type of PIM prescription [20] in a naturalistic psychiatric setting.

Special feature of this study was the approach to analyze the electronic patient data in the hospital information system, reflecting the actual prescribing at psychiatric hospitals.

Altogether, this study revealed a high PRISCUS-PIM prevalence rate of 33.9% (regular and as-needed medication included) with the prescription of at least 1 PRISCUS-PIM during hospital stay (range 1–4, Table 1). Nearly 1% (45 patient cases) of the study group even received 3 or 4 PRISCUS-PIM simultaneously, which should be avoided to reduce the risk of ADRs and prescribing cascades.

This high PRISCUS-PIM prevalence rate in hospitalized older psychiatric patients can be explained by the fact of a large proportion of psychotropic drugs listed as potentially inappropriate in the PRISCUS list [20], e.g., benzodiazepines. After discharge, some of these drugs will not be prescribed anymore by the general practitioner, as observed by Siebert and coworkers [49]. In this study by Siebert and coworkers [49], 43% of the patients received a PRISCUS-PIM while hospitalized and 29% at discharge. While hospitalized, the mean number of administered PIM per patient was 0.5 based on the PRISCUS list [49]. In this study, patients received an average number of 0.24 ± 0.45 PIM per day during hospital stay. As this is a longitudinal study, these results are hardly comparable. Nevertheless, PIM prescriptions should be further decreased in the inpatient psychiatric setting, e.g., "as needed" benzodiazepines or first generation antihistamines.

CGI at admission (clinical global impression score), length of stay, and number of comorbidities, treated with multiple drugs (Table 1, Fig. 1), were positive influencing factors for the prescription of PRISCUS-PIM. This can be explained by the fact that with increasing number of ingested drugs because of comorbidities or a severe psychiatric illness, the possibility of PRISCUS-PIM prescription is increasing, too.

Patient cases with PRISCUS-PIM were younger ($p < 0.001$) and had a longer ($p < 0.001$) hospital length of stay (Table 3). The longer hospital stay could possibly be due to a reduced tolerability of the medication regime and a higher rate of ADRs [25, 35–40]. But it could also reflect that patients receiving PIM did not tolerate other drugs or more tolerable drugs were ineffective. Due to the need of tapering in and tapering out psychotropic drugs, the switch of medications prolongs the length of hospitalization.

The most frequently prescribed PRISCUS-PIM ($n = 2144$, Table 2) were zopiclone > 3.75 mg/day ($n = 310$), lorazepam > 2 mg/day ($n = 269$), haloperidol > 2 mg/day ($n = 252$), and diazepam ($n = 182$). In a study by Hefner, more than half ($n = 89$; 53.0%) of older psychiatric patients took at least 1 PRISCUS-PIM. Overall, lorazepam > 2 mg/day ($n = 31$), zopiclone > 3.75 mg/day ($n = 11$), diazepam ($n = 10$), and haloperidole > 2 mg/day ($n = 8$) were the most frequently prescribed PRISCUS-PIM [45], similar to this study. The higher prevalence rate of 53.0% in the study by Hefner, compared with the prevalence rate of 33.9% in this study, may be explained by the fact that the study was conducted much earlier, and therefore, the PRISCUS list was not that famous in clinical practice. Furthermore, the small sample size in the study by Hefner should be considered.

A significantly higher prevalence of PIM could be detected in female patients, compared with male patients, in concordance with previous studies [41, 42]. In the past, some studies reported female sex as an independent factor for PIM use [50–54]. Furthermore, benzodiazepines are a drug group of potentially inappropriate medication that is more frequently used by women than men [41].

The high rate of PIM prescription especially in patients with a diagnosis of dementia should be reduced, first of all the prescription of benzodiazepines which can increase the risk for, e.g., falls, delirium, or cognitive decline [55]. Hessmann also identified a high prevalence rate of benzodiazepines of 12.4% ($n = 49$) in 395 patients with a diagnosis of Alzheimer's disease as well [56]. The inappropriate prescribing and use of benzodiazepines conflict with national and international guidelines and are a public health problem worldwide. Several major medical and psychiatric organizations, e.g., the American Geriatrics Society, advise not to use benzodiazepines in older adults. Despite these recommendations, benzodiazepines are still prescribed very often to a group of patients with the highest risk of serious adverse effects from these exact medications. Alternative medications for treating insomnia and anxiety in older adults should be preferably prescribed, e.g., sedative antidepressants as mirtazapine or selective serotonin reuptake inhibitors as escitalopram [55–61].

Due to age-related changes in pharmacokinetics and pharmacodynamics [7, 8], older people are more vulnerable to develop, e.g., anticholinergic ADRs [12–19].

Rational deprescribing especially of anticholinergics, benzodiazepines, and antipsychotics in older patients may be a key factor to diminish the risk of ADRs [26]. Clinical advice to reduce PRISCUS-PIM use is shown in Table 4. This table also includes the recommended upper limits of benzodiazepine dosage, given in the PRISCUS list. They should only be prescribed if the risk of ADRs outweighs the clinical benefit, in the recommended dose range per day. Alternative, more tolerable, medications in older adults should be preferably prescribed. According to indication, alternative drugs are prescribed in the PRISCUS list.

Clinical advice to reduce PRISCUS-PIM use is presented in Table 4.

Replacing benzodiazepines and z-substances, haloperidol > 2 mg, tricyclic antidepressants, first generation antihistaminergic drugs, and clonidine by non-PIM could reduce 81.6% of PRISCUS-PIM prescription. Furthermore, replacing clozapine and olanzapine by non-PIM could avoid 8.1% of PIM prescription.

Study limitations

The interpretation of the study results is limited by the naturalistic and retrospective study design but represents a real-word setting for psychiatric patients. The presented results are explorative and do not prove any causal relationship. Lastly, a patient bias could have occurred when inpatients were registered more than one time during the study period or changed to day hospital care, respectively.

Table 4 Clinical advice to reduce the use of potentially inappropriate medications (PIM) in the elderly (PRISCUS list)

Clinical advices to reduce PIM use	Clinical consequence
Replace benzodiazepines and z-substances, e.g., alprazolam, bromazepam, brotizolam > 0.125 mg/day, diazepam, flunitrazepam, flurazepam, lorazepam > 2 mg/day, lormetazepam > 0.5 mg/day, nitrazepam, oxazepam, temazepam, triazolam, zolpidem > 5 mg/day, zopiclone > 3.75 mg/day with, e.g., valerian, sedative antidepressants (mirtazapine), pipamperone, lorazepam ≤ 2 mg/day, lormetazepam ≤ 0.5 mg/day, brotizolam ≤ 0.125 mg/day, zolpidem ≤ 5 mg/day, zopiclone ≤ 3.75 mg/day	Avoiding 81.6%% ($n = 1750$) from 2144 PRISCUS-PIM
Replace tricyclic antidepressants, e.g., amitriptyline, clomipramine, doxepine, imipramine, nortriptyline, and trimipramine with different antidepressants, e.g., escitalopram, sertraline	
Replace dimenhydrinate, diphenhydramine, dimetindene with domperidone, metoclopramid, pipamperone, loratadine, cetirizine, sedative antidepressants (mirtazapine) ➔ according to indication	
Replace clonidine with, e.g., ACE-inhibitors, AT1-receptor antagonists, beta-blocker	
Replace hydroxyzine, doxylamine with, e.g., valerian, sedative antidepressants (mirtazapine), pipamperone, lorazepam ≤ 2 mg/day, lormetazepam ≤ 0.5 mg/day, brotizolam ≤ 0.125 mg/day, zolpidem ≤ 5 mg/day, zopiclone ≤ 3.75 mg/day, loratadine, cetirizine ➔ according to indication	
Avoid the use of haloperidol > 2 mg	
If possible, replace clozapine and olanzapine with different antipsychotics, e.g., risperidone, pipamperone	Avoiding 8.1% ($n = 176$) from 2144 PRISCUS-PIM

CAVE, avoid inappropriate prescribing of benzodiazepines and z-substances. They should only be prescribed if the risk of ADRs outweighs the clinical benefit, in the recommended dose range per day. Alternative, more tolerable, medications in older adults should be preferably prescribed

A prescribed medication is potentially inappropriate if the risk of ADRs outweighs the clinical benefit in an older patient. Therefore, medications in the PRISCUS list are not generally contraindicated in older patients. After an individual patient-based risk-benefit analysis, more tolerable alternatives not listed as PRISCUS-PIM are often available [20]. Nevertheless, in some cases, PRISCUS-PIM are not avoidable in older patients. This investigation had no information about possibly conducted risk-benefit analysis. The longer length of stay in patients with PIM could be due to the non-efficacy or ADRs of the first choice drugs in these patients required a switch of the drugs to PIM. Therefore, final conclusion can be drawn in respect of the overall prevalence of PIM-prescribing (PRISCUS list drugs), but not in respect of the overall prevalence of definitively inappropriate prescribing in existence of more tolerable alternative drugs.

Conclusions

The prevalence of PRISCUS-PIM in psychiatry is relatively high. More than one-third of older patients, especially with a diagnosis of dementia, received at least 1 PRISCUS-PIM at at least 1 day of their hospital stay in this study. PIM-prescribing should be markedly reduced in hospitalized psychiatric patients above 65 years old. PIM were more commonly associated with ADRs or medication errors, lower quality of life, hospitalizations, and higher health care costs than non-PIM in older patients. The inappropriate prescribing and use especially of benzodiazepines conflict with national and international guidelines and are a global public health problem. Alternative, more tolerable medications in older adults should be preferably prescribed [55–57]. The PRISCUS list should be integrated in a complex treatment model for geriatric psychopharmacotherapy. Rational deprescribing especially of inappropriate anticholinergics, benzodiazepines, and antipsychotics in older patients may play a key role to lower the risk of ADRs [26].

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Availability of data and material Data transparency was given and controlled by external government in Hesse, Germany.

Authors' contributions G. Hefner did literature search, did analysis, pharmacological interpretation, and wrote the final manuscript. M. Hahn, S. C. Roll, S. Toto, and C. Hiemke did analysis and pharmacological interpretation of the manuscript. J. Wolff did statistical analysis of patient data. A. Klimke gave the idea and made data analysis and interpretation of study results.

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Compliance with ethical standards

Conflict of interest Gudrun Hefner, Martina Hahn, Sibylle C. Roll, Jan Wolff, and Ansgar Klimke declare no conflicts of interest/competing interests. Sermin Toto has been a member of an advisory board for Otsouka, and has received speaker's honoraria from Janssen Cilag, Lundbeck, Otsouka, and Servier. Christoph Hiemke has received speaker's and consultancy fees from Stada, Lohmann Transdermal Systems, and Otsuka during the last 2 years.

Ethics approval Ethical approval in November 2017 in Hesse, Germany; reference number FF 116/2017.

Consent to participate and for publications All authors consent to participate in this study and for publication of this study results.

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