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Drug safety in older patients with alcohol use disorder: a retrospective cohort study

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Abstract

Background: Older patients with alcohol use disorder are at particular risk of developing adverse drug reactions due to multimorbidity, polypharmacy, and altered organ function.

Objectives: In this study, we investigated the frequency and characteristics of potentially serious alcohol–medication interactions, potentially inappropriate medications (PIMs) for older adults, and potential drug–drug interactions (pDDIs) in a population of older patients with alcohol use disorder over a 10-year period.

Design: Retrospective monocentric cohort study.

Methods: Prescribed medications were screened for potentially serious alcohol–medication interactions, PIMs, and pDDIs using the POSAMINO (POtentially Serious Alcohol–Medication INteractions in Older adults) criteria, the PRISCUS 2.0 list, the FORTA (Fit fOR The Aged) classification, and the drug interaction program AiD*Klinik*®.

Results: We enrolled 114 patients aged ⩾65 years with alcohol use disorder, who were treated in an addiction unit of a university hospital in Germany. About 80.7% of the study population had at least one potentially serious alcohol–medication interaction. Potentially serious alcohol–medication interactions most commonly affected the cardiovascular (57.7%) and the central nervous system (32.3%). A total of 71.1% of the study population received at least one prescription of a FORTA C or D drug, compared with 42.1% who received at least one PIM prescription according to the PRISCUS 2.0 list. A total of 113 moderate and 72 severe pDDIs were identified in the study population.

Conclusion: Older patients with alcohol use disorders are frequently exposed to potentially serious alcohol–medication interactions, PIMs, and pDDIs. Improvements in the quality of prescribing should primarily target the use of cardiovascular and psychotropic drugs.

Keywords: alcohol use disorder, alcohol–medication interactions, drug safety, drug–drug interactions, older patients, potentially inappropriate medications

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Introduction

Alcohol use disorders are a major risk factor for morbidity and mortality worldwide.[1] Older individuals with alcohol use disorders are at increased risk for alcohol-related harm due to various pathophysiological changes, for example, lower volume of distribution, decreased alcohol dehydrogenase activity, and susceptibility to balance disorders.[2,3]

In medical practice, higher age correlates with increasing drug prescriptions, making older alcohol-consuming individuals, particularly susceptible to potentially detrimental alcohol–medication interactions.[4] Alcohol–medication interactions may cause increased sedation, hypoglycemia, orthostatic hypotension, risk of gastrointestinal bleeding, and liver damage.[5] This particularly affects older patients with alcohol use

disorders.[6] Some alcohol–medication interactions may arise with any amount of alcohol, whereas others exhibit a dose–response relationship, in which the severity and risk of the interaction increase proportionally with the amount of alcohol consumed.[4] Studies suggest that an increase in adverse drug reactions (ADRs) may be observed even with moderate alcohol consumption and concomitant use of drugs.[7]

Several studies have examined potential alcohol-interacting medications in older adults; however, most studies lacked a consistent classification for alcohol-interacting medications.[8] To address this shortcoming, the POSAMINO (POtentially Serious Alcohol–Medication INteractions in Older adults) criteria were proposed by Holton *et al.*[9]

Older patients are particularly susceptible to ADRs.[10] In addition to advanced age and drug–drug interactions, prescription of potentially inappropriate medications (PIMs) for older adults increases the risk of ADR.[11,12] In recent years, several classification systems for PIMs have been developed and used in clinical practice. Their primary goal is to raise awareness among clinicians for potentially deleterious effects of PIMs for older adults. In many clinical instances, however, prescriptions of PIMs are inevitable, for example, because a more suitable pharmacological alternative does not exist, was ineffective in the past, or was not tolerated by the patient. In this regard, PIM classification systems differ from deprescribing tools, which primarily focus on the deliberate discontinuation of drugs with a presumed negative benefit–risk ratio.[13–15] In Germany, the PRISCUS (Latin: ancient, venerable) list and the FORTA (Fit fOR The Aged) classification are the preferred PIM evaluation tools, as they specifically take into account German prescribing characteristics and the German pharmaceutical market.[16,17] The recently updated PRISCUS list (i.e. the PRISCUS 2.0 list) has not yet been extensively studied.[17]

Several studies have examined the prevalence and characteristics of potential alcohol–medication interactions and PIM use in older patients, but to the best of our knowledge, no study has focused on older patients with alcohol use disorder thus far.[8,14]

The aim of the present study, therefore, was to determine the frequency and characteristics of potentially serious alcohol–medication interactions, PIMs, and potential drug–drug interactions (pDDIs) in older patients with alcohol use disorder over a 10-year period.

Methods

Ethical approval

This study was approved by the Ethics Committee of Hannover Medical School (No. 10764_BO_K_2023) and adhered to the Declaration of Helsinki and its later amendments.

Study design and eligibility criteria

The study was conducted as a retrospective cohort study. Patients were included in the study, if (i) they were treated in the addiction unit of the Department of Psychiatry, Social Psychiatry and Psychotherapy of Hannover Medical School between January 2012 and December 2021, (ii) if they were ⩾65 years old, (iii) if they suffered from alcohol use disorder, (iv) if they were prescribed at least one drug, and (v) if they or their legal representative had provided written informed consent that patient-related data can be used for clinical research. Hannover Medical School is a large university hospital and tertiary care referral center in northern Germany. The addiction-specific unit is specialized in the treatment and care of patients with substance use disorders. All patients were inpatients. There were no specific exclusion criteria.

The reporting of this study conforms to the STROBE statement.[18]

Identification of demographic data

Demographic characteristics, that is, age, sex, and diagnoses, were obtained from patient records.

Medication evaluation tools

All prescribed drugs of the enrolled patients were analyzed by an interdisciplinary team of experts in psychiatry, clinical pharmacology, and clinical toxicology using the POSAMINO criteria, the PRISCUS 2.0 list, the FORTA classification, and the electronic drug interaction program AiD*Klinik*® (Arzneimittel-Informations-Dienste, Dosing GmbH, Heidelberg, Germany).

The POSAMINO criteria, which apply to people 65 years of age and older, include 38 potentially serious alcohol–drug interactions related to the

central nervous system (15 criteria), cardiovascular system (9 criteria), endocrine system (5 criteria), musculoskeletal system (3 criteria), infections (3 criteria), malignancies and immunosuppression (2 criteria), and respiratory system (1 criterion).[9] The POSAMINO criteria have the limitation that they are not approved for use in patients diagnosed with alcohol use disorders because chronic heavy alcohol consumption can significantly increase the activity of the cytochrome P450 (CYP) isoenzyme 2E1. However, all of the medications taken by patients in the present study were metabolized by CYP isoenzymes other than CYP2E1. Therefore, we decided to apply the POSAMINO criteria in our study.

The PRISCUS 2.0 list includes a total of 187 drugs that are considered potentially inappropriate for people aged ⩾65 years.[17] Additionally, the PRISCUS 2.0 list provides recommendations for suitable pharmacological and non-pharmacological alternatives for the treatment of older patients. PIM use as defined by the PRICUS 2.0 list was also examined in the present study. The FORTA classification contains 299 entries across 30 indications relevant to geriatric medicine and assigns drugs to four different classes (A–D) based on their therapeutic indications for older patients: 'A' are essential drugs for pharmacological treatment of older patients; 'B' are drugs with proven or evident efficacy in older patients; 'C' comprises drugs with uncertain efficacy and safety profiles; and 'D' includes drugs that should be avoided in older individuals.[16] Like the PRISCUS list, the FORTA classification was developed in Germany and is applicable to individuals aged ⩾65 years. We used the FORTA classification to examine PIM use in our study population and to allow a comparison between two different PIM classification systems (i.e. the PRISCUS 2.0 list and the FORTA classification), in analogy to a study by Schulze Westhoff *et al.*[19]

Patients' medications were screened for pDDIs using the electronic drug interaction program AiD*Klinik*®. Only pDDIs classified as 'moderate', 'severe', or 'contraindicated combination' by AiD*Klinik*® were included in the statistical analysis.

Statistics

All statistical analyses were conducted with IBM® SPSS® Statistics 28 (Armonk, New York, USA).

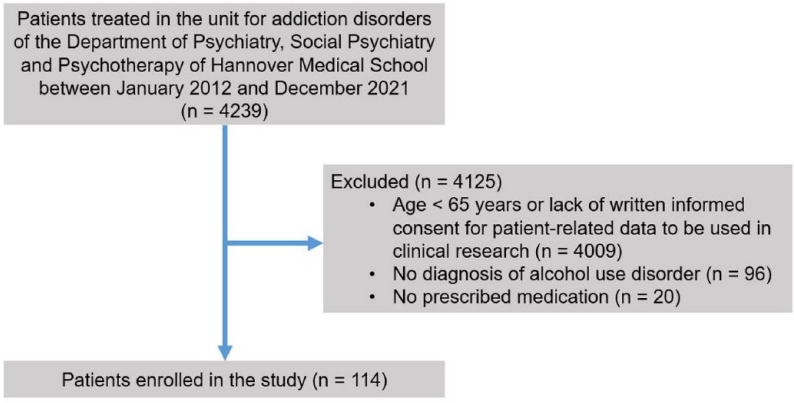

Figure 1. Flow of patients.

Descriptive statistical methods were used to summarize the data. Absolute and relative frequencies were calculated for categorical variables. Quantitative variables were checked for normal distribution with the Shapiro–Wilk test and by inspection of histograms and Q–Q plots. As all quantitative variables were not normally distributed, medians with interquartile ranges (IQRs) were reported instead of means and standard deviations. The Mann–Whitney *U*-test and Pearson's chi-squared test were used for inferential statistics. Due to the exploratory nature of our study, no adjustments were made for multiple testing.

Results

Study population

A total of 4239 patients were treated in the addiction unit from 2012 to 2021, of which 114 were enrolled in the study [male 64.9% (74/114); female 35.1% (40/114)] (Figure 1). The most common reason for exclusion was age <65 years or lack of informed consent ($n = 4009$). The median age of the study population ($n = 114$) was 66 years (IQR 65–69; minimum 65; maximum 79), and the patients were prescribed a median number of five drugs (IQR 2–8; minimum 1; maximum 20). Approximately one-third of the study population suffered from comorbid depression (35.1%; 40/114), and nearly half of the study population had arterial hypertension (46.5%; 53/114) (Table 1). Other common somatic comorbidities included hypothyroidism (16.7%; 19/114), type-2 diabetes mellitus (14.0%; 16/114), and status post stroke (13.2%; 15/114).

Table 1. Characteristics of the study population ($n = 114$).

Variables	*n*	%
Sex		
Female	40	35.1
Male	74	64.9
Psychiatric diagnoses (more than one diagnosis possible per patient)		
Alcohol use disorder	114	100.0
Other addiction disorders (benzodiazepines, Z-drugs, etc.)	24	20.3
Depression	40	35.1
Bipolar affective disorder	3	2.6
Dementia	12	10.5
Other psychiatric disorder(s)	24	21.1
Somatic diagnoses (more than one diagnosis possible per patient)		
Arterial hypertension	53	46.5
Coronary heart disease	8	7.0
Chronic heart failure	8	7.0
Atrial fibrillation	12	10.5
Status post stroke (ischemic or hemorrhagic)	15	13.2
Type-2 diabetes mellitus	16	14.0
Chronic obstructive pulmonary disease	11	9.6
Hypothyroidism	19	16.7
Urinary tract infection	6	5.3
Other somatic disorder(s)	83	72.8

POSAMINO criteria

About 80.7% (92/114) of the study population fulfilled at least one POSAMINO criterion (Table 2). Study participants displayed a median of two POSAMINO criteria (IQR 1–4; minimum 0; maximum 7). In total, 260 POSAMINO criteria were detected in the study population. POSAMINO criteria were mainly related to the cardiovascular (57.7%; 150/260) and central nervous system (32.3%; 84/260). The most frequent POSAMINO criterion in the cardiovascular system category was 'Heavy alcohol consumption with diuretics [e.g. loop diuretics (furosemide), thiazide diuretics (bendroflumethiazide) and potassium-sparing diuretics (amiloride)]' (24.2%; 63/260), followed by 'Heavy alcohol consumption with multiple antihypertensive combinations' (17.3%; 45/260). The most frequent POSAMINO criterion in the central nervous system category was 'Heavy alcohol consumption with all antipsychotics' (10.0%; 26/260), followed by 'Heavy alcohol consumption combined with opioids' (5.0%; 13/260).

Distribution of age and sex did not differ significantly between patients affected by at least one POSAMINO criterion and patients not affected by POSAMINO criteria [median 66 years (IQR 65–69) *versus* median 65.5 years (IQR 65–69), $p = 0.524$; 64.1% (59/92) male *versus* 68.2% (15/22) male, $p = 0.721$]. The number of prescribed drugs was significantly higher in patients

Table 2. POSAMINO criteria detected in the study population.

POSAMINO criteria	*n*	%
Total	260	100
Cardiovascular system	**150**	**57.7**
Heavy alcohol consumption with multiple antihypertensive combinations	45	17.3
Heavy alcohol consumption with regular use of low-dose aspirin	27	10.4
Heavy alcohol consumption with both regular and as required nitrates (e.g. glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate)	1	0.4
Heavy alcohol consumption with diuretics [e.g. loop diuretics (furosemide), thiazide diuretics (bendroflumethiazide), and potassium-sparing diuretics (amiloride)]	63	24.2
Heavy alcohol consumption with alpha blockers (e.g. terazosin)	8	3.1
Heavy alcohol consumption with centrally acting antihypertensives (e.g. clonidine or methyldopa)	6	2.3
Respiratory system	**1**	**0.4**
Any alcohol consumption with first-generation antihistamines (e.g. promethazine)	1	0.4
Central nervous system	**84**	**32.3**
Heavy alcohol consumption with benzodiazepines (e.g. diazepam) and benzodiazepine-related medications (e.g. zopiclone)	11	4.2
Heavy alcohol consumption combined with opioids	13	5.0
Heavy alcohol consumption with duloxetine	3	1.2
Heavy alcohol consumption with all antipsychotics	26	10.0
Heavy alcohol consumption with antiepileptic drugs	11	4.2
Any alcohol consumption with tricyclic antidepressants	8	3.1
Any alcohol consumption with mirtazapine	9	3.5
Heavy alcohol consumption with gabapentin (when used for neuropathic pain)	2	0.8
Heavy alcohol consumption with levodopa (alone or in combination with carbidopa)	1	0.4
Endocrine	**14**	**5.4**
Heavy alcohol consumption with insulin	4	1.5
Heavy alcohol consumption with metformin	7	2.7
Heavy alcohol consumption with sulfonylureas	3	1.2
Musculoskeletal and joint diseases	**11**	**4.2**
Heavy alcohol consumption with any non-steroidal anti-inflammatory drugs (including COX-2 inhibitors)	7	2.7
Heavy alcohol consumption combined with methotrexate or leflunomide	3	1.2
Heavy alcohol consumption with oral muscle relaxants (e.g. baclofen)	1	0.4

COX, cyclooxygenase; POSAMINO, POtentially Serious Alcohol–Medication INteractions in Older adults.

affected by at least one POSAMINO criterion compared to patients not affected by POSAMINO criteria (median five drugs (IQR 4–9) *versus* median 1.5 drugs (IQR 1–2), $p < 0.001$).

PIM prescriptions according to the PRISCUS 2.0 list

A total of 42.1% (48/114) of the study population were prescribed at least one PIM prescription according to the PRISCUS 2.0 list (one PRISCUS 2.0 PIM prescription: 28.1% (32/114); two PRISCUS 2.0 PIM prescriptions: 11.4% (13/114); three PRISCUS 2.0 PIM prescriptions: 2.6% (3/114)). A total of, 67 PRISCUS 2.0 PIM prescriptions were detected in the study population involving a wide range of drugs (Table 3) but in particular psychotropic drugs. The two most common PRISCUS 2.0 PIM categories were antidepressants (29.9%; 20/67) and the group 'anxiolytics, hypnotics, and sedatives' (16.4%; 11/67), followed by (opioid) analgesics (7.5%; 5/67) and antipsychotics (6.0%; 4/67). Regarding non-psychotropic drugs, the most frequently prescribed PRISCUS 2.0 PIM categories were antihypertensives (7.5%; 5/67), calcium-channel blockers (7.5%; 5/67), and potassium-sparing drugs (6.0%; 4/67) – pharmacodynamically, the latter two drug groups also exert blood pressure-lowering effects (and might therefore also be considered antihypertensives); however, they are listed as separate categories by the PRISCUS 2.0 list.

Distributions of age and sex did not differ statistically significantly between patients prescribed at least one PRISCUS 2.0 PIM and patients not prescribed PRISCUS 2.0 PIMs [median 66 years (IQR 65–69) *versus* median 66 years (IQR 65–69), $p = 0.807$; 60.4% (29/48) male *versus* 68.2% (45/66) male, $p = 0.391$]. Patients prescribed at least one PRISCUS 2.0 PIM were treated with more drugs than those not prescribed PRISCUS 2.0 PIMs (median six drugs (IQR 5–10) *versus* median four drugs (IQR 2–6), $p < 0.001$].

Uncertain PIM prescriptions

In addition to 67 definite PRISCUS 2.0 PIM prescriptions, we identified 76 uncertain PRISCUS 2.0 PIM prescriptions in the study population, which were due to missing information on dosage and/or duration of treatment. A total of 59.2%

Table 3. Prescriptions of potentially inappropriate medications according to the PRISCUS 2.0 list.

PIM prescriptions according to the PRISCUS 2.0 list	*n*	%
Total	67	100
Antidiabetic drugs	**3**	**4.5**
Glibenclamide, gliquidone, gliclazide, glimepiride	3	4.5
Cardiac treatment	**1**	**1.5**
Digoxin and derivatives	1	1.5
Antihypertensives	**5**	**7.5**
Methyldopa, clonidine, moxonidine	3	4.5
Doxazosin	2	3.0
Potassium-sparing drugs	**4**	**6.0**
Spironolactone > 25 mg/d	4	6.0
Beta-adrenoceptor antagonists	**2**	**3.0**
Pindolol, propranolol, sotalol	2	3.0
Calcium-channel blockers	**5**	**7.5**
Non-slow-release nifedipine	5	7.5

(Continued)

Table 3. (Continued)

PIM prescriptions according to the PRISCUS 2.0 list	*n*	%
Drugs acting on the renin–angiotensin system	**1**	**1.5**
Aliskiren	1	1.5
Sexual hormones and modulators of the genital system	**1**	**1.5**
Oral estrogens	1	1.5
Urologics	**1**	**1.5**
Oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin, fesoterodine, desfesoterodine	1	1.5
Antibiotics for systemic use	**1**	**1.5**
Fluoroquinolones	1	1.5
Analgesics	**5**	**7.5**
Pethidine, tapentadol, tramadol	5	7.5
Antiepileptics	**1**	**1.5**
Phenobarbital, primidone, phenytoin, carbamazepine	1	1.5
Antipsychotics	**4**	**6.0**
Levomepromazine, perazine, thioridazine, chlorprothixene, zuclopenthixol, prothipendyl	4	6.0
Anxiolytics, hypnotics, and sedatives	**11**	**16.4**
Lorazepam	1	1.5
Moderately long-acting benzodiazepines (e.g. oxazepam)	5	7.5
Zopiclone, zolpidem	5	7.5
Antidepressants	**20**	**29.9**
Tricyclics (e.g. amitriptyline), nortriptyline	2	3.0
Opipramol	2	3.0
Doxepin	4	6.0
Fluoxetine, paroxetine, fluvoxamine	4	6.0
Sertraline $>$ 100 mg/d	1	1.5
Bupropion	1	1.5
Agomelatine	6	9.0
Drugs for obstructive respiratory tract diseases	**1**	**1.5**
Sympathomimetics for systemic use, no inhalation (e.g. salbutamol)	1	1.5
Antihistamines for systemic use – First generation	**1**	**1.5**
Diphenhydramine, clemastine, dimetindene, cyproheptadine, ketotifen	1	1.5

PIM, potentially inappropriate medication.

Table 4. Uncertain prescriptions of PIMs (due to missing information about the dosage and/or duration of treatment) according to the PRISCUS 2.0 list.

Uncertain PIM prescriptions according to the PRISCUS 2.0 list	*n*	%
Total	76	100
Drugs for acid-related diseases	**45**	**59.2**
Proton pump inhibitors (unclear if prescribed > 8 weeks)	45	59.2
Antipropulsives	**1**	**1.3**
Loperamide (unclear if prescribed > 3 d, > 12 mg/d)	1	1.3
Non-steroidal anti-inflammatory and antirheumatic drugs	**7**	**9.2**
Ibuprofen (unclear if prescribed > 3 × 400 mg/d, > 1 week or > 3 × 400 mg/d, with PPI > 8 weeks)	7	9.2
Antipsychotics	**23**	**30.3**
Melperone (unclear if prescribed > 100 mg/d, > 6 weeks)	2	2.6
Pipamperone (unclear if prescribed > 120 mg/d, > 6 weeks)	10	13.2
Quetiapine (unclear if prescribed > 100 mg/d, > 6 weeks)	7	9.2
Risperidone (unclear if prescribed > 6 weeks)	4	5.3

PIM, potentially inappropriate medication; PPI, proton pump inhibitor.

(45/76) of uncertain PIM prescriptions were related to proton pump inhibitors, followed by antipsychotics (30.3%; 23/76), ibuprofen (9.2%; 7/76), and loperamide (1.3% (1/76) (Table 4).

Prescriptions of FORTA C and D drugs

About 71.1% (81/114) of the study population received at least one prescription of a FORTA C or D drug. Study participants were treated with a median of one FORTA C/D drugs (IQR 0–2; minimum 0; maximum 5). In total, 145 FORTA C/D prescriptions were detected in the study population (114 FORTA C prescriptions, 31 FORTA D prescriptions). FORTA C prescriptions most often included metoprolol (12.3%; 14/114), bisoprolol (9.6%; 11/114), mirtazapine, pipamperone, and spironolactone (7.9% each; 9/114). The most common FORTA D prescriptions were ibuprofen (22.6%; 7/31), agomelatine (19.4%; 6/31), and oxazepam (16.1%; 5/31).

Distributions of age and sex did not differ statistically significantly between patients prescribed at least one FORTA C/D drug and patients not treated with FORTA C/D drugs [median 66 years (IQR 65–69) *versus* median 66 years (IQR 65–68.5), $p = 0.712$; 67.9% (55/81) male *versus* 57.6% (19/33) male, $p = 0.295$)]. The number of prescribed drugs was statistically significantly higher in patients treated with at least one FORTA C/D drug compared to patients without FORTA C/D prescriptions [median six drugs (IQR 4–9.5) *versus* median three drugs (IQR 1–4), $p < 0.001$] (Table 5).

Potential drug–drug interactions

A total of 113 moderate and 72 severe pDDIs were recorded in the study population. Moderate pDDIs were most commonly caused by a combination of antihypertensive drugs, increasing the risk of (orthostatic) hypotension (24.8%; 28/113). The most common severe pDDIs were an increased risk of electrolyte disturbances (23.6%; 17/72), for example, due to combinations of potassium supplements with renin–angiotensin–aldosterone system inhibitors (risk of hyperkalemia). In addition, one contraindicated drug combination was detected in our study population: the combination of valsartan and aliskiren which increases the risk of hyperkalemia,

Table 5. Prescriptions of FORTA C and D drugs.

Prescriptions of FORTA C and D drugs	*n*	%
FORTA C drugs	**114**	**100**
Metoprolol	14	12.3
Bisoprolol	11	9.6
Mirtazapine	9	7.9
Pipamperone	9	7.9
Spironolactone	9	7.9
Quetiapine	6	5.3
Tramadol	5	4.4
Pregabalin	4	3.5
Risperidone	4	3.5
Valproate	4	3.5
Venlafaxine	4	3.5
Zolpidem	4	3.5
Doxepin in low dosage (10–25 mg/d)	3	2.6
Duloxetine	3	2.6
Amitriptyline	2	1.8
Carvedilol	2	1.8
Digitoxin	2	1.8
Doxazosin	2	1.8
Gabapentin	2	1.8
Melperone	2	1.8
Morphine	2	1.8
Acetylcysteine	1	0.9
Aliskiren	1	0.9
Beta-acetyldigoxin	1	0.9
Bupropion	1	0.9
Carbamazepine	1	0.9
Fluoxetine	1	0.9
Lorazepam	1	0.9
Naloxone	1	0.9
Ranolazine	1	0.9
Tilidine	1	0.9
Zopiclone	1	0.9
FORTA D drugs	**31**	**100**
Ibuprofen	7	22.6
Agomelatine	6	19.4
Oxazepam	5	16.1
Clonidine	3	9.7
Glibenclamide	3	9.7
Opipramol	2	6.5
Atenolol	1	3.2
Ciprofloxacin	1	3.2
Doxepin	1	3.2
Estradiol as hormone replacement therapy	1	3.2
Ketotifen	1	3.2

FORTA, Fit fOR The Aged.

hypotension, and non-fatal stroke, in particular in patients with pre-existing diabetes or renal insufficiency (Table 6).

Discussion

The present study investigated the prevalence and characteristics of potentially serious alcohol–medication interactions, potentially inappropriate medications for older individuals, and potential drug–drug interactions in older patients treated for alcohol use disorders on the addiction unit of a university hospital in Germany over a period of 10 years. To the best of our knowledge, this is the first study to apply the POSAMINO criteria, the PRISCUS 2.0 list, the FORTA classification, and the interaction program AiD*Klinik*® to older patients with alcohol use disorder.

Our study population differed from previous studies regarding age, sex, and comorbidity profiles.[8,19,20] The median age of our study

Table 6. Severity, subcategorization, and frequency of potential drug–drug interactions detected in the study population.

Potential drug–drug interactions (pDDIs)	*n*	%
Moderate pDDIs leading to/increasing the risk of. . .	**113**	**100**
Hypotension	28	24.8
Electrolyte disturbances	15	13.3
Impairment of kidney function	8	7.1
Increased bleeding risk	6	5.3
Metabolic disturbances	6	5.3
Pharmacodynamic antagonism	4	3.5
Electrocardiographic alterations	3	2.7
Central nervous system depressant effects	2	1.8
Pharmacokinetic interactions	32	28.3
Miscellaneous	9	8.0
Severe pDDIs leading to/increasing the risk of. . .	**72**	**100**
Electrolyte disturbances	17	23.6
Pharmacodynamic antagonism	8	11.1
Central nervous system depressant effects	5	6.9
Increased bleeding risk	5	6.9
Electrocardiographic alterations	4	5.6
Impairment of kidney function	4	5.6
Hypertension	3	4.2
Risk of myopathy/rhabdomyolysis	3	4.2
Risk of serotonin syndrome	2	2.8
Risk of seizures	2	2.8
Pharmacokinetic interactions	11	15.3
Miscellaneous	8	11.1

pDDI, potential drug–drug interaction.

population was 66 years, and the most prevalent psychiatric diagnosis besides alcohol use disorder was depression. In prior investigations, the prevalence and characteristics of potential alcohol–medication interactions were examined in the general population.[21,22] These studies have consistently shown that a significant proportion of the general population was prescribed medications with potential interactions with alcohol.[21,22]

The prevalence of drug prescriptions potentially interacting with alcohol varied widely, ranging from 13 to 42%.[21,22] This variation may be attributed to different study designs and settings.

Regarding the older population, several studies have examined the prevalence and risk factors for potential alcohol-interacting medications.[23–26] Qato *et al.* reported that 20% of the older population in the United States received potential alcohol-interacting medications.[24] A systematic review by Holton *et al.*[8] found that one in five to one in three older adults may be at risk for alcohol–medication interactions.[8]

The POSAMINO criteria have been investigated in different populations of older individuals. Holton *et al.* examined the prevalence and characteristics of POSAMINO criteria among older alcohol-consuming individuals in public pharmacies and in a population-based survey, and detected prevalence of 42% and 18%, respectively.[20,27] In our study, however, a considerably larger proportion of the study population (80.7%) fulfilled at least one POSAMINO criterion, which could be explained by the high number of psychiatric and somatic comorbidities in older patients with alcohol use disorder and by the often associated polypharmacy. In the two studies by Holton *et al.*, POSAMINO criteria most frequently involved cardiovascular medications (19% and 15%, respectively) and central nervous system medications (15% and 4%, respectively),[20,27] which is comparable to our study, where drugs affecting the cardiovascular (57.7%) and the central nervous system (32.3%) accounted for the largest proportions of fulfilled POSAMINO criteria.

In the two Holton *et al.* studies, a higher number of POSAMINO criteria correlated with younger age, male gender, and a higher number of comorbidities.[20,27] By contrast, distributions of age and sex did not differ significantly between patients who fulfilled at least one POSAMINO criterion and those who did not fulfill POSAMINO criteria in our study. However, we found that patients who fulfilled at least one POSAMINO criterion were treated with a significantly higher number of drugs than patients who did not fulfill POSAMINO criteria.

The findings of our study suggest that a significant proportion of drugs prescribed to patients with alcohol use disorders should be critically

evaluated. Although the POSAMINO criteria were not developed specifically for patients with alcohol use disorders but rather for assessing alcohol–medication interactions in the older general population, they may still be helpful in improving drug safety in older patients suffering from alcohol use disorders. The POSAMINO criteria may help guide a comprehensive evaluation of prescribed medications in older patients with alcohol use disorder, which requires a thorough analysis of the benefits and risks, as well as careful consideration of alternative (non-)pharmacological options. The POSAMINO criteria have the advantage of focusing on potentially *serious* alcohol–medication interactions and excluding interactions that are of minor clinical relevance. This reduces the risk of overalerting and alert fatigue.

In the field of geriatric psychiatry, several studies have examined the frequency and risk factors for PIM prescriptions in inpatients.[19,28,29] In a multicenter, retrospective analysis, Hefner *et al.* reported that 33.9% of geriatric psychiatric patients received PRISCUS-PIMs.[28] Previous studies described polypharmacy and a diagnosis of schizophrenia as predisposing factors for PIM prescriptions.[10] By contrast, the presence of dementia and moderate alcohol consumption appeared to be associated with a reduced risk of PIM prescriptions.[10,30]

In our investigation, 42.1% of the study population were treated with at least one PRISCUS 2.0 PIM, whereas 71.1% were prescribed at least one drug classified as FORTA C or D. These findings are largely in accordance with a study by Schulze Westhoff *et al.*, in which 30% of geriatric psychiatric inpatients were prescribed PIMs according to the first version of the PRISCUS list,[31] and 93.5% and 43.5% received FORTA C and D medications, respectively.[19]

Our study indicates that a significant proportion of medications used in the treatment of older individuals with alcohol use disorders should be evaluated critically according to the PRISCUS 2.0 list and the FORTA classification. Antidepressants were the most commonly prescribed the PIM group according to the PRISCUS 2.0 list in our study population, whereby the anticholinergic burden of tricyclic antidepressants deserves particular attention in this regard.[32] It is important to note that there is some evidence that selective serotonin reuptake inhibitors may not only be ineffective in people with alcohol use disorder, but may actually have a worsening effect on dependence.[33] Schulze Westhoff *et al.*[19] described sedatives as the most commonly prescribed PIM group; however, they used the first version of the PRISCUS list in their study. In our study, FORTA C prescriptions most often included metoprolol, bisoprolol, mirtazapine, pipamperone, and spironolactone. There is evidence that beta-blockers are associated with an increased risk of falls in older patients.[34] Similarly, aldosterone antagonists should be prescribed with caution in older patients because their mechanism of action is associated with an increased risk of electrolyte disturbances, particularly hyperkalemia.[35] Interestingly, whereas the PRISCUS 2.0 list considers pipamperone ($<$120 mg/d, $<$6 weeks) and mirtazapine as pharmacological alternatives to PIMs, the FORTA classification states that pipamperone and mirtazapine should be viewed critically and only be used with caution.[16,17]

In our study population, ibuprofen, agomelatine, and oxazepam were the most commonly prescribed FORTA D drugs. Non-steroidal anti-inflammatory drugs such as ibuprofen should be used with caution in older individuals due to their renal and gastrointestinal toxicity; patients concomitantly treated with anticoagulants are at a particularly high risk for gastrointestinal bleeding.[36] Agomelatine should be used with utmost caution in patients with liver disease, which is common in patients with alcohol use disorder.[37] According to the German summary of product characteristics, agomelatine is contraindicated in patients with hepatic impairment (e.g. patients with hepatic cirrhosis).[38] The PRISCUS 2.0 list recommends the sleep-inducing antidepressant mirtazapine as a pharmacological alternative to agomelatine, benzodiazepines, or Z-drugs.[17]

In our study, a combination of antihypertensive drugs – increasing the risk of (orthostatic) hypotension – was the most common type of moderate pDDIs. (Orthostatic) hypotension is also one of the most common ADRs of antihypertensive drugs.[39] Severe pDDIs were most often associated with an increased risk of electrolyte disturbances, for example, due to combinations of potassium supplements with renin–angiotensin–aldosterone system inhibitors (risk of hyperkalemia). In a study by Shehab *et al.*, renin–angiotensin–aldosterone system inhibitors were among the drugs most frequently associated with US emergency department visits due to

adverse drug events, resulting in hospitalization in up to 25% of cases, which underscores the clinical relevance of this potential interaction.[40]

Conclusion

In conclusion, our study revealed that a considerable proportion of older patients with alcohol use disorder were treated with drugs that may interact with alcohol or are generally inappropriate for older adults. The use of drug evaluation tools such as the POSAMINO criteria, the PRISCUS 2.0 list, the FORTA classification, and the AiD*Klinik*® interaction program appears to be useful in clinical practice to improve drug safety for older patients with alcohol use disorders. One caveat of these drug evaluation tools is that they were not specifically designed for patients with substance use disorders. Moreover, unlike the PRISCUS 2.0 list, the POSAMINO criteria and the FORTA list do not specify more suitable (non-) pharmacological alternatives.

Limitations

One might question the choice of the analyzed medications in our study. The medications were extracted from patients' medication charts during their inpatient treatment. The therapeutic goal is to achieve abstinence from alcohol after qualified withdrawal therapy, so in theory alcohol–medication interactions should not occur after patients' release from hospital. Unfortunately, relapses to alcohol consumption after release from hospital are not uncommon; therefore, alcohol–medication interactions represent a serious concern in clinical practice that healthcare providers need to address and should familiarize themselves with.[41]

Limitations of our study are the monocentric design and the setting in a highly specialized unit of a university hospital; hence, our results may not fully apply to other healthcare settings. Furthermore, due to the retrospective design of our study, we were unable to examine whether the potentially serious alcohol–medication interactions, PIM prescriptions, or pDDIs detected in our study population, actually resulted in the occurrence of adverse effects. Future research should use a prospective design in order to analyze the true risk of adverse outcomes associated with potentially serious alcohol–medication interactions, PIM prescriptions, and pDDIs in older patients with alcohol use disorders. This will help healthcare professionals to stratify patients with alcohol use disorder based on their individual risk profiles at the time of prescribing. Moreover, randomized controlled trials should prospectively investigate whether reducing alcohol-interacting medications and PIMs can actually reduce the incidence of adverse effects in older patients with alcohol use disorder.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hannover Medical School (No. 10764_BO_K_2023) and adhered to the Declaration of Helsinki and its later amendments. Patients were only included if they or their legal representative gave written consent for patient-related data to be used for clinical epidemiological research.

Consent for publication

Patients were only included if they or their legal representative gave written consent for patient-related data to be published for clinical epidemiological research.

Author contributions

Sebastian Schröder: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Visualization; Writing – original draft.

Martin Schulze Westhoff: Formal analysis; Methodology; Validation; Writing – review & editing.

Tabea Pfister: Formal analysis; Investigation; Validation; Writing – review & editing.

Johanna Seifert: Formal analysis; Methodology; Validation; Writing – review & editing.

Stefan Bleich: Formal analysis; Methodology; Validation; Writing – review & editing.

Felix Koop: Formal analysis; Methodology; Validation; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data that support the findings of this study are available upon reasonable request from the corresponding author.

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