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Pharmacological Investigation of Potential Drug-Drug Interactions in the Context of Polypharmacy and Medical Communication in a German Health Network

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Abstract

Background: In general, management of patients with polypharmacy is a challenge for medical practice. Polypharmacy often is accompanied by Adverse Drug Reactions (ADRs) due to Drug-Drug Interactions (DDIs).

Objective: This study aimed to identify, categorize and appraise potentially harmful DDIs in patients with polypharmacy in the ambulatory setting.

Patients and Methods: A non-interventional cross-sectional study including 500 patients with a mean (± SD) age of 67, 4 years (± 13.3) (male, n=248; female, n=252). The sample was obtained from n=12 general practitioners in Frankfurt, Germany.

Results: The number of prescribed drugs significantly correlates with comorbidities ($p<0.001$), pharmacodynamic DDIs ($p<0.001$) and DDIs, categorized as potentially harmful (category "A"; $p=0.003$).

DDIs categorized as "A" were correlated to age, cardiac arrhythmias, renal insufficiency, Type II diabetes mellitus, intake of oral anticoagulants, antiarrhythmics, Proton Pump Inhibitors (PPI)/antiacids, analgesics and systemic corticoids (univariate analysis, $p \leq 0.05$). A multivariate regression analysis revealed a significant correlation to the drug strata ($p<0.001$), Type II Diabetes mellitus ($p=0.033$) and intake of PPI/antacids ($p=0.047$). Of all DDIs (n=1465), the majority were (n=1311, 89.5%) pharmakodynamic DDIs, n=634, 48.4% of these categorized as clinically relevant, i.e. (1) alterations of serum Natrium/Potassium, affecting (2) anti-diabetic therapy, (3) anti-hypertensive treatment, (4) blood coagulation or (5) the ECG ($n \geq 50$). N=154 DDIs (10.5%) were of pharmacokinetic origin.

Conclusion: The number of detected pharmacokinetic DDIs was low; the majority of clinically relevant DDIs were pharmacodynamic. Training of medical staff should focus on pharmacodynamic DDIs in patients with polypharmacy, especially those with Type II diabetes mellitus.

Keywords: Drug-drug interactions; Polypharmacy; Diabetes mellitus

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Introduction

The demographic transition in the elderly population constitutes a significant challenge for health authorities worldwide as with advancing age multiple chronic diseases such as hypertension, diabetes mellitus, arthritis, chronic heart disease, renal diseases, etc. are evolving. As a result, chronically taken multiple medications either given for primary or as secondary prevention or just symptomatic treatment accumulates to polypharmacy. The proportion of patients >60 years of age is growing continuously and amounts to nearly 30% in 2020 in Germany [1]. This leads to the situation that patients aged >60 years are already taking an average of 3 drugs, patients aged >70 years 5 drugs and >80 years 8 different drugs daily, which goes in accordance to European or US surveys [2-4]. Hence, polypharmacy and the related problems of mortality, adherence, DDIs and medication

costs are one focus of health care maintenance [5-11]. A number of past studies in the field showed that patients did not adhere to their medication without reporting to the prescribers due to side effects by undetected DDIs [9,12]. Also, polypharmacy is an independent risk factor for hospital admission among older patients [13] and significantly influences Quality of Life (QoL) [14,15]. Polypharmacy can even be associated with malnutrition and Activities of Daily Living (ADL) disability in elderly patients [16].

In general, there are various instruments to support Doctors, Pharmacists and Patients regarding the prescription of drug combinations, either printed [17] or being part of PC-based software in the general practice [18]; these provide general information e.g. about Adverse Drug Reactions (ADRs), DDIs, contraindications or health warnings. Past investigations showed that at least in Germany- according to conservative approximations - about 30,000 cases of hospitalization and about 3,000 deaths occur every year due to DDIs or ADRs [19]. The reasons are manifold: First, every chronically ill patient is treated by a number of different specialists, often without proper communication between the professions [20]. Second, patients are taking Over-The-Counter drugs (OTC), which are considered being harmless in use but can have a considerable potential for DDIs, e.g. Proton Pump Inhibitors (PPI), Antacids, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [21]. Third, if a patient is taking more than three different drugs it is very difficult for prescribers/pharmacists to predict potential DDIs [22].

In Germany, the standardized Federal Medication Plan (FMP) is expected to be an important instrument in recording all drugs that are prescribed by doctors and taken by the patient. Especially general practitioners and pharmacists shall cross-check the medication for potential DDIs, and in case revise the plan. In daily routine, this is a time-intensive procedure, afflicted with random errors. Also, warnings about potential DDIs are not always helpful, especially if a certain medication should not be used in special patients merely due to the lack of information/data, or if the declarations on clinical relevance and management of a DDI are vague. Especially elderly patients came into the focus due to their vulnerability regarding DDIs and therapy-limiting or even life-threatening ADRs, primarily prescribed against hypertension, neuropsychiatric disorders or pain. But also chronically ill patients are affected, if they concomitantly take more than three drugs each day [23]. The subsequently reported study evaluated potential DDIs between prescribed drugs that were taken at least 4 weeks or longer by-mostly elderly patients, who took at least 3 or more drugs on a daily base. This systematic investigation of potential prescription DDIs aimed to identify and categorize potentially harmful DDIs in order to propose preventive algorithms for the general practice. In addition this study aimed to generate new hypothesis for future health services research. The study was conducted in a German Health Care Network using a predefined, traceable and correctible referral process.

Study design

A non-interventional cross-sectional study evaluated potential DDIs of medication taken by n=500 patients who took 3 or more prescribed drugs daily for at least 4 weeks. The duration of the study was 12 Months. The study was conducted in accordance with the Declaration of Helsinki, the ICH-GCP and the local medical laws; it was approved by the Ethics Committee of the Medical Chamber of the State of Hessen. All study data were anonymized by the treating physicians and then transmitted to the coordinating center/trials unit for evaluation. Data were analyzed according to the study flow chart, discussed later on in this article. Protection of data privacy followed the new European Law (EU-DSGVO), valid from 25.05.2018.

Study objectives

The aims of the study were a). The investigation of potential DDIs in ambulatory health care at the intersection between medical specialists and general practitioners. b). The evaluation of the potential clinical relevance of DDIs and their qualification as either potentially severe or less severe. c). The generation of hypotheses for future studies of DDI and drug safety in polypharmacy in ambulatory health care. All data were anonymized for analysis and no treatment recommendations were deflected from the results of this study.

Study parameters

The primary study parameter was the quantification of potential DDIs in three different groups of patients, taking 3-4, 5-7 or ≥ 8 different active components per day.

Secondary parameters were

- The categorization of DDIs into (1) none, (2) mild, (3) moderate or (4) severe
- The identification of relevant medication being involved in DDIs
- The identification of the major pharmacological mechanisms of DDI
- Registering potentially endangered groups of patients

Data were accessed from the standardized Federal Medication Plan (FMP) and the following parameters were recorded: Age, gender, chronic diagnoses, chronic medication, comorbidities, DDIs (categorized into (1) none, (2) mild, (3) moderate or (4) severe, (v) clinically relevant or (vi) not relevant). Patients were stratified into groups taking (A) 3-4, (B) 5-7 or (C) ≥ 8 different active components per day and into age-groups (i) <60, (ii) 60- <70, (iii) 70- <80, (iv) ≥ 80 years of age. Further on, we recorded main medication groups, pharmacological mechanisms and potentially endangered groups of patients regarding DDIs.

Statistical analysis

The primary parameter was analyzed by descriptive statistics (relative frequency, 95% CI), the difference between groups was analyzed by means of Chi^2-tests and Fishers exact tests for contingency tables. If it is possible to observe about 100 or 300 patients in three subgroups, the 95%-confidence interval for the frequency of potential DDIs is 20% or 12%, respectively, so that a valid predication for this parameter can be given. A chi^2-test with 6 freedom degrees at a level of 5%-significance can reach a statistical power of 80%, if a small to moderate W=0.2 according to Cohen is given and the number of cases is at least n=341. All other parameters were analyzed by means of descriptive statistics (relative frequency, 95% CI). Differences in quantitative parameters were analyzed by parametrical tests if equally distributed (T-Test, log-PK values and geometrical means). Again, the difference between categorized parameters was analyzed by means of Chi^2-tests and Fishers exact tests for contingency tables.

The significance level was set as α=0.05 and Bonferroni correction was applied for multiple testing. The statistical analysis plan was approved by the Department of Medical Statistics of the Goethe University Frankfurt/Main, Germany.

Methods

The n=12 participating outpatient centers used the PC-based DDI software i:fox® [18], which categorizes DDIs according to a traffic light-system: Green=in offensive, Yellow=caution or Red=contra indication. Our study focused solely on the yellow scope, as the yellow rating only means "doctors should be cautious" and "the benefit of drug intake must outweigh the risks" without giving clear advice for prescribing healthcare staff. Thus, the first 500 FMPs matching with the inclusion criteria for this study were included in the analysis. Data recording was conducted between 15.08.2018 and 01.04.2019 and the software used for categorization and inclusion of the FMPs into the analysis was i:fox® [18], a software widely used in German outpatient centers or practices.

The software used to analyze the data according to the study protocol was the German Pharmacists Database (ABDA of the German federal Institute for Medical Devices, BfArM) [24] and a cross-check of 10% random samples were conducted by means of the hospital-based AID Clinic [25] software. The ABDA software is mainly based on the Summary of Product Characteristics (SmPC), but also includes legal text, publications of health care authorities' worldwide, primary- and secondary literature of chemistry, pharmacology and clinics of drugs. Subsequently, a personal evaluation and appraisal was performed by a clinical pharmacologist and discussed separately.

We recorded the following groups of medications, according to the ATC-Classification: (1) Antibiotics/antimyotics, (2) antiarrhythmics, (3) antihypertensives, (4) oral anticoagulants, (5) antidepressants/hypnotics, (6) antiepileptics/neuroleptics, (7) oral antidiabetics, (8) Proton Pump Inhibitors (PPI)/antacids, (9) analgesics/Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (10) Lipid lowering drugs, (11) Others, e.g. corticosteroids/immunosuppressants/phosphodiesterase-inhibitors/thyroxin. The classification of and grouping refers to former trials, such as PRIMA-eDS [26,27]. Pharmacological mechanisms were sub-classified as Pharmacodynamic (PD) interactions or Pharmacokinetics (PK) interactions, such as absorption, first-pass or elimination; pharmacokinetic pathways evaluated were CYP 3A4, CYP 2D6, CYP 2C9 and other cytochrome pathways, cellular transporter pathways, i.e. P-gp, BCRP, OATP and others or renal cellular transporter pathways, i.e. OCT, MATE and others. Patients potentially exposed to a detected DDI were sub-classified according to age-groups, gender, and chronic diagnoses or drugs taken.

Results

Altogether, n=513 datasets have been screened, n=500 were taken to the analysis after exclusion of n=13 due to protocol violations.

Patient´s characteristics and demographics

The distribution of male/female was n=248/252 (49.8%/50.2%). The mean age (± Standard Deviation, SD) was 67, 4 years (± 13.3), the age ranged from 26 to 97 years. The age strata were as follows: (i) <60 (n=146, 28.9%), (ii) 60-<70 (n=138, 27.7%), (iii) 70- <80 (n=115, 23.1%), (iv) ≥ 80 (n=103, 20.7%) years of age. On average, patients took n=7.3 (± 3.5) different drugs, with a range between n=3 to n=19. 18.7% of patients took 3-4, 44.6% 5-7 and 36.7% ≥ 8 active components. The number of pills does not necessarily match with the number of drugs taken due to co-formulated combination tablets.

The mean age for the prescription drug strata was group 1=60.8 (± 12.7), group 2=66.6 (± 12.0) and for group 3=71.6 (± 11.3) years (T-Test, p=0.010) (Table 1).

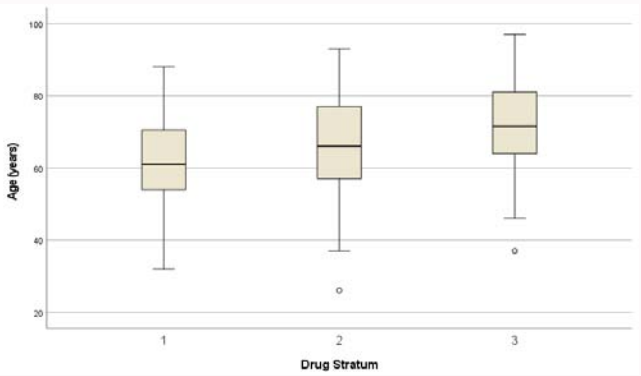

Figure 1: Drug strata in correlation to the age of patients.
1=stratum 1, 3-4 drugs; 2=stratum 2, 5-7 drugs; 3=stratum 3, ≥ 8 drugs

The total number of drugs taken by n=500 patients was n=3615. In detail, these were antibiotics/antimykotics (n=3), antiarrhythmics (n=97), antihypertensives (n=429), oral anticoagulants (n=80), antidepressants/hypnotics (n=60), antiepileptics/neuroleptics (n=40), oral antidiabetics (n=289), PPI/Antacids (n=120), Pain Medication/Anesthetics (n=93), Lipid lowering drugs (n=323), Insulin (n=191) and Others (n=296). As the least group (n=296, 100%) showed a considerable number of drugs, these have been recorded subsequently as single substances, which were cortisone (n=33, 11.1%), the uric acid lowering drugs febuxostat/allopurinol (n=36, 12.2%), the selective prostatic α1A/1L-receptor inhibitor tamsulosin (n=35, 11.8%), minerals/vitamin-complex formulations (n=30, 10.1%), or L-Thyroxin (n=31, 10.2%) Antibiotics/antimycotics (n=3, 0.08%), antiepileptics/neuroleptics (n=40, 1.1%), anti-cancer drugs (n=5, 1.2%), antidepressives/hypnotics (n=58, 1.6%) were of little relevance as no statistically significant differences could be detected between the drug strata. With higher age, the probability of taking more drugs increased, as shown in Figure 1 (drug strata in correlation to the age of patients, Pearson-regression analysis r^2=0.27, p<0.01). This goes in accordance with previous analyses from the German Health Care system and thus confirms the liability of the recorded data [26,27].

Primary parameters

Altogether, in n=500 patients we detected n=1311 pharmacodynamic and n=154 pharmacokinetic DDIs. 51.9% or n=680 of these were categorized as "A" or clinically relevant: The number of taken active compounds was significantly correlated to the number of comorbidities (p<0.001), the number of PD DDI (p<0.001) and the number of clinically relevant DDI, categorized as "A" (p=0.003; Pearson regression analysis). The number of clinically relevant DDI, categorized as "A" itself showed significant correlations to the number of PK DDI (p<0.001), PD DDI (p<0.001), taken active compounds (p<0.001), DM II (p<0.001) and hypothyreosis (p=0.004, Bonferroni-correction for multivariate testing). The trends show a clear correlation between the number of patients per drug stratum experiencing DDIs and the number of DDIs detected per case (Figure 2). A smaller number of patients in stratum 1 experiences DDIs and none of the patients had more than 5 DDIs. The range of DDIs in stratum 2 and 3 is between 1 and 9 cases, strata 2 and 3 do not differ markedly regarding the risk for DDI.

1=stratum 1, 3-4 drugs; 2=stratum 2, 5-7 drugs; 3=stratum 3, ≥ 8 drugs

Again, Figure 3 shows the correlation between the number of

Table 1: Patient demographics and characteristic.

	Stratum 1 3-4 drugs	Stratum 2 5-7 drugs	Stratum 3 ≥ 8 drugs	Chi² -Test (two-sided)
	n= (%)	n= (%)	n= (%)	p-value
Absolute	94	222	184	0.508
Female	51	114	87	
Male	43	108	97	
Age mean [T-Test] (± SD)	60.8 (± 12.7)	66.6 (± 12.0)	71.6 (± 11.3)	0.01
Comorbidities n=3278				
Comorbidities mean [T-Test] (± SD)	3.7 (± 0.8)	6.3 (± 1.3)	19.3 (± 2.5)	<0.001
	n (%)	n (%)	n (%)	
Type II diabetes mellitus	39 (1.2)	147 (4.5)	130 (4.0)	<0.001
Hypertension	64 (2.0)	198 (6.0)	174 (5.3)	<0.001
Hyperlipidemia	51 (1.6)	143 (4.4)	137 (4,3)	0.003
Cardiac arrhythmia	8 (0.2)	54 (1.7)	67 (2.1)	<0.001
Coronary artery disease/CHF	9 (0.2)	49 (1.6)	72 (2.2)	<0.001
Apoplexia	1 (0.03)	11 (0.3)	28 (0.9)	<0.001
Depression/Anxiety disorder	19 (0.6)	40 (1.2)	33 (1.0)	0.881
Chronic Pain	13 (0.4)	53 (1.6)	66 (2.0)	<0.001
Hypothyreosis	17 (0.5)	60 (1.9)	59 (1.9)	0.046
Carcinoma	2 (0.06)	15 (0.5)	28 (0.9)	<0.001
Polyneuropathy/RLS	7 (0.2)	59 (1.9)	68 (2.1)	<0.001
Adipositas	20 (0.6)	73 (2.2)	67 (2.0)	0.073
Kidney insufficiency	8 (0.2)	64 (2.0)	83 (6.2)	<0.001
Age strata				
Age <60	48	66	32	<0.001
Age 60-69	25	65	48	0.751
Age 70-79	14	51	50	0.071
Age >80	7	40	54	<0.001
Medication n=3615				
drugs mean (T-Test) (± SD)	3.9 (± 2.0)	6.0 (± 2.2)	8.6 (± 2.5)	<0.001
	n (%)	n (%)	n (%)	
Antibiotics	0	0	3 (0.1)	0.075
Anti-hypertensives	63 (1.7)	196 (5.4)	170 (4.8)	<0.001
Anti-arrhythmics	12 (0.3)	32 (0.9)	53 (1.5)	<0.001
Oral anticoagulants	3 (0.1)	26 (0.9)	51 (1.5)	<0.001
ASS/Clopidogrel/Ticagrelor	15 (0.4)	78 (2.5)	87 (2.6)	<0.001
Antidepressants	9 (0.3)	28 (0.9)	23 (0.7)	0.724
Anti-epileptics/Neuroleptics	9 (0.3)	11 (0.3)	20 (0.6)	0.075
Oral Anti-diabetics	40 (1.2)	132 (4.1)	117 (3.6)	0.003
PPI/Antacids	11 (0.3)	37 (1.0)	72 (2.0)	<0.001
Pain Medication	1 (0.03)	33 (0.8)	59 (1.6)	<0.001
NSAIDs	0	14 (0.4)	12 (0.4)	0.042
Lipid lowering drugs	43 (1.2)	141 (3.9)	139 (3.9)	<0.001
Insulin	18 (0.5)	83 (2.3)	90 (2.4)	<0.001
Corticosteroids/Immunosuppressants	31 (0.8)	119 (3.3)	146 (4.0)	<0.001
Cortisone	0	8 (0.3)	25 (0.7)	<0.001
Febuxostat/Allopurinole	1 (0.03)	13 (0.4)	22 (0.6)	0.002
Tamsulosine/Finasteride	0	15 (0.4)	20 (0.6)	0.003

CHF: Chronic Heart Failure; RLS: Restless Legs Syndrome; PPI: Proton Pump Inhibitors; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Table 2: Differences between male and female patients.

Parameter	Female	Male	p-value Chi²-Test
Age strata	1=58, 2=74, 3=60, 4=43	1=87, 2=68, 3=50, 4=43	0.034
No. of components			0.284
Strata components	1=51, 2=114, 3=87	1=43, 2=108, 3=97	0.508
DDI PD	178	181	0.484
DDI PK	59	53	0.513

Table 3: Drug-drug interactions, detected in n=500 standardized federal medication plans, according to drug strata.

	Stratum 1	Stratum 2	Stratum 3	Chi²-Test
	3-4 drugs	5-7 drugs	≥ 8 drugs	(two-sided)
	n= (%)	n= (%)	n= (%)	p-value
Drug-Drug Interactions				
DDI mean (± SD)	0.7 (± 1.5)	0.94 (± 1.2)	2.4 (± 2.0)	<0.001
DDI PD	26	159	181	<0.001
DDI PK	15	43	59	0.055
DDI Absorption	11	38	79	<0.001
DDI First Pass	13	41	54	0.071
DDI Elimination	1	2	3	0.791
Cat. A /risk factors	21	116	158	<0.001
Cat A/risk factors mean (± SD)	0.4 (± 0.8)	0.9 (± 1.2)	2.4 (± 2.0)	<0.001

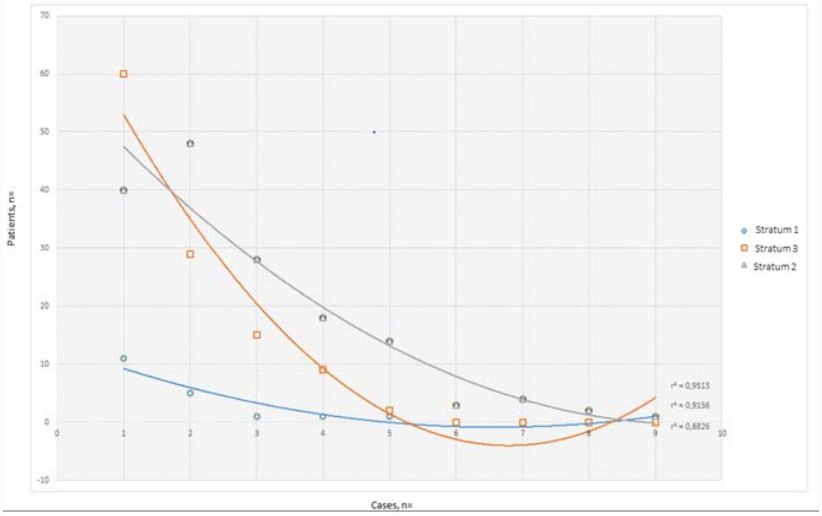

Figure 2: Strata of drug intake, correlated to the number of detected drug-drug interactions per case; lines show the polynomic trend.

taken drugs and the incidence of all DDIs.

Secondary parameters

Gender-specific analyses: We could not detect any gender-specific differences regarding primary parameters (no. of drugs; drug strata; PK or PD interactions (Chi²-Test, Fisher´s Exact Test). One difference detected was found regarding age; the prevalence of in the strata of older age is significantly higher, in contrary male patients do belong significantly more frequent to the group of multimorbid patients <60 years (Table 2).

Comorbidities: The distribution of comorbidities shows a spectrum expectable in general and internal medicine. Type II diabetes mellitus II (n=316), hypertension (n=436), hyperlipidemia (n=331), cardiac arrhythmias (n=129), chronic heart failure/coronary artery disease (n=130), apoplexy (n=40), depression/panic/others psychiatric co-diagnoses (n=92), chronic pain (n=132), hypothyreosis (n=136), cancer (n=45) polyneuropathy/Restless Legs Syndrome (n=134), obesity (n=169) and renal insufficiency (5%), at a total number of 2,243 recorded co-morbidities.

In Figure 3, 4 show the correlations between the number of comorbidities and age- and drug-strata, which were significant in both analyses: Pearson regression analysis for number of comorbidities *vs.* drug strata $p<0.001$, $r^2=0.53$ (Figure 4a, 4b) and for number of comorbidities *vs.* age strata $p<0.01$, $r^2=0.28$ (Figure 5a, 5b). Whisker box plots show median, upper/lower quartiles of values.

Also, the trend shown in Figure 4b, the correlation between the number of comorbidities and the number of drugs taken at the same

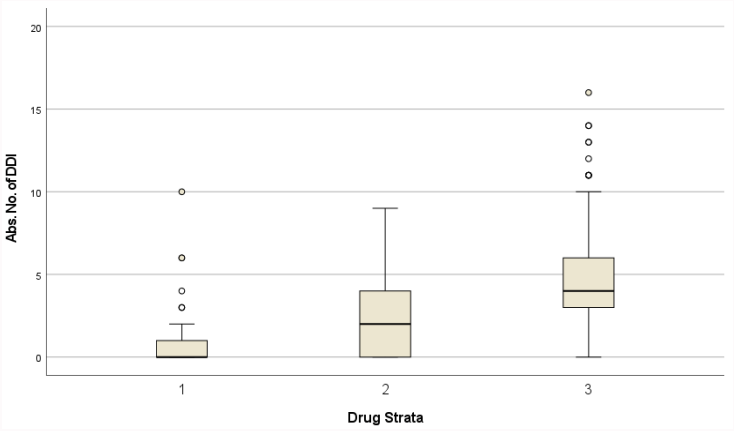

Figure 3: Absolute No. of DDI per drug stratum.
1=stratum 1, 3-4 drugs; 2=stratum 2, 5-7 drugs; 3=stratum 3, ≥ 8 drugs

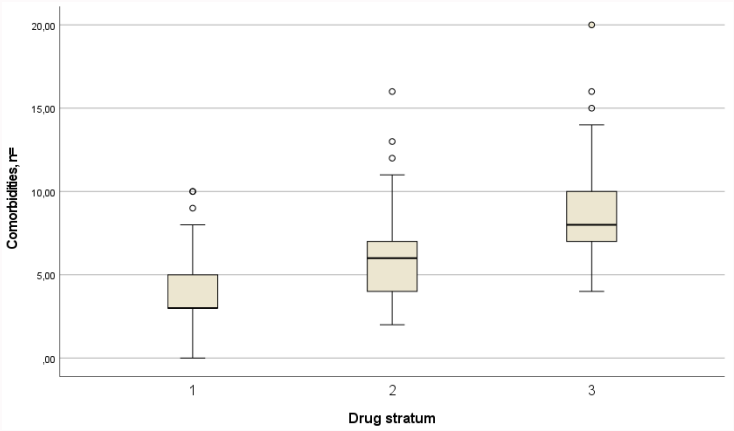

Figure 4a: Drugs strata in relation to the number of comorbidities.
1=stratum 1, 3-4 drugs; 2=stratum 2, 5-7 drugs; 3=stratum 3, ≥ 8 drugs
Whisker boxplots show median, upper/lower quartiles of values.

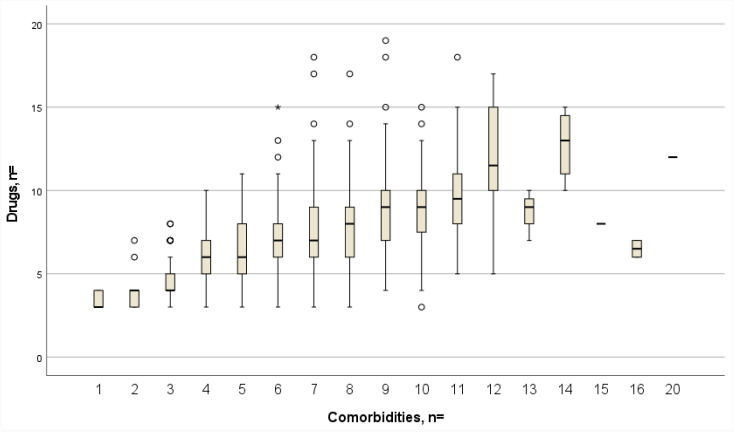

Figure 4b: Number of drugs taken in relation to the number of comorbidities.
Whisker boxplots show median, upper/lower quartiles of values.

time is statistically significant (Pearson regression analysis, p<0.001).

However, the number of taken active components significantly correlate with the no of comorbidities (p<0.001), the number of PD DDI (p<0.001) and the number of DDI, categorized as "A" (p=0.003).

Clinically relevant DDIs: The intake of drugs correlates significantly with the occurrence of potential DDIs, especially those of a pharmacodynamic origin (p<0.001). But, although to a lesser extent, pharmacokinetic DDIs also correlate with the number of taken drugs, especially regarding absorption DDIs (p<0.001). The occurrence of DDI in the clinical relevant category A is significantly correlated (p ≤ 0.0014, Bonferroni-correction for multiple testing) with the

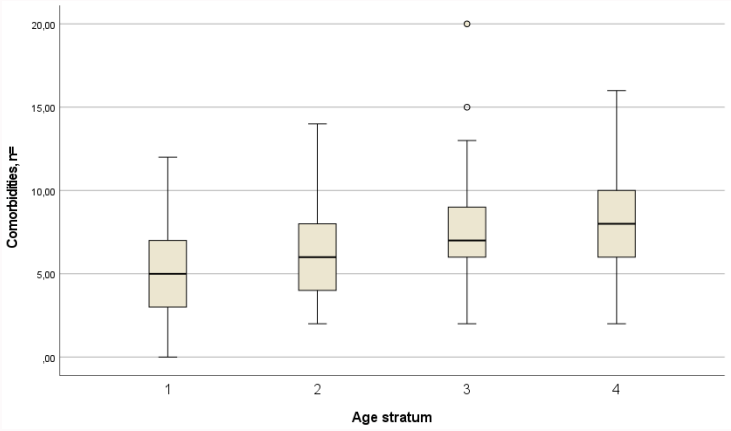

Figure 5a: Age strata in relation to the number of comorbidities.
1=<60; 2= 60-<70; 3= 70-<80; 4= ≥ 80 years of age
Whisker boxplots show median, upper/lower quartiles of values.

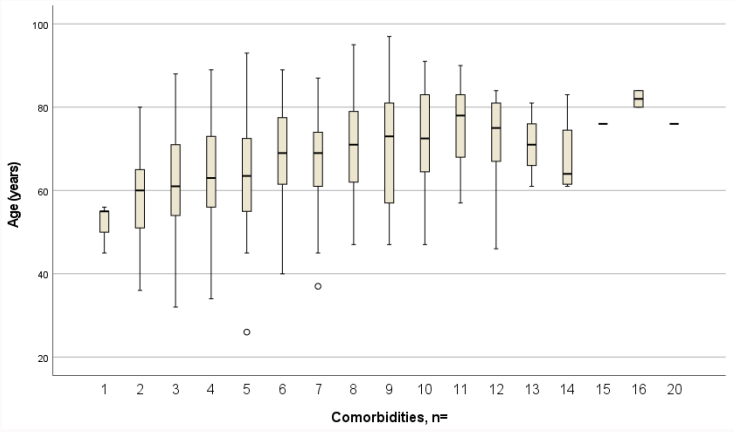

Figure 5b: Age (years) in relation to the number of comorbidities.
Whisker boxplots show median, upper/lower quartiles of values.

Table 4: Results of the multivariate regression analysis for the parameters accounting for the incidence of a clinically relevant drug-drug interactions.

Effect Parameter	-2 log Likelihood in the reduced model	p-value
Diabetes mellitus II	8.72	0.033
Cardiac Arrhythmia	0.262	0.967
No. Comorbidities	28.875	0.995
Strata Components	54.301	<0.001
Strata Age	16.185	0.183
Anti-arrhythmics	7.006	0.072
Oral Anticoagulants	0.629	0.89
PPI/Antacids	7.935	0.047
Analgesics/NSAIDs	7.335	0.062
Others	4.704	0.195

following parameters: Age, No. of components, cardiac arrhythmias, renal insufficiency, Type II diabetes mellitus, comorbidities, drug strata, age strata, intake of oral anticoagulants, antiarrhythmics, PPI/antiacids, pain medication/NSAIDs, cortisone or others and finally, the total No. of PK/PD DDI. Subsequently, these parameters were transferred to a multivariate regression analysis (Table 4). As shown in Table 4, the results of the multivariate regression analysis calculated the probability of the occurrence of a clinically relevant DDI. A significant correlation is detected regarding three parameters: Strata of Components ($p<0.001$), Type II Diabetes mellitus ($p=0.033$) and the intake of PPI/Antacids ($p=0.047$).

Pharmacokinetic drug-drug interactions: Of all 154 pharmacokinetic DDIs, the vast majority was detected at first pass (n=141; n=111 patients), only n=7 in n=6 patients at elimination. But, n=138 patients take PPIs on a daily base and n=30 patients were taking Ca/Potassium-formulations or multivitamins, known as chelating agents. These were not considered by the DDI software used.

The n=141 first-pass DDIs involve CYP3A4 (n=49), CYP2D6 (n=50), CYP2C19 (n=19), other (n=19) cytochrome oxidize pathways and p-Glycoprotein (n=35). Regarding cellular transmembrane transporters only n=5 were assigned to BCRP (Breast Cancer Resistance-Protein) and n=6 to OATP (Organic Anion Transporter).

N=26 of these DDI were categorized as clinically relevant ("A") (Table 3).

Pharmacodynamic drug-drug interactions: We observed n=1311 pharmakodynamic DDIs, n=634 categorized as clinically relevant ("A") (Table 3).

The majority occurred in 5 different categories (DDIs n ≥ 50):

1. Alterations of blood sodium/potassium concentrations
2. Alterations of blood sugar or HBA1c
3. Alterations of blood pressure
4. ECG changes, especially QTc-interval prolongation
5. Alterations of bleeding time/coagulation parameters

Discussion

Patient demographics and characteristics of this study collective match with formerly reported collectives of multimorbid patients in outpatient care regarding age, comorbidities or the amount of drugs taken on a daily base [26,27]. Thus, our study collective is representative for mostly elderly patients with multiple diseases and polypharmacy. First of all, we can state that the total number of pharmacokinetic DDIs was low. Pharmacokinetic DDIs represented only 2.0% of all clinically relevant DDIs. These were limited to a few, already well known pathways [i.e. CYP3A4], shown e.g. in n=15 cases for the combination of simvastatin and amlodipine (dose reduction of simvastatin ≤ 20 mg QD is recommended). This revealed one of the limitations of the PC-based DDI programs, as these do not consider dosage, only the combination of drugs in general, when indicating a potential DDI. Regarding the above mentioned example it was shown that none of the participating GPs exceeded the dose of 20 mg QD Simvastatin when combined with amlodipine. Another limitation is the disregard of possibly disturbed drug resorption by the concomitant intake of chelating agents, such as multivitamin-formulations or Ca/Mg/Potassium capsules. These can decrease the resorption of many oral drug formulations due to the creation of insoluble chelate complexes.

As discussed before, polypharmacy can even be associated with malnutrition and Activities of Daily Living (ADL) disability in elderly patients, i.e. especially if Proton pump inhibitors, anti-constipation drugs, anti-dyslipidemia drugs, and antidiabetic drugs were involved. Thus, medication plans and PC-based DDI programs should include the retrieval and appraisal of PPI intake. In n=25 cases (3.4% of all cases, indicated as category "A"), ABDA distinguished n=14 contraindicated drug-drug combinations, which were not shown in i:fox® [18].

The results of the multiple regression analysis show the probability of the occurrence of a clinically relevant DDI correlated to one of the following parameters: Strata Components ($p<0.001$), Diabetes mellitus II ($p=0.033$) and intake of PPI/Antacids ($p=0.047$). This goes in accordance with previous polypharmacy studies, i.e. Al-Musawe et al. who found clinically relevant DDIs related to female gender ($p=0.0115$), obesity ($p=0.0131$), more comorbid conditions ($p<0.0001$), diabetic complications ($p<0.0001$) and the use more of glucose lowering drugs ($p=0.0326$). 10.6% of the participants in this study were found to have potential serious clinically relevant DDIs. The most frequent drug-combinations were Angiotensin-Converting Enzyme (ACE) inhibitors with Angiotensin-Receptor Blockers (ARBs), aspirin with Selective Serotonin Reuptake Inhibitors (SSRIs), and clopidogrel with calcium channel blockers [14]. Although we did not explicitly analyze PIMs, the results of our study partly correlate with previous investigations [9,10,28,29]: We could detect a correlation between the intake of PPI and potential DDIs, we also found that the prevalence of opioid intake was significantly higher in patients taking more than 8 drugs ($p<0.001$), trend wise this was detected also for NSAIDs ($p=0.042$) where as this correlation was not found for neuroleptics ($p=0.075$) and antidepressants ($p=0.721$). In addition, renal function is an issue correlated to polypharmacy and age [30]. The proportion of patients with kidney insufficiency was significantly higher in the strata of patients taking 5-7 or ≥ 8 drugs ($p<0.001$). This was not correlated to the chronic intake of NSAIDs ($p=0.415$), age ($r^2=0.022$; $p=0.628$) or hypertonia ($r^2=0.063$; $p=0.162$) but the number of drugs taken ($r^2=0.241$; $p=0.001$) and again, type 2 diabetes mellitus ($r^2=0.319$; $p<0.001$).

The majority of pharmacodynamic DDIs occurred in 5 different fields, which are clinically relevant, especially in elderly patients). Especially the decrease of serum sodium is a severe concern amongst elderly patients with polypharmacy [31,32]. Also, the prolongation of the ECG QTc-interval can cause severe adverse events, often leading to hospitalization. Multiple pharmacodynamic DDIs relate to QTc-prolongation, hyperkalemia and hemorrhage and are frequently associated with a negative outcome in older adults with chronic kidney disease and often require recurrent medical treatment or re-hospitalization [33,34].

Thus, the training and awareness rising of medical staff should focus more on pharmacodynamics DDIs, whereas regarding pharmacokinetic DDIs and their relatively low clinical relevance in the evaluated database showed a sufficient grade of education and awareness of the reporting medical staff. This could be assisted by the implementation of algorithms regarding the control of relevant DDIs, the frequent periodical evaluation relevant parameters (e.g. creatinine-clearance, transaminases, ECG) following the prescription of new drugs and the detection of DDIs categorized as clinically relevant ("A" or yellow light). These algorithms can complement the according treatment guidelines. For more complex questions, we propose using the personal expertise of pharmacologists/pharmacists being experts in the field, i.e. the implementation of a counseling service.

For the additional reporting of such DDIs of prescription drugs, a database should be implemented, improving the rate of reports on DDI by means of low-barrier online access. This study amongst others can provide relevant parameters and criteria for the specific evaluation of DDIs in vulnerable patients, certain morbidities or drug combinations. In contrary to big data mining [35,36], this reduces the amount of data and improves the quality of analysis due to the possible correlation with clinical data.

Although the reporting of DDI increased during the past decade, the AKDÄ, the German Commission on Drug Safety, estimates that only a small percentage of DDIs are reported every year. The total number of reported relevant DDIs amounts to 3617 in the year 2018 [37,38]. By enhancing the number of reports it will be also easier to detect rather rare signals in the database, artificial intelligence could help detect these signals faster and safer than by human observance.

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