PHARMACOLOGY

POTENTIAL DRUG-DRUG INTERACTIONS IDENTIFIED AS DRUG-RELATED PROBLEMS IN THE TREATMENT OF HOSPITALIZED PATIENTS WITH GASTRITIS AND/OR DUODENITIS OR PEPTIC ULCER DISEASE IN LUBLIN (POLAND) – AN OBSERVATIONAL STUDY

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Abstract: According to the Pharmaceutical Care Network Europe, a drug-related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes. Apart from medication errors or adverse drug reactions, the term also embraces drug-drug interactions. The aim of our study was to identify the potential drug-drug interactions in patients with gastritis and/or duodenitis or peptic ulcer disease (PUD) hospitalized in 4 hospitals located in Lublin (Poland). These diseases occur quite often in Poland. PUD afflicts about 4-6% of Polish people, holding an important place amongst the so-called diseases of affluence in Poland. 206 anonymous medical records of randomly selected patients hospitalized between 2011 and 2015 for inflammation of the mucous membrane of the stomach and/or duodenum or gastric and/or duodenal ulcers were analyzed retrospectively. The introduced therapy was involved in 107 potential interactions: 1 interaction was classified as highly significant, 55 were classified as significant, and 51 interactions were regarded as insignificant. Mostly they were attributed to the modulations of the function of cytochrome P450, and they were detected primarily for co-prescriptions of proton-pump inhibitors, fluoroquinolones, metronidazole, and macrolides with other drugs. Education of healthcare professionals and patients, correction of current treatment schedules along with the implementation of effective strategies preventing drug-drug interactions, including reporting all suspected interactions concerning both new and well-known medicinal products are crucial in order to increase the quality and safety of pharmacotherapy.

Keywords: drug-drug interactions, drug-related problems, peptic ulcer disease, proton-pump inhibitors, cytochrome P450

Gastritis, duodenitis and peptic ulcer disease (PUD) belong to the most common health problems of the gastrointestinal system. Gastritis is an inflammatory process of the gastric mucosa, whereas duodenitis is an inflammation of the duodenal mucosa. Gastritis and duodenitis share similar causes, such as *Helicobacter pylori* infection, long-term use of

non-steroidal anti-inflammatory drugs, chemotherapy, radiation therapy, inflammatory bowel disease, excessive consumption of alcohol or tobacco smoking, damage or injury to the stomach/small intestine (including surgery), and others. Furthermore, autoimmune enteropathy, acid reflux-induced gastritis, or celiac disease-induced duodenitis are diagnosed.

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Patients with gastritis/duodenitis usually report abdominal pain, nausea, vomiting, and indigestion. Gastritis and duodenitis are perceived as precursors of gastric and duodenal ulcers, respectively (1, 2). PUD refers to painful breaks in the lining of the stomach or in the first part of the small intestine, the duodenum. PUD has an important place amongst the so-called diseases of affluence in Poland, it afflicts about 4-6% of Polish people. Apart from gnawing or burning pain in the middle or upper stomach that appears between meals or at night, patients with PUD may also report a lack of appetite with weight loss, abdominal distension, heartburn, dyspepsia, nausea, and constipation. Vomiting blood, anemia, and dark or black stool (due to bleeding) may be the signs of serious complications (3). Though *Helicobacter pylori* infection and chronic therapy with non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequent causes of PUD, genetic factors, lifestyle (tobacco smoking, stress, inadequate diet), concomitant conditions, and some other medications (i.e., ampicillin, erythromycin, theophylline, oral preparations of iron and potassium, digoxin) may also contribute to the damage of the mucous membrane lining of the upper digestive tract (3, 4).

Effective gastritis, duodenitis, and PUD therapy should both slow down the progression of the disease and prevent its recurrence. The above-mentioned goals could be obtained by the implementa-

tion of rational pharmacotherapy supported by prophylaxis and a healthy lifestyle. Treatment regimens in gastritis/duodenitis differ depending on the type of disease. Apart from drugs that reduce stomach acid (i.e., antacids, proton pump inhibitors – PPIs, blockers of H₂ receptors), in *H. pylori*-associated gastritis/duodenitis a triple- or quadruple-therapy should be introduced, whereas in autoimmune gastritis, supplementation of vitamin B12 and/or iron is needed. Furthermore, stress management, as well as, the cessation of alcohol, smoking, spicy food, and anti-inflammatory drugs are advised (1, 2). Drugs recommended for the treatment of PUD belong to four groups: H₂-receptor antagonists (i.e., ranitidine, famotidine), PPIs (i.e., omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole), mucoprotective drugs (i.e., sucralfate, bismuth citrate), and *H. pylori* eradication agents (i.e., clarithromycin, amoxicillin, tetracycline, levofloxacin, metronidazole, tinidazole). In some cases, spasmolytics, antacids, antimuscarinic (pirenzepine), prostaglandin analogs (misoprostol), and antidepressants are also prescribed (3, 5, 6). *H. pylori* eradication therapy is offered only to patients with positive test results for this bacterium (3, 6). In accordance with the Maastricht IV/Florence Consensus Report (7, 8), in areas of high clarithromycin resistance (i.e., in Poland), bismuth-containing quadruple therapies are recommended for the first-line empirical treatment. If this regimen is not available, sequential treatment

Table 1. *Helicobacter pylori* eradication therapy (7, 8,12).

First-line therapy	Second-line therapy
Triple therapy without clarithromycin (10 days): 1) 1.0 g of amoxicillin twice daily, 2) 0.5 g of metronidazole twice daily, 3) standard dose of PPI twice daily.	Bismuth quadruple therapy
Bismuth quadruple therapy (10-14 days): 1) 0.120 g of bismuth citrate 2-4 times daily 2) 0.5 g of tetracycline 4 times daily, 3) 0.5 g of metronidazole 3 times daily, 4) standard dose of PPI twice daily.	Sequential therapy
Sequential therapy: 1) 1.0 g of amoxicillin twice daily for 5 days, 2) standard dose of PPI twice daily for 5 days, followed by: 3) 0.5 g of clarithromycin twice daily for 5 days, 4) 0.5 g of tinidazole/metronidazole twice daily for 5 days, 5) standard dose of PPI twice daily for 5 days.	Triple therapy with levofloxacin (10 days): 1) 0.25 g of levofloxacin twice daily, 2) 1.0 g of amoxicillin twice daily, 3) standard dose of PPI twice daily.
Quadruple therapy without bismuth (14 days): 1) 1.0 g of amoxicillin twice daily, 2) 0.5 g of clarithromycin twice daily, 3) 0.5 g of tinidazole/metronidazole twice daily, 4) standard dose of PPI twice daily twice.	

Table 2. Demographic data of the analyzed patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease.

Demographic data	Hospital no. 1	Hospital no. 2	Hospital no. 3	Hospital no. 4
Number of the analyzed patients	53	49	53	51
Age: mean $\pm$ SD	56.7 $\pm$ 12.9	62.7 $\pm$ 18.7	58.0 $\pm$ 15.3	70.9 $\pm$ 13.0
median (range)	57.0 (25.0 - 78.0)	64.0 (22.0 - 97.0)	59.0 (19.0 - 86.0)	72.0 (42.0 - 90.0)
Sex: male	17 (32.1%)	27 (55.1%)	21 (39.6%)	22 (43.1%)
female	36 (67.9%)	22 (44.9%)	32 (60.4%)	29 (56.9%)
Place of residence: town	33 (62.3%)	30 (61.2%)	19 (63.3%)*	36 (70.6%)*
country	20 (37.7%)	19 (38.8%)	11 (36.7%)*	15 (29.4%)*
Hospitalization (days):				
mean $\pm$ SD	5.8 $\pm$ 3.6	7.0 $\pm$ 3.6	7.8 $\pm$ 3.9	7.6 $\pm$ 5.4
median (range)	5.0 (1.0 - 15.0)	7.0 (1.0 - 15.0)	7.0 (2.0 - 17.0)	7.0 (1.0 - 31.0)

*Lack of data; statistical analysis was performed for n = 30.

or a non-bismuth quadruple therapy is recommended (3, 9-11). Following the above-mentioned guideline (8), the treatment duration of bismuth quadruple therapy should be extended to 14 days, unless the 10-day treatment is proven effective locally. The first- and second-line eradication treatments were presented in Table 1. When two eradication therapies turn out to be ineffective eradication therapies, the next one should be based on the outcomes of the antimicrobial susceptibility testing (12).

The aim of our study was to identify the potential drug-drug interactions in patients with gastritis and/or duodenitis or PUD hospitalized in 4 hospitals located in Lublin (Poland).

EXPERIMENTAL

Materials

206 anonymous medical records of randomly selected patients hospitalized between 2011 and 2015 for inflammation of the mucous membrane of the stomach and/or duodenum or gastric and/or duodenal ulcers were analyzed retrospectively. The patients aged 19-97 were hospitalized in 4 hospitals located in Lublin: 53 patients (36 women, 17 men) in the hospital no. 1, 49 patients (22 women, 27 men) in the hospital no. 2, 53 patients (32 women, 21 men) in the hospital no. 3, and 51 patients (29 women, 22 men) in the hospital no. 4. The record of each patient contained two forms: the patient information card and the individual daily medication chart.

On the basis of the received medical documentation, the following issues have been determined for each patient: (1) underlying disease entity with the concomitant conditions according to ICD-10 International Statistical Classification of Diseases and Related Health Problems, (2) prescribed therapies for both underlying and concomitant diseases, (3) drug-drug interactions.

Statistical analysis

Descriptive analysis as well as the Shapiro-Wilk test for normality were conducted. Parameters of the quantitative data were presented as the arithmetic mean and standard deviation, median, and minimum and maximum values. Parameters of count data were described numerically and shown as a total amount or percentage of the total amount. Statistical analysis was performed with Statistica 10 software (StatSoft Inc.). Identification and analysis of the drug-drug interactions were carried out using two relevant public websites (i.e., www.bil.aptek.pl and www.drugs.com).

RESULTS

Patient demographic data

Demographic data of all the patients whose medical documentation was analyzed in the present study were presented in Table 2.

Underlying disease entity with the concomitant conditions

Underlying disease entities with the concomitant conditions identified according to ICD-10 in patients were listed in Table 3.

Hospital no. 1

23% of the patients were positive for *H. pylori* infection (ICD-10: B98). Gastritis and duodenitis (ICD-10: K29) and gastric ulcer (ICD-10: K25) were the most commonly diagnosed diseases; their incidence rates were 56.6% and 37.7%, respectively. Additionally, more than 73% of the patients suffered from concomitant diseases, mainly diseases of the circulatory system, including hypertensive disease (ICD-10: I11) that occurred in 28.3% of the patients. The patients were discharged after about 6 days of hospitalization.

Hospital no. 2

10% of the patients were positive for *H. pylori* infection (ICD-10: B98). Gastric ulcer (ICD-10: K25) and duodenal ulcer (ICD-10: K26) were the most commonly diagnosed diseases; their incidence rates were 34.7% and 49%, respectively. Additionally, more than 87% of the patients suffered from concomitant diseases, mainly diseases of the circulatory system, including hypertensive disease (ICD-10: I11) that occurred in 26.5% of the patients. 26.5% of the patients were diagnosed with anemia (D64). The patients were discharged after about 7 days of hospitalization.

Hospital no. 3

30% of the patients were positive for *H. pylori* infection (ICD-10: B98). Gastritis and duodenitis (ICD-10: K26) were the most commonly diagnosed diseases; their incidence rate was 81.1%. Additionally, about 85% of the patients suffered from concomitant diseases, mainly diseases of the circulatory system, including hypertensive disease (ICD-10: I11) and angina pectoris (ICD-10: I20) that occurred in 39.6% and 26.4% of the patients, respectively. The patients were discharged after about 5 days of hospitalization.

Table 3. Underlying disease entity with the concomitant conditions identified according to ICD-10 International Statistical Classification of Diseases and Related Health Problems in the analyzed patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease.

Disease entity		Number of patients (%)			
		Hospital no. 1	Hospital no. 2	Hospital no. 3	Hospital no. 4
Diseases of the digestive system (diagnosis)	Gastritis and duodenitis (K29)	30 (56.6)	6 (12.2)	43 (81.1)	15 (29.4)
	Gastric ulcer (K25)	20 (37.7)	17 (34.7)	9 (17.0)	45 (88.2)
	Duodenal ulcer (K26)	1 (1.9)	24 (49.0)	13 (24.5)	1 (2.0)
	Gastrojejunal ulcer (K28)	4 (7.5)	7 (14.3)	2 (3.8)	3 (5.9)
	Oesophagitis (K20)	1 (1.9)	2 (4.1)	0	7 (13.7)
	Gastro-oesophageal reflux disease (K21)	3 (5.7)	3 (6.1)	4 (7.5)	1 (2.0)
	Other diseases of esophagus (K22)	2 (3.8)	0	1 (1.9)	2 (3.9)
	Diaphragmatic hernia (K44)	8 (15.1)	6 (12.2)	25 (47.2)	2 (3.9)
	Helicobacter pylori infection (B98)	12 (22.6)	5 (10.2)	16 (30.2)	14 (27.5)
	Other diseases of stomach and duodenum (K31)	4 (7.5)	3 (6.1)	0	3 (5.9)
	Inguinal hernia (K40)	1 (1.9)	0	0	0
	Ventral hernia (K43)	1 (1.9)	0	0	0
	Acute pancreatitis (K85)	2 (3.8)	0	1 (1.9)	1 (2.0)
	Irritable bowel syndrome (K58)	0	1 (2.0)	2 (3.8)	1 (2.0)
	Other diseases of pancreas (K86)	0	1 (2.0)	3 (5.7)	2 (3.9)
	Cholelithiasis (K80)	1 (1.9)	4 (8.2)	1 (1.9)	1 (2.0)
	Diverticular disease of intestine (K57)	1 (1.9)	1 (2.0)	7 (13.2)	1 (2.0)
	Other diseases of liver (K76)	0	3 (6.1)	4 (4.5)	1 (2.0)
	Ulcerative colitis (K51)	0	1 (2.0)	0	0
	Polyp of colon (K63.5)	3 (5.7)	0	1 (1.9)	0
	Gastrointestinal hemorrhage, unspecified (K92.2)	1 (1.9)	10 (20.4)	1 (1.9)	12 (23.5)
	Postprocedural disorders of the digestive system, not elsewhere classified (K91)	10 (18.9)	4 (8.2)	11 (20.8)	8 (15.7)
	Total	39 (73.6)	43 (87.8)	45 (84.9)	42 (82.4)
Concomitant diseases	Hypertensive heart disease (I11)	15 (28.3)	13 (26.5)	21 (39.6)	29 (56.9)
	Atrial fibrillation and flutter (I48)	3 (5.7)	6 (12.2)	0	9 (17.6)
	Heart failure (I50)	1 (1.9)	3 (6.1)	1 (1.9)	6 (11.8)
	Angina pectoris (I20)	0	4 (8.2)	14 (26.4)	11 (21.6)
	Non-insulin-dependent diabetes mellitus (E11)	1 (1.9)	3 (6.1)	4 (7.5)	11 (21.6)
	Spondylosis, Other spondylopathies (M48, M47)	4 (7.5)	2 (4.1)	10 (18.9)	6 (11.8)
	Thyrotoxicosis [hyperthyroidism] (E05), Other hypothyroidism (E03)	4 (7.5)	2 (4.0)	10 (18.9)	7 (14.3)
	Disorders of lipoprotein metabolism and other lipidaemias (E78)	2 (3.8)	0	11 (20.8)	2 (3.9)
	Other anemias (D64)	2 (3.8)	13 (26.5)	5 (9.4)	17 (33.3)
	Abdominal and pelvic pain (R10)	4 (7.5)	1 (2.0)	3 (5.7)	0
	Acute renal failure, Chronic kidney disease (N17, N18)	2 (3.8)	1 (2.0)	0	5 (9.8)
	Other*	8 (15.1)	6 (12.2)	8 (16.32)	2 (3.9)

*Other: Atherosclerosis (I70), Phobic anxiety disorders, Reaction to severe stress, and adjustment disorders (F40, F43), Obesity (E66), Seropositive rheumatoid arthritis, Other rheumatoid arthritis (M05, M06), Depressive episode (F32).

Table 4. Proton-pump inhibitors (PPIs) prescribed to the analyzed patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease.

Active substance	Percentage of patients receiving PPI treatment			
	Hospital no. 1	Hospital no. 2	Hospital no. 3	Hospital no. 4
Esomeprazole	51	0	0	31
Omeprazole	7	2	64	22
Pantoprazole	4	96	9	2
Esomeprazole + pantoprazole	0	0	2	2
Omeprazole + esomeprazole	2	0	0	41
Omeprazole + pantoprazole	6	0	0	0
Omeprazole + pantoprazole + esomeprazole	2	0	0	0
No PPI treatment	28	2	25	2

Table 5. Antibiotic therapy prescribed to the analyzed patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease.

Active substance	Percentage of patients receiving an antibiotic therapy			
	Hospital no. 1	Hospital no. 2	Hospital no. 3	Hospital no. 4
Amoxicillin	2	0	2	2
Cefuroxime	5	11	2	2
Ciprofloxacin	0	4	2	0
Clarithromycin	0	0	2	0
Doxycycline	0	0	2	0
Metronidazole	2	2	3	4
Amoxicillin/clarithromycin	0	0	2	0
Amoxicillin/clavulanic acid	2	0	0	2
Amoxicillin + metronidazole	2	0	11	0
Ciprofloxacin + metronidazole	0	0	0	6
Cefuroxime + metronidazole	0	0	2	0
Amoxicillin/clavulanic acid + metronidazole	2	0	2	0
No antibiotic therapy	85	83	70	84

Table 6. Combined therapy prescribed to the analyzed patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease.

Active substance	Percentage of patients receiving the combined therapy			
	Hospital no. 1	Hospital no. 2	Hospital no. 3	Hospital no. 4
Antibiotic/metronidazole therapy + PPIs	15	16	28	16

Hospital no. 4

27.5% of the patients were positive for *H. pylori* infection (ICD-10: B98). Gastric ulcer (ICD-10: K25) was the most commonly diagnosed disease; its incidence rate was 88.2%. Additionally, more than 82% of the patients suffered from concomitant diseases, mainly diseases of the circulatory system, including hypertensive disease (ICD-10:

I11) that occurred in 57% of the patients. The patients were discharged after about 7 days of hospitalization.

Prescribed therapies

An analysis of the received medical documentation demonstrated that all of the drugs used by the patients had been prescribed in compliance with the

Table 7. Very significant and significant potential drug-drug interactions related to the PUD therapy identified in the analyzed patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease.

PUD therapy	Concomitant drug	Result of interaction
Very significant drug-drug interactions		
Fluoroquinolones Ciprofloxacin	Haloperidol	Increased risk of QT prolongation and development of life-threatening cardiac arrhythmias
Significant interactions		
Aminoglycoside antibiotics Amikacin	Cefuroxime	Increased nephrotoxicity with increased antibacterial activity
	Furosemide	Increased nephro- and ototoxicity
Antiacids Dihydroxialumini sodium carbonate	Sulfasalazine	Reduced absorption of sulfonamide leading to its reduced activity
Aluminum phosphate	Levothyroxine sodium	Reduced activity of levothyroxine; increased serum level of TSH
Cephalosporin antibiotics Cefuroxime	Theophylline	Increased serum level of theophylline, increased risk of toxicity
Fluoroquinolones		
Ciprofloxacin/ norfloxacin	Metronidazole	Increased risk of adverse reactions, including seizures
	Theophylline	Increased serum level of theophylline (up to 30-50%) and dysfunctions of central nervous system, including seizures
	Tramadol hydrochloride	Increased risk of adverse reactions, including seizures
Ciprofloxacin	Iron hydroxide	Reduced activity of ciprofloxacin caused by formation of a coordination complex
	Metamizole sodium	Increased risk of adverse reactions affecting central nervous system, including seizures
	Paracetamol	Increased serum level of ciprofloxacin and delayed onset of paracetamol action
Norfloxacin	Dexamethasone sodium phosphate	Increased risk of adverse reactions (tendinitis and/or tendon rupture)
H ₂ -receptor antagonists		
Famotidine	Theophylline	Increased serum level of theophylline, increased risk of toxicity
Ranitidine Macrolides	Metoprolol succinate	Increased serum level and activity of metoprolol
Clarithromycin	Clopidogrel	Reduced activity of clopidogrel caused by inhibition of its transformation into an active form
	Hydroxyzine	Increased risk of QT prolongation and development of life-threatening cardiac arrhythmias
	Tramadol hydrochloride	Increased serum level of tramadol and increased risk of adverse reactions
Nitroimidazole metronidazole	Atorvastatin	Increased serum level of atorvastatin and increased risk of adverse reactions
	Dexamethasone sodium phosphate	Increased serum level of dexamethasone and increased risk of adverse reactions
	Fexofenadine hydrochloride	Increased serum level of fexofenadine and increased risk of adverse reactions
	Lidocaine	Increased serum level of lidocaine and increased risk of adverse reactions
	Prednisone	Increased serum level of prednisone and increased risk of adverse reactions

Table 7. Continued.

PUD therapy	Concomitant drug	Result of interactionProton-pump inhibitors
Proton-pump inhibitors		
Esomeprazole/ omeprazole /pantoprazole	Cyanocobalamin	Reduced activity of cyanocobalamin caused by its reduced absorption
	Statins (atorvastatin/ simvastatin)	Increased serum level of statins and increased risk of muscle-related adverse reactions
	Theophylline	Increased activity of theophylline caused by its accelerated release from a prolonged-release pharmaceutical form
Omeprazole /pantoprazole	Alprazolam/diazepam/ estazolam/midazolam	Increased serum level of benzodiazepines and potentiated and prolonged central nervous system depression
	Cefuroxime	Reduced serum level of cefuroxime
Esmoprazole	Diazepam	Increased serum level of diazepam and its prolonged activity
	Warfarin	Increased serum level of R-warfarin
Omeprazole	Carbamazepine	Increased serum level and activity of carbamazepine
	Clopidogrel	Reduced activity of clopidogrel and reduced risk of bleeding in the digestive tract
	Fentanyl	Increased serum level of fentanyl and increased risk of adverse reactions
	Fexofenadine hydrochloride	Increased serum level of fexofenadine and increased risk of adverse reactions
	Gliclazide	Increased serum level of gliclazide and increased hypoglycemic activity

current guidelines in the recommended doses. In the case of *H. pylori* infection, combined treatment (i.e., PPI/H₂-receptor antagonist + antibiotic therapy) was administered (Tables 4, 5, and 6).

139 patients were administered PPIs and/or H₂-receptor antagonists, including 28/53 patients from the hospital no. 1, 38/49 patients from the hospital no. 2, 32/53 patients from the hospital no. 3, and 41/51 patients from the hospital no. 4. *H. pylori* eradication therapy was implemented in 39 cases, including 8/53 patients from the hospital no. 1, 8/49 patients from the hospital no. 2, 15/53 patients from the hospital no. 3, and 8/51 patients from the hospital no. 4. 8 patients (i.e., 7/53 patients from the hospital no 1 and 1/53 patients from the hospital no 3) were prescribed only a dedicated diet. No treatment (neither IPPs, nor H₂-receptor antagonists, antibiotic therapy, or dedicated diet) was given to 20 hospitalized patients, including 10/53 patients from the hospital no. 1, 1/49 patients from the hospital no. 2, 7/53 patients from the hospital no. 3, and 2/51 patients from the hospital no. 4.

Potential drug-drug interactions

882 potential drug-drug interactions have been identified. Amongst them, 27 interactions were clas-

sified as highly significant (1 at the hospital no. 1, 10 at the hospital no. 2, 5 at the hospital no. 3, and 11 at the hospital no. 4), 618 interactions were classified as significant (117 at the hospital no. 1, 98 at the hospital no. 2, 194 at the hospital no. 3, and 209 at the hospital no. 4), and 237 interactions were classified as insignificant (36 at the hospital no. 1, 53 at the hospital no. 2, 83 at the hospital no. 3, and 65 at the hospital no. 4).

PUD therapy was involved in 107 potential interactions; only 1 was classified as a highly significant interaction, 55 were classified as significant interactions, and 51 interactions were regarded as insignificant. All the significant potential interactions attributable to PUD treatment were presented in Table 7.

DISCUSSION

According to the Pharmaceutical Care Network Europe, drug-drug interactions belong to drug-related problems and may actually or potentially interfere with desired health outcomes (13). A drug interaction is a situation in which the presence of the second drug alters the pharmacokinetic and/or pharmacodynamic profile of the first drug.

Significance and intensity of drug-drug interactions as well as their influence on the patient's condition depend on different factors, such as patient's age, the number of prescribed drugs, route of administration, dosage, the half-life of an active substance and its active metabolites, etc. Although it is possible to take advantage of some positive drug interactions (i.e., a synergistic effect of combined therapy), the interplay between drugs may also result in health- or life-threatening effects (14, 15). Increased morbidity and mortality risks as well as elevated medical costs may be a consequence of the suboptimal pharmacotherapy attributed to drug-drug interactions (13).

The analysis of the patient information cards and individual daily medication charts from 4 hospitals located in Lublin showed that the implemented therapy for PUD, gastritis, and duodenitis was compliant with the recommended standards. The combined anti-*H. pylori* treatment (antibiotic/metronidazole therapy with PPIs) was introduced when necessary. However, a special consideration was given to the potential for interactions between PUD medications and drugs prescribed for the concomitant diseases, i.e. diabetes, hypertension, hyperlipidemia, and others. It was found out that these potential interactions could be a result of either inhibition/induction of the cytochrome P450 enzymes or reduced gastric secretion and altered (increased/decreased) absorption of certain drugs. In fact, a great number of clinical drug-drug interactions are contributed to drugs interplay on the level of cytochrome P450 enzymes, i.e., monooxygenases that catalyze the metabolism of many active substances. CYP1A2, 2C9, 2C19, 2D6, and 3A4 isoenzymes are of particular importance (16).

Potential drug-related interactions identified on the basis of the analyzed medical documentation may lead to an increased risk of adverse reactions, enhanced/reduced effect of the administered drugs, and elevated costs of the prescribed pharmacotherapy. Potential interactions of PPIs seem to be the most frequent. It is in line with the literature data since PPIs are generally known as drugs very often prescribed with other medications and frequently involved in pharmacokinetic and pharmacodynamic interactions. These interplays may be a result of poor absorption caused by gastric acid suppression, alterations in drug metabolism due to disturbances in cytochrome P450 function, or changes in drug distribution induced by inhibition of P-glycoprotein (17). All PPIs are metabolized by CYP2C19 and CYP3A4 isoenzymes, but in different proportions depending on the active substance (18). In our stud-

ies, we noted that PPIs were prescribed with the following drugs on whose pharmacokinetics they could exert a potentially adverse influence: cyanocobalamin, statins, theophylline, benzodiazepines, cefuroxime, warfarin, carbamazepine, clopidogrel, fentanyl, fexofenadine hydrochloride, and glimepiride. According to available data, the omeprazole-clopidogrel interaction is particularly not recommended due to the higher risk of serious cardiac events, myocardial infarction, stroke (17, 19, 20), or acute coronary syndrome (21). Clopidogrel is a pro-drug converted by CYP2C19 and CYP3A4 (depending on the drug's concentration) into the active form and it competes with PPIs for isoenzymes (22). Literature data suggest that omeprazole gives the most significant interaction with clopidogrel since omeprazole is irreversible (or quasi-irreversible) metabolism-dependent inhibitor of CYP2C19 (20, 23, 24). Where necessary, pantoprazole or rabeprazole could be used, and at least a 6-hour interval between intake of PPI and clopidogrel should be introduced (18). It has been shown that lansoprazole or dextansoprazole may also be a better alternative to omeprazole (25). Other potential interactions reported in our study associated with the prescription of PPIs seem to be less harmful to a patient, though they are also described in the available literature.

Another group of therapeutics used in PUD with a high potential for drug-drug interactions are fluoroquinolones. They decrease the biotransformation of active substances metabolized by CYP3A4 and CYP1A2 isoenzymes due to the competitive inhibition (26). In fact, ciprofloxacin was involved in a very significant potential interaction detected in our study. Since both ciprofloxacin and haloperidol may prolong the QT interval, and ciprofloxacin inhibits biotransformation of haloperidol by CYP3A4 isoenzymes (27), their concurrent use may lead to the development of life-threatening cardiac arrhythmias (28). QT-interval-related adverse events associated with fluoroquinolones induced by a blockage of voltage-gated potassium channels are quite rare, and ciprofloxacin is most probably one of the safest agents within the group in relation to the risk for QT prolongation and torsades de pointes rate (29). In certain patients, haloperidol-ciprofloxacin interplay may also lead to the development of extrapyramidal side effects, due to increased serum levels of haloperidol (30). The concurrent use of fluoroquinolones and theophylline, metamizole sodium, metronidazole, or tramadol hydrochloride, which was detected in our study, may induce neurological symptoms (31-35), whereas combination

with paracetamol, dexamethasone sodium phosphate, or iron hydroxide may result in a delayed onset of paracetamol analgesic and antipyretic effects (36), fluoroquinolone-induced tendinopathy/tendon rupture (37), or the reduced fluoroquinolone absorption from the bounded form (i.e., chelate complex) (38), respectively.

Potential interactions associated with other drugs used in the treatment of PUD (i.e., aminoglycosides, metronidazole, macrolides, or antacids) seem to be less risky. It is generally known that treatment with aminoglycoside antibiotics poses an increased risk of ototoxicity, nephrotoxicity, neurotoxicity, and neuromuscular blockage. These undesirable effects may be potentiated by a concurrent administration of other drugs (31), and in our study, a potentially nephrotoxic interaction between amikacin and furosemide or cefuroxime was discovered. For metronidazole, potential interactions detected in our study were mostly attributed to CYP450, since this chemotherapeutic seems to be an inhibitor of CYP3A4 and CYP2C9 (39, 40). This mechanism is probably responsible for a potential increase in serum levels of statins (41), corticosteroids (42, 43), lidocaine (44), and fexofenadine hydrochloride (45) when both drugs are administered concomitantly. Macrolide antimicrobials are also known to cause slowly reversible inhibition of CYP isoenzymes. In the present study, they were co-prescribed in 3 combinations that may result in clinically significant effects, i.e., with clopidogrel, tramadol hydrochloride, and hydroxyzine (22, 46). Antibiotic therapy with macrolides is also associated with prolongation of QT and development of torsades de pointes, since they block the rapid delayed rectifier potassium current (47, 48). Therefore, co-administration of clarithromycin with hydroxyzine, i.e. another substance that has the potential to prolong the QT interval (28), which was detected in our study, may result in a serious cardiac adverse reaction. And lastly, antacids, which are additionally used in certain patients with PUD, have a high potential to interfere with the bioavailability of various classes of drugs, including antimicrobial agents. Therefore, the introduction of a 2-hour or even a 4-hour gap between taking an antacid and antimicrobial medication should be recommended (49).

Education of healthcare professionals and patients, as well as implementation of effective strategies preventing drug-drug interactions, are crucial for adequate control and resolution of drug-related problems. Education of healthcare professionals should be particularly focused on these groups of drugs that are known to have a high poten-

tial for clinically significant interactions, i.e., active substances with narrow therapeutic index (i.e., warfarin, digoxin, anticonvulsants, theophylline, cyclosporine, and others) and active substances that induce (i.e., rifampicin, phenytoin, carbamazepine, barbiturates, and others) or inhibit (i.e., ketoconazole, ciprofloxacin, erythromycin, and others) liver enzymes. If possible, they should be superseded by other compounds with a lower risk burden for interactions. According to the literature data (50), the SAIL protocol seems to be a useful tool in the management of polypharmacy. It involves the following issues: (1) Simple drug regimen with once or twice daily dosing (if possible), (2) avoiding Adverse effects of drugs by identification of all potential interactions and prescription of drugs with broad rather than narrow therapeutic indices, (3) using drugs with clear Indications only and defining of a therapeutic goal for each prescribed active substance, (4) keeping the List of all medications taken by a patient (both Rx and OTC drugs, as well as herbal preparations). 10 Steps to Prudent Prescribing by Carlson (51) could be also helpful to the process of pharmacotherapy optimization and avoiding undesired drug-drug interactions. They comprise the identification of all drugs taken by a patient (including their trade names and therapeutic groups), drug choice in accordance with its approved indications, awareness of drugs' safety profiles, careful risk assessment of the adverse effects, giving up ineffective therapy, and therapy that indication is not evidence-based, selection of a drug with a lower risk of adverse effects, avoiding prescription cascade, and if possible, respecting the rule "one disease entity – one drug – once a day". The likelihood of drug interactions considerably increases with the number of administered drugs. Polytherapy with 8 (or more) drugs is related to 82% (or higher) risk of drug-drug interaction (14, 15).

Both safety and effectiveness of the pharmacotherapy depend on its individualization. Patient's age (changed pharmacokinetics, increased frequency of adverse reactions, age restrictions), concomitant diseases, contraindications (pregnancy, breastfeeding), drug-disease interactions, other drugs, dietary supplements, food ingredients, and risk of adverse effects should be taken into account. Deprescribing a given drug that interacts with another active substance is not always the best solution. Reversal of drug-drug interaction when a compound with a narrow therapeutic index is involved may also result in a harmful outcome. In those cases, gradual discontinuation by dose tapering should be taken into consideration (52). In situations when the

interaction is theoretical only, rare, not clinically significant or it ensures optimal treatment, it is usually not necessary to adjust drugs dosage or/and administration schedule. However, when a potential risk of significant interaction exceeds the beneficial effects of the prescribed drug combination, a safer drug combination should be chosen. When it is not possible to change one drug for another, modification of administration schedule is needed (i.e., the introduction of intervals between administration of the interacting drugs). Moreover, monitoring of drug levels and functioning of the organs at risk of toxicity (particularly kidneys and liver) is advised. In situations when interaction results in an increase or reduction of drug activity, dose modification of one or/and both drugs should be taken into consideration, particularly when given drugs have the potential for synergistic toxicity. Dose modification may also be necessary when one of the interacting drugs is introduced to or withdrawn from the prescribed combination therapy.

Since about 25% of hospital expenses are costs generated by adverse reactions of therapy or undesirable effects of using a medical device, new reasonable administrative solutions that will help to optimize the treatment costs should be implemented. Improvement of pharmacoeconomic knowledge of the medical staff seems to be an important factor, given the need for both correction of current treatment schedules and establishment of better treatment strategies. Similarly, reporting all suspected interactions concerning both new and well-known medicinal products is highly significant. Those two above-mentioned steps will contribute to an increase in the quality of pharmacotherapy, including its safety.

In summary, this is the first study evaluating potential drug-drug interactions observed in the treatment of patients hospitalized for gastritis and/or duodenitis or peptic ulcer disease in four hospitals located in Lublin. Though the implemented therapy was generally compliant with the recommended standards, a number of highly significant and significant interactions between PUD medications and drugs prescribed for concomitant diseases were identified. Most probably, the effects of the introduced treatment were partially disturbed by either inhibition/induction of the cytochrome P450 enzymes or reduced gastric secretion and altered (increased/decreased) absorption of certain drugs. We suggest that education of both healthcare professionals and patients as well as implementation of effective strategies preventing drug-drug interactions are crucial in order to increase the quality and safety of pharmacotherapy.

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Conflict of interest

No conflicts of interest have been declared.

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