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Potential clinically significant drug-drug interactions in prescribed pharmacotherapy in an outpatient setting

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Received April 26, 2021, accepted May 24, 2021

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Pharmazie 76: 390-395 (2021) *doi: 10.1691/ph.2021.1561*

The aim of this study was to determine the most common potential clinically significant drug-drug unteractions (DDIs) in prescribed pharmacotherapy in an outpatient setting in Croatia. Twelve community pharmacies were randomly selected in this research. Retrospective pharmacotherapy record data analysis was conducted on consecutive eligible patients. Potential DDIs were detected using Lexicomp software that categorizes DDIs according to clinical significance. Categories C (monitor drug therapy), D (consider therapy modification) and X (avoid combination) are of clinical concern. In total, 1211 patients were enrolled in this study. The results showed that 84% of patients had at least one clinically significant interaction. The average number of interactions per patient was 4. Overall, 4798 potentially clinically significant DDIs were identified; 3945 (82.2%) required therapy monitoring, while other interactions (D and X category) required specific therapy modification. According to the level of clinical significance the most common clinical consequences of identified potential drug interactions were increased risk of hypotension, impaired renal function, central nervous system depression, gastrointestinal toxicity and QTc prolongation. Research indicates the high exposure to potential clinically significant DDIs in the prescribed pharmacotherapy in an outpatient setting and imposes the need for standardised models of pharmacist interventions.

1. Introduction

Patient safety is a health care discipline which aims to prevent and reduce risks, errors and harm that can occur to patients during health care provision (WHO 2021). Special emphasis has been placed on preventive measures to counteract the occurrence of events that can negatively affect the pharmacotherapy outcomes (Błeszyńska et al. 2020).

A drug-drug interaction (DDI) can be defined as the effect that one drug has on another. DDIs are among the most common drug-related problems which represent an important aspect of patient safety and are generally preventable (Mallet et al. 2007; Schorr et al. 2014, Marušić et al. 2013; Peterson and Gustafsson 2017). According to data from the Spontaneous Reporting Database of Pharmacovigilance Department of Croatian Agency for Medical Products and Medical Devices (HALMED), 7.8% of reported adverse drug reactions (ADR) were caused by DDIs (Mirosevic Skvrce et al. 2011). Most drug interaction research shows interaction rates in hospital setting. Less is known about DDIs in prescribed pharmacotherapy in outpatients, especially how community pharmacists should contribute to DDI prevention and risk management (Toivo et al. 2016).

Community pharmacists have an obligation to contribute to medication risk management in outpatient care (Kallio et al. 2020). Problems related to DDIs are usually summarized at the point of dispensing process and pharmacists are the most accessible health care providers able to intervene when faced with potential DDIs (Lien and Lien 1994). The pharmacists, by their role and position in health care system, take the place of the last professional pharmacotherapy supervisor who provides safe and rational drug administration, which also includes DDIs risk consideration. Reliable decision support platforms are useful to pharmacist in detecting clinically significant DDIs (Juurlink et al. 2003). Although there are software tools for DDIs detection, critical professional interpretation and risk assessment are irreplaceable (Bacic Vrca et al. 2005).

There is a growing need for more active community pharmacists' involvement in DDIs risk management, especially as the population is aging. Due to comorbidities, polytherapy and impaired physiological functions, elderly patients are particularly sensitive to DDIs (Palleria et al. 2013). However, pharmacist' involvement requires models of DDI-related interventions which will assist community pharmacist in assessment of necessary interventions.

One of the prerequisites for the intervention models is to regularly establish the list of the most common DDIs in prescribed pharmacotherapy. Currently there are no established professional norms regarding lists of critical DDIs (Somogyi-Végh et al. 2019). Regularly conducted research on prevalence and types of DDIs in prescribed pharmacotherapy is necessary to resolve contemporary pharmacotherapy issues and encompass new drugs and guidelines. The aim of this study was to determine the most common potential clinically significant DDIs in prescribed pharmacotherapy in an outpatient setting in Croatia.

2. Investigations, results and discussion

This research enrolled patients' therapies from twelve randomly selected community pharmacies in Croatia, six from urban areas and six from rural areas as defined by Eurostat. In total, study consecutively and retrospectively included 1211 pharmacotherapy cards of 1211 patients. Only prescription pharmacotherapy was taken into analysis. The potential interactions were assessed using Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., Hudson, USA) software. Lexicomp is a program with a sensitivity of 97% and specificity of 90% (Barrons et al. 2004). Lexicomp categorizes DDIs according to clinical significance in five types: A, B, C, D and X (Lexicomp 2021). Interactions of level C, D and X are considered clinically significant.

The mean age of participants was 66.3 (20–102) years (Table 1). On average, patients had 6 (2–18) prescription medications and 3.7 (1–11) comorbidities. The most frequent diagnoses were: essential hypertension, diabetes mellitus, dorsopathies, dyslipidemia and anxiety disorders. Cardiovascular system medications (according to Anatomical Therapeutic Chemical (ATC) Classification category C) were the most frequently prescribed drugs and angiotensin-converting enzyme (ACE) inhibitors were the most extensively used therapeutic subgroup followed by benzodiazepines, selective beta blocking agents, dihydropyridines and statins.

Table 1: Patients' characteristics

Characteristics, n = 1211	
Age (years), mean (min-max)	66.3 (20-102)
Female gender, n (%)	691 (57.1)
Diagnoses per patient, mean (min-max)	3.7 (1-11)
Most frequent diagnoses, n (%)	
Essential (primary) hypertension	861 (71.1)
Diabetes mellitus	315 (26.0)
Dorsopathies	310 (25.6)
Dyslipidemia	291 (24.0)
Other anxiety disorders	167 (13.8)
Gastritis	164 (13.5)
Disorders of thyroid gland	117 (9.7)
Gastro-oesophageal reflux disease	115 (9.5)
Atrial fibrillation	103 (8.5)
Prostate hyperplasia	101 (8.3)
Prescription medications, n	7299
Prescription medications per patient, mean (min-max)	6 (2-18)
The most frequent therapeutic subgroups, n (%)	
ACE inhibitors	636 (8.7)
Benzodiazepines	497 (6.8)
Beta blocking agents, selective	462 (6.3)
Dihydropyridine derivatives	437 (6.0)
HMG CoA reductase inhibitors (statins)	408 (5.9)
Proton pump inhibitors	327 (4.5)
Propionic acid derivatives	287 (3.9)
Other opioids	214 (2.9)
Biguanides	211 (2.9)
Sulfonamides	211 (2.9)

Abbreviations: ACE - angiotensin-converting enzyme; HMG-CoA - 3-hydroxy-3-methylglutaryl coenzyme A

Overall, 4798 potentially clinically significant DDIs were identified; 3945 (82.2%) required increased patient monitoring, while other interactions required specific therapy modification (n=853; 17.8%). The overall rate of clinically significant DDIs per patient was 4 (Table 2). At least one potential clinically significant interaction was found in 84% of patients.

Table 2: Frequencies of potential clinically significant DDIs

	Total	Classification of DDIs		
		Category C	Category D	Category X
DDIs (n)	4798	3945	797	56
Number of patients with DDIs	1017	963	449	51
Mean number of DDIs per patient (mean, range)	4 (0-25)	3.3 (0-22)	0.7 (0-7)	0.05 (0-2)

Abbreviations: DDI drug-drug interaction: Category C Monitor drug therapy; Category D Consider therapy modification; Category X Avoid combination

The most common potential clinically significant DDIs are presented in Tables 3-5, which also describe the possible consequences of the detected DDIs as well as their mechanism and required management. The most frequent potentially clinically significant DDI was the category C interaction between perindopril and indapamide, observed in 12.4% of patients. Of the 20 most common pairs of C interactions, 16 DDIs included drugs with antihypertensive effect. The most frequent D interaction was diazepam-tramadol and the most represented consequence of D interactions was increased risk of central nervous system (CNS) depression. In total, 56 X interactions which included 34 drug pairs were identified. Diazepam-olanzapine and indapamide-promazine were the most frequent X interactions. Non-steroidal inflammatory drugs (NSAID) were involved in 26.8% X interactions. Interactions that carried an increased risk QTc prolongation accounted for 16.1% X interactions.

The present study is the first study on our national level to report exposure to potential DDIs generally in outpatient settings. Our results show high patient exposure to DDIs in outpatient setting (84%). A recent study reported a prevalence range of 25.1% to 100% and the number of DDIs per 100 patients was 30 to 388.3 in primary care (Sánchez-Fidalgo et al. 2017). In our study the number of DDIs per 100 patients was even higher, 400. Majority of clinically significant established DDIs (82.2%) required increased patient monitoring while other DDIs required specific therapy modification. Similar share of interactions according to clinical significance was found in recent study on national level in Slovenia that used the same software for DDIs detection (Jazbar et al. 2018). Most of the interactions that required monitoring in our study were related to agents with antihypertensive effect, primarily ACEIs. According to prescription data, 71.1% of enrolled patients had essential hypertension. Many studies have shown that antihypertensive drugs are frequently involved in DDIs (Létinier et al. 2019; Sánchez-Fidalgo et al. 2017; Chatsisvili et al. 2010; Köhler et al. 2000).

The most frequent interaction in our study was that between perindopril and indapamide. The consequence of this interaction may be manifested by enhanced antihypertensive and nephrotoxic effects. This interaction applies to all ACE inhibitors. Synergistic effect of these interactions is often targeted in the treatment of hypertension, but requires increased clinical and laboratory patient monitoring. Recommendations include monitoring for symptomatic hypotension, clinical parameters for renal impairment, correction of volume and interactants dose reduction. Patients who concurrently use NSAIDs with this drug combination may be particularly at risk for acute kidney injury (Camin et al. 2015; Dreischulte et al. 2015; Fournier et al. 2014; Lapi et al. 2013).

Hypertension is an important global health challenge due to its high prevalence and effect on the development of a spectrum of cardiovascular diseases (Mills et al.2016). It is estimated that 31.1% of adults worldwide had hypertension in 2010 (Mills et al. 2020). Three-quarters of people with hypertension need more than one medication to regulate hypertension which complicates pharmacotherapeutic management. Five major drug classes were recommended for the treatment of hypertension: ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers and diuretics. Among those, ACE inhibitors are the most widely used, which is also showed in our research (Williams et al. 2018). High prevalence of hypertension and polypharmacy in treating elevated blood pressure can explain high antihypertensive drugs involvement in DDIs.

In the study conducted in three community pharmacies in Croatia, the authors showed very high exposure of elderly patients with arterial hypertension to potential DDIs; 90.6% of elderly patients had at least one potential clinically significant DDIs. Interactions between ACE inhibitors and thiazides or loop diuretics were among the most commonly determined interactions (Bacic-Vrca et al. 2010).

In a study conducted in three community pharmacies in Northern Greece, ACE inhibitors were also the most commonly involved in interactions (Chatsisvili et al. 2010). Sánchez-Fidalgo et al. (2017) as well reported ACEIs as one of the most common therapeutic group involved in DDIs in outpatient settings.

The most common identified D interactions carry increased risk of CNS depression, which requires an evaluation of interacting drugs indication, dose, duration and/limitation of therapy. Tramadol, benzodiazepines and the nonbenzodiazepine benzodiazepine receptor agonist were the most common interactants in D interactions. Indications for benzodiazepine administration include, but are not limited to, anxiety disorders, insomnia, spastic disorders, seizure disorders and agitation. Patients may not be aware of the

Table 3: The most frequent potential clinically significant category C DDIs

DDI	N	Summary	Management
Indapamide- perindopril	150	Indapamide may enhance the nephrotoxic effect and hypotensive effect of ACEI.	Monitor for hypotensive effects of ACEI and for acute renal failure.
Hydrochlorotiazide-ramipril	58	Hydrochlorotiazide may enhance the nephrotoxic effect and hypotensive effect of ACEI.	Monitor for hypotensive effects of ACEI and for acute renal failure.
Metformin- perindopril	57	ACEI may enhance the adverse/toxic effect of metformin.	Monitor for hypoglycemia and for lactic acidosis.
Hydrochlorothiazide-lisinopril	51	Hydrochlorotiazide may enhance the nephrotoxic effect and hypotensive effect of ACEI.	Monitor for hypotensive effects of ACEI and for acute renal failure.
Hydrochlorotiazide-valsartan	51	Hydrochlorothiazide may enhance the hypotensive effect of valsartan. Valsartan may increase the serum concentration of hydrochlorothiazide.	Monitor hemodynamic status, electrolyte concentrations and renal function.
Metformin- ramipril	51	ACEI may enhance the adverse/toxic effect of metformin.	Monitor for hypoglycemia and for lactic acidosis.
Indapamide- metformin	50	Indapamide may diminish the therapeutic effect of antidiabetic agents.	Increase monitoring of blood glucose control.
Hydrochlorotiazide-metformin	47	Hydrochlorothiazide may diminish the therapeutic effect of antidiabetic agent.	Increase monitoring of blood glucose control.
Bisoprolol- ibuprofen	43	NSAIDs may diminish the antihypertensive effect of beta-blockers.	Monitor for increases and decreases in blood pressure.
Furosemide- ramipril	42	Furosemide may enhance the nephrotoxic effect and hypotensive effect of ACEI.	Monitor for hypotensive effects of ACEI and for acute renal failure.
Glyclazide- metformin	38	Increases the risk for hypoglycemia.	Monitor patients closely for hypoglycemic effects.
Ibuprofen- perindopril	38	The combination may result in a significant decrease inrenal function. NSAIDs may diminish the antihypertensive effect of ACEIs.	Consider alternative for NSAID. Monitor for decreased therapeutic effects of ACEIs.
Hydrochlorotiazide-tramadol	37	Opioid agonists may enhance the adverse/toxic effect and diminish the therapeutic effect of diuretics.	Patients should be monitored for reduced efficacy of diuretics, urinary retention, and symptoms of orthostasis.
Ibuprofen- ramipril	36	The combination may result in a significant decrease in renal function. NSAIDs may diminish the antihypertensive effect of ACEIs.	Consider alternative for NSAID. Monitor for decreased therapeutic effects of ACEIs.
Ibuprofen- metformin	35	NSAIDs may enhance the adverse/toxic effect of metformin.	Close laboratory and clinical monitoring (eg, renal function, signs and symptoms oflactic acidosis).
Indapamide- tramadol	34	Opioid agonists may enhance the adverse/toxic effect and diminish the therapeutic effect of diuretics.	Patients should be monitored for reduced efficacy of diuretics, urinary retention, and symptoms of orthostasis.
Hydrochlorotiazide-ibuprofen	34	Thiazide and thiazide-like diuretics may enhance the nephrotoxic effect of NSAIDs.	Monitor clinical response to thiazide diuretics. Patients should also be monitored closely for evidence of acute kidney injury.
Insulin- metformin	33	Increases the risk for hypoglycemia.	Monitor patients closely for hypoglycemic effects.
Furosemide- tramadol	33	Opioid agonists may enhance the adverse/toxic effect and diminish therapeutic effect of diuretics.	Monitor for reduced efficacy of diuretics, urinary retention, and symptoms of orthostasis.
Allopurinol- furosemide	26	Loop diuretics may enhance the adverse/toxic effect and increase the serum concentration of allopurinol.	Avoid unnecessary combination therapy with allopurinol and loop diuretics. Monitor patients closely for signs and symptoms of allopurinol hypersensitivity-type reactions (e.g., fever, rash, eosinophilia).

Abbrevations: ACEI - angiotensin-converting enzyme inhibitor; DDI – drug-drug interaction; NSAID - nonsteroidal anti-inflammatory drug

risk of chronic benzodiazepine use. Use of benzodiazepines among eldery patients is common (Gerlach et al. 2018). Benzodiazepines comprise 20% to 25% of inappropriate prescriptions in the elderly (Brekke et al. 2008; van der Hooft et al. 2005). Benzodiazepines can cause cognitive deterioration and increase the risk of falls and hip fractures in elderly (Renom-Guiteras et al.2015; AGS Beers 2019).

Tramadol is a widely used drug in the treatment of moderate to severe pain. Tramadol, but also benzodiazepines and other types of sedative-hypnotics, such as Z-drugs (zolpidem, zaleplon, zopiclone), are not recommended in elderly patients and are considered inappropriate (Renom-Guiteras et al. 2015; AGS Beers 2019). Considering that the average age of the study population was 66.3 years, it should be outlined that there was a high share of potentially inappropriate medications (PIM) in the most common D interactions. Applying the EU(7)-PIM criteria has been shown as useful tool in reducing the harm related with potentially clinically significant DDIs in elderly patients (Marinović et al. 2020). When possible and in collaboration with physician, it is also recommended to educate the patients about the risk associated with prolong use of benzodiazepine. Evidence supports patient education as an effective method for catalyzing benzodiazepine reduction (Tannenbaum et al. 2014).

The most common consequences of X interactions were increased gastrointestinal toxicity, risk of acute kidney failure and prolongation of the QTc interval. Of all X interactions, 26.8% included NSAIDs combinations. NSAIDs are among the most commonly prescribed medications worldwide (Koffeman et al. 2014). In addition to the increased risk of gastrotoxicity, the possible nephrotoxicity associated with the NSAID use should also be emphasized. It is estimated that renal side effects associated with NSAIDs occur in about 5-18% of patients (Murray et al. 1990; Galesic et al. 2005). Incidence of interactions between NSAIDs is probably higher because these drugs are available in prescription but also in over the counter form. Reasons for taking two NSAIDs can be inadequate pain control or unawareness of their same therapeutic class. The role of pharmacists as the last pharmacotherapy supervisors is crucial in preventing NSAID duplication in therapy, especially

Table 4: Ten most frequent potential clinically significant D category DDIs

DDI	n	Summary	Management
Diazepam-tramadol	59	Increased risk for CNS depression.	These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug to the minimum possible. Warn patients/caregivers about the risk of slowed or difficult breathing and/or sedation.
Diazepam-zolpidem	33	Increased risk for CNS depression.	When possible, avoid the concurrent use.
Moxonidine-bisoprolol	31	Alpha2-agonists may enhance the AV-blocking effect of beta-blockers. Sinus node dysfunction may also be enhanced. Beta-blockers may enhance the rebound hypertensive effect of Alpha2-agonists. This effect can occur when the Alpha2-agonist is abruptly withdrawn.	Consider therapy modification. The significance of this interaction may be greater in patients with heart failure.
Alprazolam-tramadol	30	Increased risk for CNS depression.	These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect and consider dose reductions of the opioid or CNS depressant upon initiation. Warn patients/caregivers about the risk of slowed/difficult breathing and/or sedation.
Alprazolam-zolpidem	28	Increased risk for CNS depression.	When possible, avoid the concurrent use.
Tramadol-zolpidem	26	Increased risk for CNS depression.	When possible, avoid the concurrent use. If combined, consider using a lower dose of the other CNS depressant when possible.
Furosemide-ibuprofen	20	NSAIDs may diminish the diuretic effect of loop diuretics. Loop diuretics may enhance the nephrotoxic effect of NSAIDs.	Monitor for decreased therapeutic effects of loop diuretics. Patients should also be monitored closely for evidence of acute kidney injury.
Amlodipine-simvastatin	20	Amlodipine may increase serum concentration of simvastatin.	Avoid the concurrent use when possible. If used together, avoid doses of simvastatin greater than 20mg/day and monitor closely for signs of simvastatin toxicity (e.g. myositis, rhabdomyolysis).
Oxazepam-tramadol	19	Increased risk for CNS depression.	These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect and consider dose reductions of the opioid or CNS depressant upon initiation. warn patients/caregivers about the risk of slowed/difficult breathing and/or sedation.
Moxonidine-zolpidem	17	Increased risk for CNS depression.	When possible, avoid the concurrent use. If combined, consider using a lower dose of the other CNS depressant when possible.

Abbrevations: CNS - central nervous system; DDI - drug-drug interaction; NSAID - nonsteroidal anti-inflammatory drug

as it is in a position to oversee the issuance of both NSAID forms. Pharmacist should advise patients on the appropriate and safe use of the analgesic therapy.

There is an extensive list of medications that can prolong the QT interval such as antiarrhythmics, antimicrobials, antidepressants, antipsychotics, antihistamines and antiemetics (Yap and Camm 2003). QT interval prolongation is associated with an increased risk of polymorphic ventricular tachycardia, a characteristic life-threatening cardiac arrhythmia also known as torsades de pointes. Due to frequency of polytherapy there is a relatively high risk that the patient will receive at least two drugs which increase proarrhythmic potential (Wisniowska et al. 2016).

Pharmacists may help reduce the risk of serious ventricular arrhythmias by screening for potential interactions and make recommendations to prescribers for safer drug combinations. Drugs that have QT-prolonging effects should not exceed recommended dosing range. In addition, these medications should be prescribed with caution in patients who have underlying cardiac disorders and electrolyte abnormalities (Yap and Camm 2003).

High DDI exposure in outpatient setting requires more active community pharmacist involvement in supervising and managing DDIs. However, pharmacist involvement requires standardised models of pharmacists' interventions in order to ensure that all patients receive optimal and equal pharmaceutical care. Models should be created for at least the most common interactions and implemented in pharmaceutical care. Models of pharmacist DDIs interventions should be adopted by consensus of experts and regularly updated.

Understanding the interaction mechanism and assessing their frequency and clinical relevance helps in optimizing and managing DDIs. The contribution of this research is also in providing information for the creating standardised models of pharmacists' DDIs interventions.

The main limitation of our study is that OTC drugs were not included in the analysis which probably contributes to even higher exposure to DDIs in outpatient setting. The ideal circumstances for conducting DDI management would also require that medications are always dispensed to the patient in the same pharmacy and that OTC register is implemented in pharmacy record data.

3. Experimental

Pharmacies were included randomly using Research Randomizer software on the national pharmacies list, which is available on the official website of Croatian pharmaceutical chamber. Patients' pharmacotherapy data that are kept in community pharmacy record data base were taken consecutively and retrospectively. Patients were eligible if they were 18 years or older and received two or more drugs for systemic use. The patient's pharmacotherapy card records data of the prescribed pharmacotherapy contains the following informations: drug name, the prescribed amount of drug, dose, frequency and route of drug administration. It also provides information on the diagnosis for which the drug is prescribed. Medications were classified according to Anatomical therapeutic classification (ATC) and diagnosis were classified using International Classification of Diseases (ICD). Over-the-counter (OTC) drugs were excluded from the analysis as their dispensing is not regularly recorded in community pharmacies. The potential interactions were assessed using Lexicomp® Lexi-InteractTM Online (Lexi-Comp, Inc., Hudson, USA) software. Lexicomp categorizes DDIs according to clinical significance in five types as follows (Lexicomp 2021):

(A) No known interaction. Data has not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.

(B) No action needed. Data has demonstrated that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.

(C) Monitor therapy. Data has demonstrated that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use

Table 5: The most frequent potential clinically significant X category DDIs (<2 DDI cases are not presented)

DDI	n	Summary	Management
Diazepam-olanzapine	5	Olanzapine may enhance the adverse/toxic effect of benzodiazepines.	Olanzapine prescribing information recommends to avoid concomitant use of parenteral benzodiazepines and intramuscular olanzapine due to risks of additive adverse effects (e.g., cardiorespiratory depression, excessive sedation). Additive pharmacologic effects might also be expected with oral use of these agents, but specific recommendations are lacking.
Indapamide-promazine	5	Thiazide and thiazide-like diuretics may enhance the QTc-prolonging effect of promazine.	Avoid concomitant use.
Carbamazepine-tramadol	3	Tramadol may enhance the CNS depressant effect and diminish the therapeutic effect of carbamazepine. Carbamazepine may decrease the serum concentration of tramadol.	Avoid concomitant use.
Furosemide-promazine	3	Loop diuretics may enhance the QTc-prolonging effect of promazine.	Avoid concomitant use.
Tamsulozine-urapidil	3	Alpha1-blockers may enhance the hypotensive effect of other alpha1-blockers.	Avoid concomitant use.
Ketoprofen-naproxen	2	The risk for gastrointestinal toxicity is increased.	Concurrent use of more than one NSAID should be avoided.
Ibuprofen-naproxen	2	The risk for gastrointestinal toxicity is increased.	Concurrent use of more than one NSAID should be avoided.
Ibuprofen-indometacin	2	The risk for gastrointestinal toxicity is increased.	Concurrent use of more than one NSAID should be avoided.
Ibuprofen-ketoprofen	2	The risk for gastrointestinal toxicity is increased.	Concurrent use of more than one NSAID should be avoided.
Diclofenac-indometacin	2	The risk for gastrointestinal toxicity is increased.	Avoid combination.
Lorazepam-olanzapine	2	Olanzapine may enhance the adverse/toxic effect of benzodiazepines.	Olanzapine prescribing information recommends to avoid concomitant use of parenteral benzodiazepines and intramuscular olanzapine due to risks of additive adverse effects (e.g., cardiorespiratory depression, excessive sedation). Additive pharmacologic effects might also be expected with oral use of these agents, but specific recommendations are lacking.
Cefuroxim-esomeprazole	2	PPI may decrease the absorption of cefuroxime.	Avoid concomitant use.
Ramipril-telmisartan	2	Telmisartan may enhance the adverse/toxic effect of ramipril and increase concentration of ramipril.	Concurrent use of telmisartan and ramipril is not recommended.

Abbrevations: DDI - drug-drug interaction; NSAID - nonsteroidal anti-inflammatory drug; PPI - proton-pump inhibitor; QTc - corrected QT interval+

of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
(D) Consider therapy modification. Data has demonstrated that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realise the benefits and/or minimise the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empirical dosage changes, choosing alternative agents.
(X) Avoid combination. Data has demonstrated that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.
Interactions of level C, D and X are considered clinically significant.
Standard descriptive statistics were used to describe demographic and clinical data of the study population, number and types of identified DDIs. Categorical data were presented using frequencies and percentages. The mean was calculated and range was given for continuous variables.

Conflict of interest: None declared.

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