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Adverse effects of interactions between antidepressants and medications used in treatment of cardiovascular disorders

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Summary

Aim. To evaluate harmful interactions between antidepressants and medications used in treatment of cardiovascular disorders.

Method. The analysis of 66 cases of adverse reactions with a clinical picture indicating, to a degree that is probable or certain, that they were the result of the combination of antidepressantwith cardiovascular medication.

Results. The most common side effect (n = 25, 37.9%) was bradycardia (and other side effects of beta blockers) as a consequence of addition of metoprolol or propranolol to SSRI or bupropion. In one case combination of fluoxetine with propranolol resulted in cardiac arrest. We observed 8 cases of intensified side effects of amlodipine (swelling of lower limbs, headaches) after its combination with: fluoxetine, sertraline and paroxetine, and occurrence of myalgia, elevated aminotransferase levels, polyuria and hypotension after combination of lercanidipine with some of the SSRIs. We also found i.a. worsening of propafenone tolerance in combination with venlafaxine or bupropion, 2 cases of granulopenia associated with duloxetine–propafenone combination, 2 cases of hemorrhagic complications associated with the combination of vortioxetine–warfarin, 1 case of hyponatremia associated with the combination of vortioxetine and hydrochlorothiazide, as well as antagonizing clonidine's hypotensive effect by mirtazapine, and peripheral thrombosis following the combination of warfarin with trazodone.

Conclusions. Because of a high risk of interactions and related adverse effects, especially in older patients, each decision regarding combination of a particular antidepressant with a medication used in treatment of cardiovascular disorders should be preceded by a detailed

analysis of safety and risk-benefit ratio, and also be associated with the search for the safest, alternative combinations of the above-mentioned medications.

Key words: antidepressants, cardiovascular disease, drug interactions

Introduction

Both ischemic heart disease and depression (major depression disorder – MDD) are leading causes of disability worldwide [1]. There is a multifaceted relationship between MDD and cardiovascular diseases in the aspects of: comorbidity, pathophysiological mechanisms, mutual influence on prognosis, and pharmacological interactions [2, 3]. The prevalence of MDD among patients affected by heart diseases is high – up to 45% of patients with coronary artery disease (CAD) may have severe depressive symptoms [4], and around 20% fulfill criteria of depressive episode [4]. According to the meta-analysis of studies on MDD in patients with heart failure (HF), it was diagnosed on average in every fifth patient with HF [5]. Besides, prevalence of MDD depended on the severity of heart failure in NYHA classification (New York Heart Association) and reached as much as 42% in the fourth class [5]. In the population of patients after implantation of cardioverter defibrillator the prevalence of MDD seems to be same as in CAD and HF – around 20% [6].

On the other hand, available data indicate that MDD is an additional marker for evaluating risk of cardiovascular disease (CVD) [3]. The risk of developing CAD in patients with MDD may be even twice as high as in people without depressive symptoms [7]. A number of biological mechanisms potentially responsible for coexistence of MDD and CVD have been described – i.a., dysfunctions of platelets [8] and autonomic nervous system [9], increase in proinflammatory cytokines [10].

It has been observed that presence of depressive symptoms increases mortality in patients after myocardial infarction [11] or with HF [12, 13]. MDD turned out to be one of the leading factors contributing to the deterioration of quality of life in patients with chronic HF [14].

Polypharmacy is a common problem observed both in psychiatry and cardiology. Up to one third of psychiatric outpatients in the USA received simultaneously three or more psychotropic medications [15]. Furthermore, over time polypharmacy was used in an increasing proportion of patients [15]. Using many psychiatric medications at the same time is associated with a number of possible negative consequences, including: greater risk of lack of cooperation with the patient, harmful drug-drug interactions (DDI), increased toxicity of drugs and number of adverse reactions [16]. Polypharmacy in cardiology patients increases: the risk of DDI, treatment-related costs and frequency of medical side effects [17–19].

Because of the above-mentioned coexistence of MDD with heart diseases, in clinical practice it is important to be aware of potential DDI between medications used in CVD and antidepressants. Pharmacokinetic interactions require special attention – many

cardiac and antidepressant medications are metabolized in the liver by cytochrome P450 isoenzymes [20]. On the other hand, drugs from both groups may influence the activity of these isoenzymes (e.g., calcium channel blockers are inhibitors of CYP3A4, fluoxetine and paroxetine inhibit i.a. activity of CYP2D6) [21]. In the aspect of pharmacodynamic interactions, the combined use of cardiac drugs and antidepressants may cause serious side effects: hypotension, increased risk of gastrointestinal hemorrhage, prolongation of QT interval, and others [21, 22].

Objective

The aim of this paper is to assess the occurrence of adverse interactions between antidepressants and medications used in CVD. All of the patients whose medical records were included in the analysis had side effects which occurred, judging on the clinical manifestation, probably or certainly due to interaction between antidepressant and CVD medication.

Material and method

In this research, we performed a substantive analysis of 66 pharmacotherapies of patients treated in Poland from January 1st 2017 till March 30th 2018, both outpatients (in mental health, geriatric and cardiology clinics) and inpatients hospitalized in: Emergency Wards, Internal Medicine and Cardiology Departments. Data regarding drug-related complications come from the material of the University Center for Monitoring and Research on Drug Adverse Effects at the Department of Clinical Pharmacology of the Jagiellonian University Medical College in Krakow, which, as one of Regional Centers, formally monitors and reports, in accordance with legal acts in this area, complications of pharmacotherapy. Besides the Center provides specialist consultations both for clinics and hospitals from the following provinces: Małopolskie, Świętokrzyskie, Podkarpackie and Śląskie, in the area of pharmacotherapy, complications resulting from the use of drugs, as well as drug interactions whose occurrence lead to change in the effectiveness and/or safety of therapy. Annually, the number of consultations varies between 850 and 1100. Analysis of drug-related problems which are the subject of consultations is performed in the center by specialists in the field of pharmacology, clinical pharmacology and internal diseases. The Center regularly cooperates with the Department of Affective Disorders at the Chair of Psychiatry of the Jagiellonian University Medical College and the Chair of Psychiatry of the Jagiellonian University, due to the constantly increasing number of complications resulting from the interaction of a broadly defined group of psychotropic drugs with other simultaneously used medications.

The correlation between the applied pharmacological treatment and observed adverse reactions was established as part of a pharmacoepidemiological analysis. In all

the analyzed cases, a causal relationship between the applied treatment and clinical manifestation of side effects was also determined. In our research, we evaluated pharmacodynamic and pharmacokinetic interactions, as well as interactions due to addition of side effects of simultaneously used antidepressants with cardiac drugs. In the analyzed cases, the average number of medications used in one patients was 3 (min. 2, max. 8). In all cases there was a cause and effect relationship, probable (n = 38) or certain (n = 28), between addition of cardiac drugs and occurrence of complications with the clinical manifestations characteristic for the used medications. The mean age in the whole group of patients was 63.24 years (SD = 11.50).

Results

In the analyzed cases, most interactions between cardiac drugs and antidepressants concerned SSRIs (Selective Serotonin Reuptake Inhibitors) (n = 35, 53% of cases). The most commonly reported side effect (n = 25, 37.9 %) was the occurrence of bradycardia (sometimes with hypotension – mainly when bupropion was the antidepressant) as a result of addition of metoprolol or propranolol to one of the SSRIs or bupropion. The extreme form of this complication was one case of cardiac arrest associated with combination of fluoxetine and propranolol. The mean age in the subgroup of patients whose complications resulted from the combination of beta-blocker and antidepressants was 63.33 years (SD = 8.63). 8 cases (i.e., 12% of all events) of intensified side effects of amlodipine (occurrence of leg swelling, headache) after its combination with SSRI (fluoxetine, sertraline or paroxetine) were observed. In two cases the combination of fluoxetine and amlodipine was associated with acute kidney failure. Next 6 cases (9.1%) were due to the combination of lercanidipine and SSRIs resulting in hypotension (fluoxetine), myalgia (sertraline), polyuria (sertraline, paroxetine), elevation of aminotransferases level. One case of severe bradycardia was observed after combination of fluvoxamine and diltiazem. In the subgroup of patients in which the adverse effects of combining calcium channel blockers with antidepressants were observed, the mean age was 68.53 (SD = 13.44).

Table 1. **Interactions between antidepressants and medications used for the treatment of CVD in the analyzed group of cases and possible interaction mechanisms, proposed on the basis of references [21–25]**

Antidepressant medication	Medication used in cardiovascular diseases	NIIC	Sex and age of the patient	Medical comorbidities	Other concomitant medications	Clinical consequences of the interaction	Possible interaction mechanism
Fluoxetine	Propranolol	2	M/64	Hyperthyroidism, hypertension	Thiamazole, perindopril, indapamide	Cardiac arrest with subsequent effective resuscitation, bradycardia	Pharmacokinetic: inhibition of CYP2D6 by fluoxetine → increased concentration and side effects of propranolol (metabolized by CYP2D6)
			M/58	Addiction to alcohol, bleeding from esophageal varices in the past	Timonacic, Vitamin B1, B6		
Paroxetine	Propranolol	1	F/52	Hyperthyroidism	Thiamazole	Bradycardia	Pharmacokinetic: inhibition of CYP2D6 by paroxetine → increased concentration and side effects of propranolol (metabolized by CYP2D6)
Fluoxetine	Metoprolol	3	M/58	Hypertension	Zofenopril, indapamide	Bradycardia	Pharmacokinetic: inhibition of CYP2D6 by fluoxetine → increased concentration and side effects of metoprolol (metabolized by CYP2D6)
			M/49	Coronary artery disease	ASA, trimetazidine		
			M/61	STEMI in the past	ASA, nitrates		
Paroxetine	Metoprolol	4	M/67	Hypertension	Chlortalidone, perindopril	Bradycardia	Pharmacokinetic: inhibition of CYP2D6 by paroxetine → increased concentration and side effects of metoprolol (metabolized by CYP2D6)
			F/75	Sinus tachycardia	Magnesium and potassium salts		
			F/71	Hypertension	Lisinopril, hydrochlorothiazide		
			F/68	Heart failure, type II diabetes, hypercholesterolemia	Digoxin, metformin, atorvastatin		

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Citalopram	Metoprolol	2	F/45	Sinus tachycardia	Potassium salts	Bradycardia	Pharmacokinetic: inhibition of CYP2D6 by citalopram → increased concentration and side effects of metoprolol (metabolized by CYP2D6)
			F/52	Hypertension	Chlortalidone, zofenopril		
Escitalopram	Metoprolol	7	M/69	Coronary artery disease, hyperlipidemia	ASA, trimetazidine, tramadol/paracetamol, chondroitin, rosuvastatin, fenofibrate	Bradycardia, hypotension	Pharmacokinetic: inhibition of CYP2D6 by escitalopram → increased concentration and side effects of metoprolol (metabolized by CYP2D6)
			M/75	Hypertension	Enalapril, hydrochlorothiazide		
			F/74	After NSTEMI, type II diabetes, osteoarthritis, gout	Prasugrel, ASA, metformin, canagliflozin, etoricoxib, febuxostat		
			F/62	Hypertension	Zofenopril, indapamide		
			M/72	Heart failure	Perindopril, indapamide		
			M/59	Hypertension	Lercanidipine, perindopril, indapamide		
			M/71	Coronary artery disease, sciatica	ASA, pregabalin		
Fluoxetine	Amlodipine	2	M/34	Hypertension, type II diabetes	Metformin, acarbose, indapamide, torasemide	Acute non-infectious kidney failure, peripheral edema	Pharmacokinetic: competition for the same isoenzyme (CYP3A4), which metabolizes both medications, and as a result increased concentration and side effects of amlodipine
			M/77	Type II diabetes, gout, hypertension	Metformin, allopurinol, perindopril		

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Sertraline	Amlodipine	3	M/67	Hypertension, coronary artery disease	Nebivolol, zofenopril, ASA	Headache, swelling around the ankles		Pharmacokinetic: competition for the same isoenzyme (CYP3A4), which metabolizes both medications, and as a result increased concentration and side effects of amlodipine
			F/65	Hypertension, cataracts, neuralgia of the trigeminal nerve	Pregabalin, lisinopril, torasemide			
			F/59	Coronary artery disease, hypothyroidism	Thiamazole, ASA, nebivolol			
Paroxetine	Amlodipine	3	M/48	Hypertension, dyslipidemia, type II diabetes	Ezetimibe, rosuvastatin, zofenopril, metformin, canagliflozin	Swelling of lower limbs, throbbing headache with intensity that prevents life activity		Pharmacokinetic: competition for the same isoenzyme (CYP3A4), which metabolizes both medications, and as a result increased concentration and side effects of amlodipine
			M/82	Coronary artery disease, Parkinson's disease	L-DOPA, metoprolol, ASA			
			M/77	Hypertension, chronic insomnia, osteoarthritis	Perindopril, indapamide, buprenorphine, zolpidem, perazine			
Fluoxetine	Lercanidipine	1	F/69	Hypertension, venous insufficiency	Diosmin, indapamide	Hypotension		Pharmacokinetic: competition for the same isoenzyme (CYP3A4), which metabolizes both medications, and as a result increased concentration and side effects of lercanidipine
Sertraline	Lercanidipine	2	F/74	Hypertension, low back pain	Tapentadol, perindopril	Myalgia, polyuria		Pharmacokinetic: competition for the same isoenzyme (CYP3A4), which metabolizes both medications, and as a result increased concentration and side effects of lercanidipine
			F/75	Hypertension	Torasemide, zofenopril			

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Paroxetine	Lercanidipine	3	M/69	Hypertension, coronary artery disease	Nebivolol, enalapril, indapamide	Escalation of aminotransferases, polyuria	Pharmacokinetic: competition for the same isoenzyme (CYP3A4), which metabolizes both medications, and as a result increased concentration and side effects of lercanidipine
			F/70	Hypertension	Perindopril, pantoprazole		
			M/74	Coronary artery disease, peptic ulcer disease, prostatic hyperplasia	Pantoprazole, tamsulosin, finasteride, nebivolol, ASA		
Fluvoxamine	Diltiazem	1	M/88	Coronary artery disease, prostatic hyperplasia, back pain	Celecoxib, tramadol, doxazosin, ASA, nitrates	Severe bradycardia – 22/min	Pharmacokinetic: inhibition of CYP3A4 by fluvoxamine → increased concentration and side effects of diltiazem (metabolized by CYP3A4)
Paroxetine	Digoxin	1	F/54	Atrial fibrillation	Metoprolol, rivaroxaban, potassium salts	Decreased serum concentration of digoxin, tachycardia 170 bpm in one patient with atrial fibrillation	Pharmacokinetic: acceleration of hepatic metabolism of digoxin
Vortioxetine	Warfarin	2	F/57	Atrial fibrillation	Sotalol, potassium and magnesium salts	Nosebleed, bleeding from the urinary tract	Pharmacodynamic: blockade of the serotonin transporter on platelets as a result of vortioxetine's action → similarly to SSRI/SNRI, action decreasing platelet aggregation ability = additive mechanism (next to the action of warfarin) resulting in decreased coagulation
			M/44	Atrial fibrillation	Bisoprolol, digoxin, potassium salts		

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Vortioxetine	Hydrochlorothiazide (daily dose 50 mg)	1	M/38	Hypertension	No other medications	Hyponatremia		Additional risk of hyponatremia resulting from the medication's diuretic action and the risk of inducing the syndrome of abnormal secretion of antidiuretic hormone associated with blockade of reuptake of serotonin
Bupropion	Propafenone	3	M/63	Obesity, supraventricular tachycardia	Metoprolol	Bradycardia, dryness in mouth, changes in ECG, prolongation of PQ, widening of QRS complex		Pharmacokinetic: inhibition of CYP2D6 by bupropion → increased concentration and side effects of propafenone (metabolized by CYP2D6)
			M/65	Obesity, atrial fibrillation	Bisoprolol			
			M/64	Atrial fibrillation, nicotine addiction, coronary artery disease	ASA, bisoprolol, enalapril			
Bupropion	Metoprolol	6	M/56	Coronary artery disease	ASA	Bradycardia, hypotension, dizziness		Pharmacokinetic: inhibition of CYP2D6 by bupropion → increased concentration and side effects of metoprolol (metabolized by CYP2D6)
			F/61	Obesity, hypertension	Perindopril, indapamide, lercanidipine			
			F/74	Coronary artery disease	ASA, metoprolol			
			F/55	Hypertension, obesity, type II diabetes	Metformin, dapagliflozin, valsartan, indapamide			
			F/68	Ventricular arrhythmias, hypertension	Perindopril, indapamide			
			F/58	Coronary artery disease	ASA			
Bupropion	Clopidogrel	3	M/71	STEMI in the past, coronary artery disease	ASA, bisoprolol, perindopril	Seizures, generalized tremor		Pharmacokinetic: inhibition of CYP2B6 by clopidogrel → increased concentration of bupropion and its convulsive potential
			F/81	STEMI in the past	ASA, nebivolol, enalapril			
			F/65	STEMI in the past				

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Venlafaxine	Propafenone	3	M/74	Atrial fibrillation, hypertrophy of the prostate gland, osteoarthritis	Bisoprolol, rivaroxaban, tamsulosin, tramadol/ paracetamol	Bradycardia, dizziness, blurred vision		Pharmacokinetic: inhibition of CYP2D6 by venlafaxine → increased concentration and side effects of propafenone (metabolized by CYP2D6)
			M/69	Supraventricular tachycardia, hypertension	Potassium salts, perindopril, indapamide			
			M/65	Atrial fibrillation, prostate cancer surgery in the past	Dabigatran, bisoprolol			
Venlafaxine	Propranolol	2	M/74	Hyperthyroidism, coronary artery disease, osteoarthritis	Thiamazole, chondroitin, buprenorphine, ASA, diosmin	Increased muscle tone, urinary urgency		Many case reports, probable pharmacokinetic mechanism
			M/62	Alcoholism, bleeding from esophageal varices in the past	Ornithine aspartate, ursodeoxycholic acid, acamprosate			
Venlafaxine	Clopidogrel	2	F/54	STEMI in the past, hypertension	ASA, nebivolol, lisinopril	Genital tract bleeding, nosebleed		Pharmacodynamic: Blockade of the serotonin transporter on platelets as a result of venlafaxine's action → action decreasing platelet aggregation ability = additive mechanism (next to the action of clopidogrel) resulting in decreased coagulation
			F/49	STEMI in the past	ASA, metoprolol, enalapril			
Duloxetine	Propafenone	2	F/51	Atrial fibrillation, type II diabetes, painful diabetic neuropathy	Dapagliflozin, metformin, alpha-lipoic acid, nebivolol	Granulocytopenia		Pharmacokinetic: inhibition of CYP2D6 and 3A4 by duloxetine → increased concentration and side effects of propafenone (metabolized by CYP 2D6 and 3A4), including the risk of granulopenia associated with this medication
			F/68	Osteoarthritis of the knee joints, atrial fibrillation	Bisoprolol, rivaroxaban, potassium salts, tramadol, chondroitin			

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Mirtazapine	Clonidine	2	M/67	Hypertension, insomnia	Estazolam, perindopril, torasemide, doxazosin	Sudden increase in blood pressure	Pharmacodynamic: antagonizing the action of clonidine (a presynaptic alpha2 receptor agonist) by mirtazapine (a presynaptic alpha2 receptor antagonist)
			M/72	Hypertension	perindopril, chlortalidone, torasemide, doxazosin		
Clomipramine	Enalapril	2	F/74	Hypertension, heart failure	Hydrochlorothiazide, metoprolol	Accommodation disorder, reduced visual acuity	Pharmacokinetic: Inhibition of clomipramine metabolism. Enalapril is a prodrug which undergoes transition to the active form of enalaprilat. When clomipramine is administered concurrently, its metabolism slows down in the pharmacokinetic mechanism
			M/65	Hypertension, low back pain	Tapentadol, chlortalidone, tizanidine		
Trazodone	Warfarin	2	M/41	Atrial fibrillation	Bisoprolol, magnesium and potassium salts	Peripheral thrombosis	Unclear – probably a change in the binding of warfarin to plasma proteins
			M/46	Atrial fibrillation	Metoprolol		
Trazodone	Clonidine	1	F/39	Resistant hypertension	Zofenopril, torasemide, indapamide, amlodipine, doxazosin	Hypotension, sedation	Pharmacodynamic: additive hypotensive action of clonidine (an imidazoline and alpha2 receptor agonist) and metabolite of trazodone: m-chlorophenylpiperazine (blockade of afa1 receptors)

ASA – acetylsalicylic acid; CYP2B6 – cytochrome P450 CYP2B6 isoenzyme; CYP2D6 – cytochrome P450 CYP2D6 isoenzyme; CYP3A4 – cytochrome P450 CYP3A4 isoenzyme; ECG – electrocardiography; F – female; L-DOPA – levodopa; M – male; mg – milligrams; PQ – PQ interval (in ECG); QRS – QRS complex (in ECG); SNRI – serotonin-norepinephrine reuptake inhibitors; SSRI – selective serotonin reuptake inhibitor ; STEMI – ST elevation myocardial infarction; NIIC – number of identified interaction cases

Combining bupropion with cardiac medications most often, except from using SSRI, was associated with adverse events ($n = 12$, 18.2%) – apart from the above-mentioned interactions with metoprolol and propranolol, it resulted in: augmentation of propafenone side effects (3 cases of bradycardia and ECG changes) and of proconvulsive action of bupropion (combination with clopidogrel, $n = 3$). In the analyzed group, 7 cases (10.6%) of side effects or complications were related to venlafaxine and associated with bradycardia and dizziness (combination with propafenone, $n = 2$); increased muscle tension and urinary urgency (addition of propranolol, $n = 3$), vaginal and nasal bleeding (combination with clopidogrel, $n = 3$).

In the analyzed group, we indentified 2 cases of granulopenia after addition of duloxetine to propafenone; 2 cases of peripheral thrombosis after combining trazodone with warfarin and one case of severe hypotension after co-treatment with clonidine and trazodone. Moreover, combination of clonidine with mirtazapine was associated with a sudden increase in blood pressure ($n = 2$), whereas addition of enalapril to clomipramine resulted in intensification of adverse reactions such as disturbances of accommodation and blurred vision ($n = 2$).

The issue of interaction between cardiac medications and the latest antidepressant – vortioxetine is also worth mentioning. In the studied population we found 2 cases of hemorrhagic complications (nasal and vaginal bleeding after addition of warfarin) and one case of hyponatremia associated with combination of vortioxetine with hydrochlorothiazide (Table 1).

Table 2 presents the metabolism of antidepressants and their effect on the activity of individual CYP 450 isoenzymes.

Table 2. **Metabolism of antidepressants and their effect on hepatic metabolism (on the basis of [21–25])**

Antidepressant	Blockade of CYP 450 isoenzymes by antidepressant					CYP 450 isoenzymes for which antidepressant is a substrate
	3A4	2D6	1A2	2C19	2C9	
Agomelatine	0	0	0	0	0	1A2 /2C19/2C9
Bupropion	0	++	0	0	0	2B6
Citalopram/ escitalopram	0/+	+	0/+	0/+	0	3A4/2C19/2D6
Duloxetine	0/+	++	0/+	0/+	0/+	1A2/2D6
Fluoxetine	++/+++	+++	+	++	++	2D6/3A4/ 2C9/2C19
Fluvoxamine	++	+	+++	++	++	2D6/1A2
Mirtazapine	0	0/+	0	0	0	1A2/2D6/3A4
Moclobemide	0	+	0/+	+	0	2C19
Paroxetine	+	+++	+	+	+	2D6/3A4
Reboxetine	+	+	0	0	0	3A4/2D6

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Sertraline	+	+ (++)*	+	++	+	2D6/3A4/2C9/2C19
Tricyclic antidepressants	++	+++	0	+	0	2D6/3A4/1A2/2C19
Trazodone	0	+	0	0	0	3A4
Venlafaxine	+	0/+	0	0	0	2D6/3A4
Vortioxetine	0	0	0	0	0	2D6/3A4/2C9

* – for doses ≥150 mg/day; 0 – no effect; 0/+ – minimal effect; + – weak effect; ++ – moderate effect; +++ – strong effect

Discussion

In the analyzed material, the largest number of harmful interactions between antidepressants and cardiac medications and related side effects concerned the combination of SSRI (fluoxetine, paroxetine, citalopram, escitalopram) or bupropion with metoprolol or propranolol (37.9% of cases), which resulted in significant increase of serum concentration of the above-mentioned beta blockers leading to the onset or exacerbation of such side effects associated with the use of these medications as bradycardia, hypotension, dizziness, and even (in one case – combination of fluoxetine + propranolol) cardiac arrest. The mechanism of this interaction is pharmacokinetic and stems from the inhibition of CYP2D6, which is the main isoenzyme metabolizing propranol and metoprolol, activity by antidepressants (Table 2). This interaction is quite well known. 4–5 fold increase in metoprolol concentration after addition of fluoxetine, 2–3 fold increase in the case of combination with citalopram or duloxetine, 4–6 fold in combination with bupropion or paroxetine have been described. In turn, the combination of propranolol with fluvoxamine may lead to a 5-fold increase in the concentration of the former [26]. Most of this kind of interactions described so far, as opposed to the cases we present in this paper, were considered to have little clinical relevance [21, 26–28]. The only exception is a report of complete atrioventricular block in a 63-year-old woman simultaneously using metoprolol and paroxetine [29]; the same complication occurred in a 53-year-old man due to the combination of fluoxetine with propranolol [30] and the clinical case of severe bradycardia after adding bupropion to metoprolol therapy [31]. Pulmonary complications (respiratory failure) have also been reported in a patient with liver cirrhosis in whom venlafaxine and propranolol were used simultaneously [32]. The feature linking the above cases and cases of serious effects of combining certain antidepressants with metoprolol or propranolol described by us is older age of patients. In the analyzed subgroup the mean age was 63.33 years (SD = 8.63).

It is worth remembering that if it is necessary to combine antidepressants with beta-blockers, the SSRI/SNRI with the lowest risk of increased concentration and

severe side effects of metoprolol or propranolol is venlafaxine and sertraline. If it is necessary to treat patients with other medications from SSRI or SNRI group, switch of metoprolol or propranolol to nebivolol or carvedilol should be considered as they carry significantly lower risk of interaction. The exception happens for the combination of nebivolol with paroxetine or bupropion, which can cause even 6–7-fold increase in the concentration of nebivolol [33, 34].

The mechanism responsible for interaction of propafenone with antidepressants is similar as for beta blockers. The drug is metabolized primarily by CYP2D6 and 3A4. We have observed 8 cases (12.1% of all cases) of severe side effects of propafenone (Table 1) after combining it with bupropion, venlafaxine, duloxetine as a result of inhibited metabolism of the anti-arrhythmic drug by antidepressants. Cases of worsened propafenone tolerance in combination with citalopram or mirtazapine (bradycardia, prolongation of QT) [35, 36] and 2 cases of psychosis as a result of combining propafenone with venlafaxine [37, 38] can be found in the literature. However, circulatory complications due to combination of propafenone with venlafaxine and bupropion or hematological complications (granulocytopenia) after combining propafenone with duloxetine have not been described so far [39].

The second most frequent group of adverse events or complications in the analyzed material were the results of the combination of SSRI with calcium channel blocker (22.7% of all cases). Apart from the intensification of side effects of the latter, we observed 2 cases of acute renal failure (combination: fluoxetine + amlodipine) as well as isolated cases of myalgia, polyuria or elevated level of aminotransferases (combination of lercanidipine with SSRI) and severe bradycardia (fluvoxamine + diltiazem) (Table 1). So far, no clinically significant adverse effects of the combination of SSRIs with amlodipine or lercanidipine have been reported. However, descriptions of swelling, headaches and weight gain after the combined use of fluoxetine and verapamil can be found [40]. The interaction between SSRIs and calcium channel blockers appears to be predominantly pharmacokinetic and may involve drug competition for the same CYP 450 isoenzyme or blockade of the isoenzyme metabolizing the circulatory medication by antidepressant from the SSRI group (Tables 1 and 2).

The two cases of bleeding from the nose and urinary tract associated with the simultaneous use of vortioxetine and warfarin identified in the analysis are among the first such hemorrhagic complications reported in the literature related to this new antidepressant. According to the research, vortioxetine has no significant impact on the pharmacokinetic of warfarin and does not alter its concentration [41], therefore it should be assumed that the principal mechanism leading to bleeding could be blockade of serotonin reuptake on platelets – similarly to SSRI or SNRI [42]. It results in an inhibitory effect on the platelet aggregation and, in the case of SSRIs and SNRIs, is a well-documented mechanism associated with an increased risk of bleeding, especially in combination with other medications decreasing coagulation. This applies not only

to patients receiving antiplatelet drugs (acetylsalicylic acid, clopidogrel, ticagrelor), but also anticoagulants with different mechanisms of action (acenocoumarol, warfarin, dabigatran, rivaroxaban, apixaban, heparin) [27]. The situation is even more problematic if the patient simultaneously with the above-mentioned medications uses dietary supplements which can also induce hemorrhagic complications [43]. In case of simultaneous treatment with SSRI or SNRI and warfarin the additional hemorrhagic risk may be due to inhibition of warfarin metabolism (CYP 450: 2C9, 2C19, 3A4) and, consequently, its increased concentration in the blood. The highest risk of these interactions concerns fluvoxamine, fluoxetine and paroxetine, while the smallest risk is associated with the use of sertraline and venlafaxine [44].

The weakening of anticoagulant action by some antidepressants is a separate issue. The 2 observed cases of peripheral thrombosis after combining warfarin with trazodone are an example. The mechanism of this rare, but already described in the literature, interaction is not clear and is probably related to the change in the binding of warfarin to plasma proteins [45, 46]. It is also important to remember that drugs such as fluvoxamine or fluoxetine may reduce the antiplatelet effect of clopidogrel by blocking CYP2C19, because they inhibit its conversion to the active drug [47].

The use of clopidogrel in patients receiving antidepressants requires caution also due to the risk of dangerous interaction with bupropion. In the analyzed material, we reported three cases of seizures after the combination of bupropion and clopidogrel. Clopidogrel, like ticlopidine, has the ability to inhibit the cytochrome P450 2B6 isoenzyme which catalyzes the hydroxylation of bupropion to hydroxybupropion (Table 2). As a result of the described pharmacokinetic interaction high concentrations of bupropion are maintained in serum with low concentrations of hydroxybupropion, which in turn increases the risk of seizures [48].

Another area of interaction between antidepressants and medications used in cardiovascular diseases is the increased risk of hyponatremia. It concerns mainly the combination of SSRI or SNRI with high doses of loop diuretics and/or thiazides, particularly in elderly patients. In the analyzed material, we identified, to the best of our knowledge, the first ever reported case of hyponatremia after combination of vortioxetine with hydrochlorothiazide. It can be assumed that the mechanism of this interaction is similar to that of SSRIs and is based on the additive risk of hyponatremia resulting from the action of a diuretic with the risk of inducing the syndrome of inappropriate antidiuretic hormone hypersecretion associated with blockade of serotonin reuptake [27].

In patients treated with clonidine it is worth remembering that this drug is susceptible to pharmacodynamic interactions associated with its specific mechanism of action (including: agonism to presynaptic alpha 2 receptors). The examples include above-described: weakening of the hypotensive action of clonidine by mirtazapine (a presynaptic alpha 2 receptor agonist) and intensification of clonidine's hypotensive

effect by trazodone, the metabolite of which has alpha1-adrenolytic activity. Both of these phenomena were previously the subject of individual case reports [49, 50]. Tricyclic antidepressants have the most potent alpha 1-adrenergic blocking activity among antidepressants, which can be the reason for the dangerous potentiation of the hypotonizing effect of many drugs used to treat hypertension, regardless of their mechanism of action [21].

In addition to the interactions we found in the analyzed material, two other areas of risk of adverse effects of combining antidepressants with drugs used in cardiovascular diseases should be mentioned. One of them is conduction disturbances in the myocardium. Some antidepressants (especially tricyclic antidepressants, citalopram, escitalopram) can induce prolongation of the QT interval on the ECG by affecting the potassium channels. Increased risk of ventricular arrhythmias can be a consequence of their use with anti-arrhythmic drugs. Particular care should be taken with simultaneous administration of amiodarone, propafenone and sotalol [27]. The interaction of antidepressants with statins, particularly simvastatin, atorvastatin and lovastatin, whose hepatic clearance is associated with CYP3A4, is also of practical significance. The consequence of CYP3A4 inhibition by SSRI or tricyclic antidepressants may be an increased exposure to statins and the occurrence of side effects such as myopathy, myalgia or even rhabdomyolysis. The risk seems to be the highest when combining the above-mentioned statins with fluvoxamine [51]

Conclusions

Because the coexistence of affective disorders and cardiovascular diseases is more a rule than an exception, it is very often necessary to combine – usually as polytherapy – antidepressants with cardiac medications. Due to the high risk of interactions and associated adverse effects, especially in older patients, each decision regarding the combination of a specific antidepressant and cardiovascular medication should be preceded by a detailed analysis of safety together with a benefit and risk balance, and should also involve seeking the safest alternative combinations of the above-mentioned medications.

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Authors declare no conflict of interest.

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