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ORIGINAL ARTICLE

Drug-induced diseases in otolaryngology – causes, clinical signs, treatment

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Jarosław Woroń[1,2ABDEF], Dariusz Jurkiewicz[3ABDEF], Piotr Rapiejko[3ABD], Barbara Lorkowska-Zawicka[1,4ABD], Radosław Tymiński[5ABD], Jerzy Wordliczek[2,6ABD]

[1]Department of Clinical Pharmacology, Department of Pharmacology, Faculty of Medicine, Jagiellonian University Medical College in Krakow, Poland; Head: Jarosław Woroń MD PhD
[2]The University Hospital in Krakow, Anaesthesiology and Intensive Care Clinical Department, Poland
[3]Department of Otolaryngology and Laryngological Oncology with the Clinical Department of Cranio-Maxillofacial Surgery, Military Medical Institute in Warsaw, Poland; Head: prof. Dariusz Jurkiewicz MD PhD
[4]The University Hospital in Krakow, Otolaryngology Clinical Department, Poland; Head: Jerzy Tomik MD PhD
[5]Radoslaw Tyminski Law Office, Poland
[6]Clinic of Intensive Interdisciplinary Therapy, Jagiellonian University Medical College in Krakow, Poland

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ABSTRACT:

Introduction: In the daily practice of an otolaryngologist, we encounter cases where the symptoms are not the result of disease but result from pharmacotherapy. In the case of symptoms such as hearing loss, tinnitus, or dizziness, polytherapy may be used as the basis for their occurrence, which, due to the lack of rationality in combining drugs, leads to symptoms that the patient and the doctor very often interpret as a new disease syndrome.

Aim: The aim of the study is to show and to raise awareness of the fact that the symptoms of hearing organ impairment are frequently drug-related and only a modification of the currently used pharmacotherapy is a rational procedure in such cases.

Material: This paper describes 30 cases who developed side effects of polypharmacy in the form of hearing disorders, dizziness, and tinnitus. The causes of drug-related complications were discussed, as well as effective methods of their prevention.

KEYWORDS: drug interactions, otolaryngology, pharmacotherapy, side effects

INTRODUCTION

From the legal point of view, a doctor is obliged to diagnose and cure a patient in accordance with the current medical knowledge [1]. One of the elements of this action in line with medical knowledge is establishing the real causes of patient's ailments. In the everyday practice of an otolaryngologist, we encounter cases where the symptoms are not caused by a disease but result from pharmacotherapy. In case of symptoms such as hearing loss, tinnitus, or dizziness, polytherapy may be at the root of their occurrence, which, due to the lack of rationality in combining drugs, leads to symptoms that a patient, and very often a doctor, interpret as a new disease syndrome.

This type of pharmacotherapy, which is intended to help, but in practice harms a patient, is called iatrogenic. If we do not take into account that the symptoms described by a patient may constitute adverse drug reactions, we will lead to another pathology in pharmacotherapy, which is called a prescription cascade. This cascade is described as treatment of side effects of pharmacotherapy with other drugs, which in practice often leads to the occurrence of further side effects. Hence, it is so important in clinical practice to eliminate drug combinations that cause further pathologies [2–5].

Eliminating incorrect drug combinations is also of vital legal importance as it helps to prevent patient claims.

MATERIALS AND METHODS

In our study, we described 30 patients with hearing loss or tinnitus. Patients had otolaryngology and clinical pharmacology consultations, and in all 30 cases, after modification of the implemented therapy, patients' symptoms being a consequence of improperly combined polytherapy alleviated or completely disappeared. In all 30 cases, the patients previously reported their symptoms to their doctors and received a medicine to alleviate them, but in all 30 cases, it was unsuccessful.

The aim of the study is to show and to raise awareness of the fact that the symptoms of hearing organ impairment are drug-related and only a modification of the currently used pharmacotherapy is a rational procedure in such cases. It is worth remembering that before deciding to introduce another drug to therapy, it is necessary to conduct a substantive analysis of the pharmacotherapy used by a patient and exclude the fact that the symptoms could be related to the pharmacological treatment used. Such a management should be a clinical standard so as not to expose a patient to further possible complications [3, 4, 6–8].

RESULTS

The results of this study are presented in Tab. I.

Tab. I. Results.

PATIENT, AGE (YEARS), SEX – M – MALE, K – FEMALE	COMORBIDITY	COMBINATION OF DRUGS THAT CAUSED THE SIDE EFFECTS	SIDE EFFECTS AND THE MECHANISM OF THEIR FORMATION	PRACTICAL THERAPEUTIC CONCLUSIONS
TS, 65, M	Degenerative disease, functional dyspepsia	Diclofenac + omeprazole + Ginkgo biloba	Dizziness, pharmacokinetic interaction, diclofenac is metabolised by hepatic CYP3A4 and CYP2C9, the combination of omeprazole, which inhibits CYP2C9 and Ginkgo biloba, which inhibits both CYP2C9 and CYP3A4, results in increased diclofenac concentration, which may increase the risk of dizziness	Omeprazole was changed to pantoprazole, Ginkgo biloba was discontinued, dizziness subsided
ZB, 72, K	Degenerative disease, atrial fibrillation	Naproxen + omeprazole + propafenone	Dizziness, pharmacokinetic interaction, naproxen is metabolised by hepatic CYP1A2 and CYP2C9, the combination of omeprazole, which inhibits CYP2C9 and CYP1A2, and propafenone, which inhibits CYP1A2, increases the concentration of naproxen, which may increase the risk of dizziness	Omeprazole was changed to pantoprazole, the dizziness subsided
WZ, 60, K	Depression with accompanying insomnia, peripheral circulatory disorder, atrial fibrillation	Mirtazapine + ticlopidine + amiodarone	Dizziness, pharmacokinetic interaction, mirtazapine is metabolised by CYP2D6 and CYP1A2, simultaneous use of ticlopidine – which inhibits CYP1A2 and amiodarone, which is an inhibitor of CYP2D6, increases the concentration of mirtazapine and may cause headaches	Ticlopidine was changed to clopidogrel, and mianserin with a lower potential for pharmacokinetic interactions with other drugs was used instead of mirtazapine, dizziness occurred
TH, 68, K	Insomnia, shoulder impingement syndrome, functional dyspepsia	Doxepin + celecoxib + omeprazole	Dizziness, pharmacokinetic interaction, the major pathway of hepatic metabolism of doxepin is through CYP2D6 and CYP2C19, while CYP1A2, CYP2C9, CYP3A4 are involved to a lesser extent	Doxepin was changed to trazodone, celecoxib to etoricoxib, omeprazole was changed to pantoprazole, the drugs used have a lower potential to induce side effects, dizziness subsided
WS, 89, K	Depression in dementia, condition after upper gastrointestinal bleeding	Sertraline + memantine + omeprazole	Dizziness, pharmacokinetic interaction, hepatic metabolism of sertraline is mediated by 5 cytochrome P-450 isoenzymes – 2B6, 2C9, 2C19, 2D6, 3A4, memantine is an inhibitor of CYP2B6, omeprazole inhibits the activity of CYP2C9, CYP2C19, as a result, the concentration of sertraline escalated leading to adverse reactions	Sertraline was changed to vortioxetine, omeprazole to pantoprazole due to the lower risk of interactions with other simultaneously taken drugs
DS, 59, K	Hypertension, postherpetic neuralgia, tinnitus	Amlodipine + buprenorphine + Ginkgo biloba	Dizziness, pharmacokinetic interaction, amlodipine is metabolised by CYP3A4, buprenorphine and Ginkgo biloba are inhibitors of CYP3A4, amlodipine level increase causing dizziness	Ginkgo biloba was discontinued, dizziness subsided
PR, 51, K	Atrial fibrillation, dyslipidemia, onychomycosis of the lower extremities	Atorvastatin + amiodarone + terbinafine	Dizziness, pharmacokinetic interaction, atorvastatin is metabolised by CYP3A4, amiodarone and terbinafine are CYP3A4 inhibitors and, as a result of the pharmacokinetic interaction, there is an increase of atorvastatin concentration which may induce dizziness	Atorvastatin was changed to rosuvastatin, which eliminated the described interactions, dizziness subsided
PU, 67, K	Dyslipidemia, insomnia, hepatotoxicity as a result of statin treatment	Atorvastatin + trazodone + milk thistle	Dizziness, pharmacokinetic interaction, atorvastatin is metabolised by CYP3A4, trazodone and milk thistle extracts have the ability to inhibit CYP3A4, thus increasing the serum concentration of atorvastatin	Atorvastatin was changed to rosuvastatin, milk thistle was discontinued, thus the described interactions were eliminated, dizziness subsided
WK, 82, K	Dyslipidemia, qualitative changes of consciousness	Simvastatin + haloperidol + Ginkgo biloba	Dizziness, pharmacokinetic interaction, simvastatin is metabolised by CYP3A4, both haloperidol and Ginkgo biloba have the ability to inhibit CYP3A4 activity, which in turn leads to an escalation of simvastatin levels and causes complications	Simvastatin was changed to rosuvastatin, Ginkgo biloba was discontinued, which eliminated the described interactions, dizziness subsided
PR, 61, M	Dyslipidemia, coronary artery disease, sinus tachycardia	Atorvastatin + ivabradine + diltiazem	Dizziness, pharmacokinetic interaction, atorvastatin is metabolised by CYP3A4, both ivabradine and diltiazem have the ability to inhibit CYP3A4 activity, which consequently leads to an escalation of simvastatin levels and causes complications	Atorvastatin was changed to rosuvastatin, which eliminated the described interactions, dizziness subsided

PATIENT, AGE (YEARS), SEX – M – MALE, K – FEMALE	COMORBIDITY	SCOMBINATION OF DRUGS THAT CAUSED THE SIDE EFFECTS	SIDE EFFECTS AND THE MECHANISM OF THEIR FORMATION	PRACTICAL THERAPEUTIC CONCLUSIONS
WK, 74, K	Chronic obstructive pulmonary disease, heart failure, dyslipidemia	Clarithromycin + carvedilol + atorvastatin	Hearing loss, pharmacokinetic interaction, hepatic metabolism of clarithromycin is mediated by CYP3A4 and P-glycoprotein, atorvastatin has the ability to inhibit CYP3A4 and P-gp, and carvedilol is an inhibitor of P-gp. This interaction led to an increase in clarithromycin levels and hearing loss	Clarithromycin was changed to azithromycin due to a lower risk of pharmacokinetic interactions with other simultaneously taken drugs, atorvastatin was changed to rosuvastatin due to a lower risk of pharmacokinetic interactions
EK, 52, K	Multiple H. pylori eradication attempts, post-mastectomy condition, estrogen-dependent breast cancer, dyslipidemia	Klarytromycyna + tamoksifen + atorwastatyna	Hearing loss, pharmacokinetic interaction, hepatic metabolism of clarithromycin is mediated by CYP3A4 and P-glycoprotein, atorvastatin has the ability to inhibit CYP3A4 and P-gp, and tamoxifen is an inhibitor of P-gp. This interaction led to an increase of clarithromycin levels and hearing loss	Clarithromycin was discontinued, atorvastatin was changed to rosuvastatin due to the lower risk of pharmacokinetic interactions with other drugs used simultaneously, the modification of the therapy resulted in the resolution of the described side effects
DG, 67, K	Insomnia, venous insufficiency, coronary artery disease	Doxepin + ticlopidine + metoprolol	Dizziness, pharmacokinetic interaction, ticlopidine is an inhibitor of CYP2C19, while metoprolol inhibits the activity of CYP2D6, both inhibited isoenzymes are involved in the metabolism of doxepin, dizziness may occur as one of the side effects due to an increased concentration of doxepin	Doxepin was changed to mirtazapine, ticlopidine was discontinued due to no indications for use, side effects resolved
SK, 63, K	Degenerative disease, dyslipidemia	Etoricoxib + Ginkgo biloba + atorvastatin	Tinnitus, pharmacokinetic interaction, Ginkgo biloba and atorvastatin are the inhibitors of CYP3A4 and by inhibiting this isoenzyme, they increase the concentration of etoricoxib, which may cause tinnitus as an adverse effect	Ginkgo biloba was discontinued, atorvastatin was changed to rosuvastatin, tinnitus subsided
BS, 61, K	Pain in the locomotor system, insomnia	Tramadol + Ginkgo biloba + diphenhydramine	Tinnitus, Gingko biloba inhibits the activity of CYP3A4, while diphenhydramine inhibits the activity of CYP2D6, which escalates the concentration of tramadol, which may induce tinnitus	Ginkgo biloba was discontinued, diphenhydramine was changed to mirtazapine, side effects subsided
RS, 71, K	Degenerative disease, arrhythmias, insomnia	Tramadol + metoprolol + diphenhydramine	Tinnitus, diphenhydramine, and metoprolol inhibit the activity of CYP2D6, which causes an escalation of the concentration of tramadol, which may induce tinnitus	Diphenhydramine was discontinued, metoprolol was changed to bisoprolol, the side effects subsided
PD, 78, K	Sciatica, atrial fibrillation, insomnia	Tramadol + quetiapine + propafenone	Tinnitus, diphenhydramine, and quetiapine inhibit the activity of CYP2D6 resulting in an escalated tramadol concentration which may induce tinnitus	Diphenhydramine was discontinued, quetiapine was changed to mirtazapine, side effects subsided
TF, 75, M	Depression, dizziness	Sertraline + Ginkgo biloba + omeprazole	Tinnitus, pharmacokinetic interaction, Ginkgo biloba inhibits the activity of CYP2C9, and omeprazole inhibits the activity of CYP2C9, CYP 2C19, resulting in escalated sertraline concentration, which may cause tinnitus	Ginkgo biloba was discontinued, omeprazole was changed to pantoprazole, side effects subsided
DO, 74, M	Atrial fibrillation, diabetic neuropathy, atrial fibrillation	Duloxetine + omeprazole + propafenone	Tinnitus, pharmacokinetic interaction, omeprazole and propafenone have the ability to inhibit CYP1A2 activity, the interaction leads to escalated duloxetine concentrations which may cause tinnitus	Omeprazole was changed to pantoprazole, the side effects subsided
WS, 67, K	Hypertension, depression, dizziness	Amlodipine + Ginkgo biloba + trazodone	Tinnitus, pharmacokinetic interaction, Ginkgo biloba and trazodone, especially at doses above 150 mg daily, inhibit the activity of CYP3A4, which results in an escalation of amlodipine levels, which may cause tinnitus	Ginkgo biloba was discontinued, unfortunately, it was not possible to replace trazodone with another antidepressant, the intensity of tinnitus was significantly reduced

PATIENT, AGE (YEARS), SEX – M – MALE, K – FEMALE	COMORBIDITY	SCOMBINATION OF DRUGS THAT CAUSED THE SIDE EFFECTS	SIDE EFFECTS AND THE MECHANISM OF THEIR FORMATION	PRACTICAL THERAPEUTIC CONCLUSIONS
SK, 62, K	Hypertension, toenail fungus	Amlodipine + Ginkgo biloba + terbinafine	Tinnitus, pharmacokinetic interaction, Ginkgo biloba and terbinafine inhibit the activity of CYP3A4 resulting in an escalation of amlodipine levels which may cause tinnitus	Ginkgo biloba was discontinued, terbinafine was changed to the topical form of ciclopiroxolamine (nail varnish) the symptoms described subsided
BW, 70, M	Hypertension, insomnia	Irbesartan + omeprazole + lorazepam	Irbesartan is metabolised in the liver via CYP2C9 and is also conjugated with glucuronic acid, omeprazole is an inhibitor of CYP2C9, and omeprazole is an inhibitor of glucuronidation, these interactions lead to an increase in irbesartan concentrations which may cause tinnitus	Irbesartan was changed to telmisartan which has no clinically significant pharmacokinetic interactions with other drugs, omeprazole is changed to pantoprazole, tinnitus is subsided
TD, 74, K	Depression, atrial fibrillation	Vortioxetine + amiodarone + propafenone	Tinnitus, which may be induced by vortioxetine, amiodarone and propafenone are the inhibitors of CYP 2D6, in addition, amiodarone inhibits CYP3A4 resulting in inhibition of vortioxetine metabolism	Due to the worsened tinnitus and the inability to discontinue amiodarone and propafenone, vortioxetine was replaced with agomelatine, resulting in a resolution of tinnitus
WA, 76, M	Prostatic hypertrophy, atrial fibrillation	Doxazosin + amiodarone	Tinnitus, pharmacokinetic interaction, amiodarone has the ability to inhibit the activity of CYP2C9 and CYP2D6 with a consequent escalation of doxazosin concentration which may cause tinnitus as an adverse effect	Doxazosin was changed to uroselective tamsulosin, side effects subsided
PG, 81, M	Prostatic hypertrophy, post-stroke condition, insomnia	Doxazosin + atorvastatin + diphenhydramine	Tinnitus, pharmacokinetic interaction, atorvastatin has the ability to inhibit CYP3A4 activity, while diphenhydramine is an inhibitor of CYP2D6 with a consequent escalation of doxazosin concentration which may cause tinnitus as an adverse effect	Doxazosin was changed to uroselective tamsulosin, diphenhydramine was also discontinued due to its cholinolytic effect, which may limit the effectiveness of alpha-1 blockers used in patients with prostatic hypertrophy, the side effects subsided
UK, 81, K	Depression, insomnia, cataracts	Escitalopram + Ginkgo biloba + omeprazole + quetiapine	Tinnitus, pharmacokinetic interaction, Ginkgo biloba and omeprazole have the ability to inhibit the activity of CYP2C19, while quetiapine inhibits the activity of CYP2D6 with the consequent escalation of the concentration of escitalopram which may cause tinnitus as an adverse effect	Ginkgo biloba was discontinued, omeprazole was changed to pantoprazole, the side effects subsided
BA, 77, M	Degenerative disease	Acemetacin + Ginkgo biloba + omeprazole	Tinnitus, pharmacokinetic interaction, Ginkgo biloba and omeprazole have the ability to inhibit the activity of CYP2C9, CYP2C19 and consequently escalate the concentration of indomethacin, which is formed from acemetacin as the prodrug. Indomethacin is metabolized by CYP2C9, CYP2C19, escalation of its concentration as an adverse effect may cause tinnitus	Ginkgo biloba was discontinued, omeprazole was changed to pantoprazole, the side effects subsided
ZB, 72, K	Rheumatoid arthritis, cataracts	Diclofenac + Ginkgo biloba + omeprazole	Tinnitus, pharmacokinetic interaction, Ginkgo biloba inhibits the activity of CYP3A4 and CYP2C9 isoenzymes, while omeprazole has the ability to inhibit the activity of CYP2C9, escalation of diclofenac concentration may cause tinnitus	Ginkgo biloba was discontinued, omeprazole was changed to pantoprazole, the side effects subsided
RN, 74, K	Osteoarthritis, post--herpetic neuropathy	Diclofenac + omeprazole + buprenorphine	Tinnitus, pharmacokinetic interaction, buprenorphine inhibits the activity of the CYP3A4 isoenzyme, while omeprazole has the ability to inhibit the activity of CYP2C9, escalation of diclofenac concentration may cause tinnitus	Omeprazole was changed to pantoprazole, buprenorphine to tapentadol, the described side effects subsided
BR, 70, M	Depression, peripheral circulatory disorders	Sertraline + omeprazole + clopidogrel	Tinnitus, pharmacokinetic interaction, clopidogrel is a strong inhibitor of the isozyme CYP2B6, while omeprazole inhibits the activity of the isoenzymes CYP2C19 and CYP2C9, the interaction leads to an escalation of the concentration of sertraline which may cause tinnitus as an adverse effect	Omeprazole was changed to pantoprazole, and clopidogrel to sulodexide, side effects subsided

Tab. II. Drugs that induce dizziness.

DRUG GROUP	ACTIVE SUBSTANCES WHICH MOST COMMONLY MAY INDUCE DIZZINESS AS AN ADVERSE REACTION
Non-opioid analgesics	Ibuprofen Celecoxib Diclofenac Naproxen Acetylsalicylic acid Paracetamol
Antidepressants	Mirtazapine Paroxetine Sertraline Amitriptyline Doxepin Trazodone
Fluoroquinolones	Ciprofloxacin Levofloxacin
Macrolides and azalides	Clarithromycin Azithromycin
Angiotensin converting enzyme inhibitors	Zofenopril, enalapril
AT1 antagonists	Irbesartan
Calcium antagonists	Amlodipine, lacidipine
Muco-regulating drugs	Carbocysteine
Statins	Atorvastatin, simvastatin
Azole antifungal drugs	Itraconazole, fluconazole
Antipsychotic drugs	Clozapine
Drugs that act on the dopaminergic system	Bromocriptine, Levodopa

Tab. III. Drugs that can cause hearing loss as an adverse reaction.

Macrolide antibiotics and azalides – clarithromycin, azithromycin
Other antibiotics – amikacin, vancomycin
Fluoroquinolones – moxifloxacin
Methotrexate
Fluorouracil
Vinca alkaloids
Paclitaxel
Cisplatin
Interferon alpha-2b
Thalidomide

Tab. IV. Drugs that may induce tinnitus.

DRUG GROUP	ACTIVE SUBSTANCES THAT MOST OFTEN INDUCE TINNITUS
Alpha-1 blockers	Doxazosin
Beta blockers	Metoprolol, nebivolol, bisoprolol
Calcium antagonists	Amlodipine
Angiotensin converting enzyme inhibitors	Ramipril
AT1 antagonists	Irbesartan
PDE5 inhibitors	Tadalafil, sildenafil
Analgesics	Indomethacin Diclofenac Etoricoxib Tramadol
Antidepressants	Paroxetine Escitalopram Sertraline Vortioxetine Duloxetine
Topical ophthalmic medications for the treatment of glaucoma	Timolol
Other drugs	Anti-tuberculosis drugs Sofosbuvir Ledipasvir Etoposide Abatacept

Tab. V. Special populations of patients at increased risk of pharmacotherapy-induced adverse reactions.

Elderly patients
Comorbid anxiety disorders
Depression
Insomnia
Inefficiently treated pain
Concomitant electrolyte deficiencies
Multi-drug intolerance syndrome
Patients sensitive to the nocebo effect
Loneliness

DISCUSSION

In all the described cases, the existence of a cause-and-effect relationship between the applied polytherapy and the occurrence of the symptoms reported by the patient was established. In a situation where we use polypharmacotherapy, we must always remember not to generate interactions between drugs when combining them and to modify the therapy in such a way as to minimize the risk of complications. The most common interactions we encounter in the practice of an otolaryngologist are related to the pharmacokinetic profile of the drugs used, and in particular to the influence of these drugs on cytochrome P450 isoenzymes, which are involved in the metabolism of numerous drugs. The second problem that we encounter in practice is the simultaneous use of drugs that exhibit a similar profile of side effects, so if they are combined, we can deal with the sum of side effects, and this may cause complications in the patient with the different clinical picture. The most important in practice is the knowledge of individual clinical symptoms of complications and their correlation with the medications taken by the patient. Drugs that most commonly induce adverse reactions with which patients may report to an otolaryngologist are summarized in Tab. II.–IV. On the other hand, it is important to remember about special populations of patients with an increased risk of drug-related complications [4, 6–8].

It should also not be forgotten that some patient populations may be characterized by an increased risk of adverse reactions to pharmacotherapy. These special patient groups are summarized in Tab. V.

In our work, commonly used medicinal products containing Ginkgo biloba extracts often caused interactions with concomitantly taken drugs. Drugs used in dizziness or tinnitus, as we have shown in our work, due to the inhibitory effect on several cytochrome P450 isoenzymes, may, in the pharmacokinetic mechanism, even cause symptoms such as dizziness or tinnitus.

In turn, when there are indications for the use of drugs from the group of proton-pump inhibitors, and a patient uses polytherapy, omeprazole should be avoided due to the significant risk of pharmacokinetic interactions – this drug inhibits the metabolism of other drugs, often used in polypharmacotherapy. In the group of patients using polypharmacotherapy, if there are indications for the use of proton-pump inhibitors, the use of pantoprazole or dexlansoprazole is recommended due to the lowest risk of pharmacokinetic interactions in this group of drugs.

Attention should also be paid to patients taking antidepressants and neuroleptics also due to the risk of pharmacokinetic interactions related to the influence of these drugs on the activity of cytochrome P450 isoenzymes, which are involved in the hepatic metabolism of drugs [2–5].

Finally, the legal aspect cannot be overlooked. When prescribing a drug, a physician issues a decision on the patient's health condition (Article 42 of the Physician and Dentist Professions Act). The decision shows that the patient has medical indications for taking a specific medicinal product and there are no contraindications. The so-called pharmaceutical cascade is an unequivocal medical error. The essence of this error is that acting in accordance with medical knowledge, the doctor should determine that a certain symptom is the result of an adverse reaction and not a symptom of a new disease. In the event of a court case – depending on the circumstances – the doctor may be charged if he does not recognize that the symptom is due to side effects. In particular, the cases of adverse reactions described in the article could lead to the professional liability of a physician (before medical courts) and civil liability of a physician for violation of the patient's right to benefits in accordance with current medical knowledge.

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Corresponding author: Jarosław Woroń MD PhD; Department of Clinical Pharmacology, Department of Pharmacology, Faculty of Medicine, Jagiellonian University Medical College in Krakow; Grzegórzecka street 16, 31-531 Krakow, Poland; Phone: +48 12 421 1168; E-mail: woron@medi-pharm.pl

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