Research Results in Pharmacology

Research Results in Pharmacology 5(4): 1–6
UDC: 615.065
DOI 10.3897/rrpharmacology.5.39681

Research Article

Potential drug-drug interactions in the psychiatric hospital: Frequency analysis

Oleg O. Kirilochev[1], Inna P. Dorfman[1], Adelya R. Umerova[1], Svetlana E. Bataeva[1]

1 *Astrakhan State Medical University, 121 Bakinskaya St., Astrakhan 414000 Russian Federation*

Corresponding author: *Oleg O. Kirilochev* (kirilochev@gmail.com)

Academic editor: *Tatyana Pokrovskaya* ♦ **Received** 3 September 2019 ♦ **Accepted** 27 October 2019 ♦ **Published** 12 December 2019

Citation: Kirilochev OO, Dorfman IP, Umerova AR, Bataeva SE (2019) Potential drug-drug interactions in the psychiatric hospital: Frequency analysis. Research Results in Pharmacology 5(4): 1–6. https://doi.org/10.3897/rrpharmacology.5.39681

Abstract

Introduction: Drug-drug interactions are an important clinical problem in pharmacotherapy. This study is focused on different types of drugs used in a psychiatric hospital.

Materials and methods: The pharmacoepidemiological study included the analysis of medical records of 500 psychiatric inpatients. The patients were divided into 2 groups: under 65 and over 65 years of age. All the drug prescriptions were analyzed to identify the combinations of drugs that can induce drug-drug interactions and determine their clinical significance.

Results and discussion: Over 77% of hospitalized patients were administered drug combinations that could induce drug-drug interactions, most of which were of moderate clinical significance. A reliable association was found between the patient's age, the clinical significance of drug-drug interactions, and the pharmacotherapy structure. The most common irrational drug combinations were identified.

Conclusion: Timely analysis of drug prescriptions for potential drug-drug interactions can enhance the safety of pharmacotherapy and decrease the risk of adverse drug reactions in the psychiatric inpatient setting.

Keywords

adverse drug reactions, drug-drug interactions, pharmacotherapy safety.

Introduction

The current rational drug therapy of psychiatric diseases is based on the two main principles of efficacy and safety. The former aspect is quite successfully controlled by clinical practitioners on the basis of changes in the clinical condition, whereas safety monitoring requires certain skills from the physician. A correct drug combination is one of the approaches to safe psychopharmacotherapy. Comorbidities, drug resistance, and willingness to accelerate recovery are the causes of multiple drug prescription, which increases the risk of adverse drug reactions, which in this case are mainly due to drug-drug interactions.

Drug-drug interactions lead to changes in the efficacy and safety of a medication administered concomitantly or sequentially with another medication. Investigators believe that the rather frequent development of adverse effects as a result of the aforementioned mechanism may be associated with some underestimation of the risk by clinical practitioners (Hahn et al. 2013, de Leon 2019) and depends on the number of co-administered medications (Castilho et al. 2018). Development of adverse drug

reactions resulting from the use of an irrational drug combination can lead to drug-induced issues associated with a worsening clinical condition of the patient, prolonged hospitalization, higher expenses for a healthcare institution, and, according to some authors, decreased life expectancy (Oertle 2012, Murtaza et al. 2015).

It should be mentioned that irrational combinations do not necessarily involve drug-drug interactions; therefore this paper will touch upon potential interactions. According to B.Astrand, 17% to 23% of drug combinations are associated with such a risk, and only from 6% to 8% of them actually result in an interaction (Astrand 2009). However, a number of factors, such as a narrow therapeutic index of many psychoactive drugs (Spina et al. 2016, Hiemke et al. 2018), predominantly hepatic metabolism involving the cytochrome P450 system (Guo et al. 2012, de Leon and Spina 2018), and antipsychotic polytherapy (use of several antipsychotic drugs) (Tranulis et al. 2008, Correll et al. 2009, Misawa et al. 2011), can increase the occurrence of drug-drug interactions in the treatment of psychiatric inpatients.

In view of the existing risk of decreased safety of drug therapy, timely identification of irrational combinations and prediction of drug-drug interactions appears to be the optimal approach. Foreign researchers believe that consideration of potential drug-drug interactions allows to avoid up to 72% of adverse drug reactions (Pirmohamed et al. 2004) and that their timely identification is an essential treatment safety factor (Andersson et al. 2013).

Objective of the Study: To conduct a frequency analysis of potential drug-drug interactions in the psychiatric hospital.

Materials and methods

This was a pharmacoepidemiological study that included an analysis of medical records of patients hospitalized in a psychiatric medical institution, undertaken to identify combinations of drugs that could be involved in an interaction. This analysis was aided by a drug-drug interaction identification tool, the Drug Interaction Checker found at http://www.drugs.com, which provides data that is in agreement with the official prescribing information for medicinal products approved by the United States Food and Drug Administration (FDA).The information obtained on potential drug-drug interactions was compared with the official instructions for medical use from the State Register of Medicines. The Drug Interaction Checker divides potential interactions into major (highly clinically significant, potentially hazardous), moderate (moderately clinically significant), and minor (least clinically significant) ones, based on clinical significance grade.

The inclusion criteria for the study were the presence in the patient's prescription list of a medications of the Psycholeptics or Psychoanaleptics subgroup (Anatomical Therapeutic Chemical Classification System codes N05 and N06) and polypharmacy (concomitant use of 5 or more medications).

Statistical processing of the data was performed by means of descriptive statistics, as well as the non-parametric Pearson's chi-squared test, using the AnalystSoft Inc., StatPlus:mac, Version 6.8.1.0 software.

Results and discussion

The study enrolled 500 patients receiving psychiatric care in inpatient settings. Since elderly patients are at higher risk of serious adverse drug reactions as a result of polypharmacy and physiological specifics, the sample was divided into 2 equal groups: patients under 65 and over 65 years of age. This division is used by most foreign tools designed to counteract irrational drug prescription in elderly patients. The mean age of the study subjects was 62.23 ± 16.11 years; in patients under 65, it was 49.32 ± 11.76 years, and in patients aged over 65, the mean age was 75.14 ± 6.88 years. Of the younger subjects, 106 (42.40%) were males and 144 (57.60%) were females. In the elderly patients' group, 72 (28.80%) were males and 178 (71.20%) were females. Overall, there were 178 (35.60%) male and 322 (64.40%) female subjects.

The mean number of administered drugs was 7.67 ± 2.11; in patients under 65 it was 7.27 ± 1.83, and patients aged over 65 received 8.07 ± 2.30 drugs concomitantly. Assessment of co-administration percentages revealed that most subjects (21%) concomitantly received 6 medications, while 17.2%, 16.4%, 14.8%, and 11% of the patients were co-administered 8, 7, 5, and 9 drugs, respectively. The proportions of patients with other numbers of co-administered drugs were less than 10%. It should be emphasized that all the medications recorded in the prescription lists were registered under their international nonproprietary names for the purpose of this study, with active ingredients in combination drugs considered separately. The pharmacological characteristics of drugs prescribed to the study subjects are categorized in accordance with the international Anatomical Therapeutic Chemical (ATC) Classification System (Table 1).

The nosological analysis of the sample revealed that 155 (31%) and 152 (30.4%) patients were diagnosed with "Other mental disorders due to brain damage and dysfunction and to physical disease" and "Schizophrenia", respectively. "Dementia in other diseases classified elsewhere" was diagnosed in 65 patients (13.6%), "Vascular dementia" – in 36 (7.2%), "Personality and behavioural disorders due to brain disease, damage and dysfunction" – in 14 (2.8%), "Schizoaffective disorders" – in 11 (2.2%), "Other anxiety disorders" – in 11 (2.2%), "Dementia in Alzheimer's disease" – in 10 (2%), "Moderate mental retardation" – in 9 (1.8%), and "Specific personality disorders" – in 6 (1.2%) patients. Diagnoses that had a frequency of less than 1% are not mentioned.

The analysis of the prescription rates of drug combinations which can lead to drug-drug interactions in the psychiatric inpatient setting demonstrated that 386 (77.2%) subjects were at risk; such combinations were taken by

Table 1. Pharmacological characteristics of prescribed drugs in accordance with the ATC classification system

ATC code	Number of drugs	Percentage (%)
N05 Psycholeptics	19	12.58%
N06 Psychoanaleptics	18	11.92%
J01 Antibacterials for systemic use	17	11.26%
A11 Vitamins	6	3.97%
A02 Drugs for acid related disorders	5	3.31%
A10 Drugs used in diabetes	5	3.31%
B03 Antianemic preparations	5	3.31%
B05 Blood substitutes and perfusion solutions	5	3.31%
C01 Cardiac therapy	5	3.31%
C07 Beta blocking agents	5	3.31%
N04 Anti-parkinson drugs	5	3.31%
R06 Antihistamines for systemic use	5	3.31%
C03 Diuretics	4	2.65%
C09 Agents acting on the renin-angiotensin system	4	2.65%
N07 Other nervous system drugs	4	2.65%
B01 Antithrombotic agents	3	1.99%
C08 Calcium channel blockers	3	1.99%
C10 Lipid modifying agents	3	1.99%
J05 Antivirals for systemic use	3	1.99%
N03 Antiepileptics	3	1.99%
A03 Drugs for functional gastrointestinal disorders	2	1.32%
A12 Mineral supplements	2	1.32%
C05 Vasoprotectives	2	1.32%
J04 Antimycobacterials	2	1.32%
M01 Anti-inflammatory and antirheumatic products	2	1.32%
A05 Bile and liver therapy	1	0.66%
A07 Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	1	0.66%
A09 Digestives, including enzymes	1	0.66%
A13 Tonics	1	0.66%
B06 Other hematological agents	1	0.66%
C04 Peripheral vasodilators	1	0.66%
G04 Urologicals	1	0.66%
H02 Corticosteroids for systemic use	1	0.66%
M03 Muscle relaxants	1	0.66%
N02 Analgesics	1	0.66%
R05 Cough and cold preparations	1	0.66%
R07 Other respiratory system products	1	0.66%
S01 Ophthalmologicals	1	0.66%
V03 All other therapeutic products	1	0.66%

199 (79.6%) elderly patients and 187 (74.8%) subjects under 65 years of age, which was not statistically significant, apparently due to the fact that polypharmacy was an inclusion criterion in this study and because the patients under 65 years of age also received 5 or more medications at baseline. Out of 500 patients, 114 (22.8%) had no risk of drug-drug interaction.

There were 1352 cases of drug combinations potentially leading to a drug-drug interaction in the study sample in total; 652 (48.22%) of these cases were registered in patients under 65 years of age and 700 (51.78%) – in subjects aged over 65 years. The number of unique drug pairs was 373.

The analysis of the frequency of occurrence of irrational drug combinations by their clinical significance grade is of particular practical interest for predicting the risk of adverse drug reactions resulting from drug-drug interactions. The results of the analysis are presented in Table 2.

As Table 2 shows, highly significant drug interactions (potentially hazardous, major) were observed in 6.14% of the elderly patients and 17.02% of the subjects under 65 years of age, whereas interactions of moderate clinical significance accounted for most of the cases (78.77%). With regard to patients with different clinical significance grades of drug-drug interactions, potential major interactions prevailed in patients under 65 years of age (odds ratio [OR] = 3.512, 95% confidence interval [CI] 2.251–5.479); while moderate (OR = 1.496, 95% CI 1.007–2.221) and minor (OR = 4.125, 95% CI 2.412–7.054) interactions prevailed in patients over 65 years of age (statistically significant difference).

On the basis of the obtained results, the goal of the present study was to determine the possible causes of this distribution. To do this, all the potential drug interactions were divided into 3 groups based on the pharmacological class of the medication and a type of the hospital: interactions between neurotropic drugs, interactions between neurotropic drugs and somatic drugs, and interactions between somatic drugs. According to the ATC Classification System developed by the WHO, in this study all the medications affecting the nervous system (code N) were classified as neurotropic drugs and all other drugs as "so-

Table 2. Pharmacoepidemiological characteristics of potential drug-drug interactions by clinical significance grade

Potential drug-drug interactions by clinical significance grade	Patients under 65 years of age: n (%)	Patients over 65 years of age: n (%)	Total number of patients: n (%)
Number of major interactions	111 (17.02%)	43 (6.14%)	154 (11.39%)
Number of moderate interactions	502 (76.99%)	563 (80.43%)	1065 (78.77%)
Number of minor interactions	39 (5.98%)	94 (13.43%)	133 (9.84%)
Number of patients (major interactions)	89* (35.60%)	34 (13.60%)	123 (24.60%)
Number of patients (moderate interactions)	171* (68.40%)	191 (76.40%)	362 (72.40%)
Number of patients (minor interactions)	20* (8.00%)	66 (26.40%)	86 (17.20%)

Notes: * – p<0.05, statistically significant differences between study groups.

matic" drugs. This division was used to establish the role of principal drugs for the treatment of psychiatric diseases in the development of drug interactions, their clinical significance and association with the patient's age. The main results of this analysis are presented in Table 3.

The detected predominance of potential major (OR = 2.407, 95% CI 1.093–5.303) and moderate (OR = 4.877, 95% CI 3.735–6.368) drug-drug interactions between neurotropic medications in patients under 65 years of age was due to antipsychotic polypharmacy, attempts to overcome drug resistance, and, possibl,y practitioners' focus on the efficacy of the drug therapy rather than its safety due to the age of patients in this group. The predominance of potential major (OR = 6.688, 95% CI 2.131–20.991) and moderate (OR = 5.444, 95% CI 3.965–7.477) drug-drug interactions between somatic drugs in patients above 65 years of age was apparently due to comorbidities of the elderly and, as a result, to the changes in the pharmacological structure of drugs involved in interactions.

It should be mentioned that the Drug Interaction Checker tool, which was used to detect potential drug interactions, prescribes certain courses of action for clinical practitioners and grades interactions in the following manner: "Contraindicated", "Generally avoid", "Monitor closely", "Adjust dose" for major interactions; "Generally avoid", "Monitor", "Adjust dose", "Adjust dosing interval" for moderate interactions. An assessment of the frequency of potential drug interactions depending on the case management strategy is presented in Table 4. Minor interactions do not require strategy-based grading.

The identification of certain potentially interacting drug pairs is of particular importance and significance, because

Table 3. Occurrence of drug-drug interactions based on drug prescription structure

Drug-drug interactions based on drug prescription structure	Major (under 65 years of age)	Major (over 65 years of age)
Neurotropic + Neurotropic	91* (81.2%)	27 (64.2%)
Neurotropic + Somatic	16 (14.2%)	5 (11.9%)
Somatic + Somatic	5* (4.4%)	10 (23.8%)
Drug-drug interactions based on drug prescription structure	**Moderate (under 65 years of age)**	**Moderate (over 65 years of age)**
Neurotropic + Neurotropic	290* (57.8%)	124 (21.9%)
Neurotropic + Somatic	151 (30.1%)	200 (35.4%)
Somatic + Somatic	60* (11.9%)	240 (42.5%)
Drug-drug interactions based on drug prescription structure	**Minor (under 65 years of age)**	**Minor (over 65 years of age)**
Neurotropic + Neurotropic	1 (2.5%)	0 (0%)
Neurotropic + Somatic	10* (25.6%)	10 (10.6%)
Somatic + Somatic	28* (71.7%)	84 (89.3%)

Notes: * – p<0.05, statistically significant differences between study groups.

Table 4. Pharmacoepidemiological characteristics of potential drug-drug interactions according to management strategy

Potential drug-drug interactions by management strategy	Patients under 65 years of age: n (%)	Patients over 65 years of age: n (%)	Total number of patients: n (%)
Types of major interactions and frequency			
Contraindicated	32 (28.83%)	11 (25.58%)	43 (27.92%)
Generally avoid	1 (0.90%)	0 (0.00%)	1 (0.65%)
Monitor closely	78 (70.27%)	32 (74.42%)	110 (71.43%)
Adjust dose	0 (0.00%)	0 (0.00%)	0 (0.00%)
Types of moderate interactions and frequency			
Generally avoid	1 (0.20%)	7 (1.24%)	8 (0.75%)
Monitor	498 (99.20%)	541 (96.09%)	1039 (97.56%)
Adjust dose	0 (0.00%)	1 (0.18%)	1 (0.09%)
Adjust dosing interval	3 (0.60%)	14 (2.49%)	17 (1.60%)

Table 5. Pharmacoepidemiological Characteristics of Irrational Drug Combinations and Their Occurrence

Interacting drug pairs	Number	Percentage	Clinical significance grade
haloperidol + trihexyphenidyl	72	5.33%	Moderate
acetylsalicylic acid + enalapril	49	3.62%	Moderate
clozapine + trihexyphenidyl	43	3.18%	Moderate
chlorpromazine + trihexyphenidyl	38	2.81%	Moderate
enalapril + thioridazine	34	2.51%	Moderate
clozapine + haloperidol	30	2.22%	Major
acetylsalicylic acid + metoprolol	29	2.14%	Minor
chlorpromazine + haloperidol	27	2.00%	Major
acetylsalicylic acid + bisoprolol	21	1.55%	Minor
trifluoperazine + trihexyphenidyl	21	1.55%	Moderate
amitriptyline + trihexyphenidyl	19	1.41%	Moderate
acetylsalicylic acid + lisinopril	19	1.41%	Moderate
carbamazepine + chlorpromazine	19	1.41%	Moderate
enalapril + risperidone	15	1.11%	Moderate
risperidone + trihexyphenidyl	15	1.11%	Moderate

this may help draw the practitioner's attention to the most clinically relevant combinations. The frequency rates of these combinations detected during the pharmacoepidemiological analysis of drug therapy in psychiatric inpatient settings are presented in Table 5. Combinations with occurrence rates of less than 1% are excluded from the table.

The aforementioned most common drug combinations warrant some comment. The most common potential drug-drug interaction, that between haloperidol and trihexyphenidyl, is moderate and, based on the information included in the Drug Interaction Checker database, can result in CNS inhibition, development of tardive dyskinesia, and enhanced anticholinergic effects on the body. Evidently, in most cases this combination is used to treat extrapyramidal disorders developing during neuroleptic therapy; however, the practitioner should remember about the possible adverse effects of this therapy and avoid prescribing antiparkinsonian drugs for prophylactic purposes, which is also confirmed in the clinical guidelines for the diagnosis and treatment of schizophrenia. The same type of interaction was registered for the third and fourth most common drug combinations, clozapine plus trihexyphenidyl and chlorpromazine plus trihexyphenidyl, as well as for the combinations of trifluoperazine plus trihexyphenidyl, amitriptyline plus trihexyphenidyl, and risperidone plus trihexyphenidyl.

The second most common potential drug interaction, that between acetylsalicylic acid and enalapril, and the combination of acetylsalicylic acid plus lisinopril, which was among the top fifteen combinations, have the same mechanism of action and require the same management strategy. This interaction may result in diminished effects of ACE inhibitors due to blocked prostaglandin synthesis. To a lesser extent, this applies to low doses of acetylsalicylic acid, which was observed in the present study. However, the potential of acetylsalicylic acid to increase the incidence of decompensated conditions should be borne in mind (Ponikowski et al. 2016).

The fifth most common combination, enalapril plus thioridazine, as well as the combination of enalapril and risperidone, is classified as moderate and associated with a possible increase in the hypotensive effect of the ACE inhibitor during antipsychotic therapy and with a risk of orthostatic hypotension.

The combinations of clozapine plus haloperidol and chlorpromazine plus haloperidol are the only ones classified according to the potential drug interaction identification tool (Drug Interaction Checker) as major and dangerous, and observed in more than 1% of all the cases. The former combination is associated with a risk of orthostatic hypotension, collapse, respiratory depression, and enhanced anticholinergic effects. The latter combination may be associated with prolongation of the QT interval on the electrocardiogram and a risk of "torsade de pointes". It should be emphasized that the service used in the study permits use of this treatment and allows, in some cases, administration of antipsychotic combination therapy; however, it prescribes "Monitor closely" as a management strategy.

Combinations of acetylsalicylic acid and beta-blockers have the lowest clinical significance, particularly with the anti-platelet agent's doses recommended for use. The pair of carbamazepine and chlorpromazine requires monitoring of the general depressant effects on the central nervous and respiratory systems.

Conclusion

The reported analysis of frequency of potential drug interactions in the psychiatric hospital yielded the following findings. Over 77% of the hospitalized patients were administered drug combinations that could induce drug-drug interactions, most of which were classified as potential interactions of moderate clinical significance. Comparing age-related specifics, it was found that major potential drug interactions, particularly between neurotropic agents, prevailed in patients under 65 years of age, whereas moderate and minor interactions, particularly between somatic drugs, were predominant in patients aged over 65 years. A timely analysis of drug prescriptions for potential drug-drug interactions can enhance the safety of pharmacotherapy and decrease the risk of adverse drug reactions in the psychiatric inpatient setting.

References

- Andersson ML, Böttiger Y, Lindh JD, Wettermark B, Eiermann B (2013) Impact of the drug-drug interaction database SFINX on prevalence of potentially serious drug-drug interactions in primary health care. European Journal of Clinical Pharmacology 69(3): 565–571. https://doi.org/10.1007/s00228-012-1338-y [PubMed]
- Astrand B (2009) Avoiding drug-drug interactions. Chemotherapy 55(4): 215–220. https://doi.org/10.1159/000218100 [PubMed]
- Castilho ECD, Reis AMM, Borges TL, Siqueira LDC, Miasso AI (2018) Potential drug-drug interactions and polypharmacy in institutionalized elderly patients in a public hospital in Brazil. Journal of Psychiatric and Mental Health Nursing 25(1): 3–13. https://doi.org/10.1111/jpm.12431 [PubMed]
- Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S (2009) Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophrenia Bulletin 35(2): 443–457. https://doi.org/10.1093/schbul/sbn018 [PubMed] [PMC]
- Guo JJ, Wu J, Kelton CML, Jing Y, Fan H, Keck PE, Patel NC (2012) Exposure to potentially dangerous drug-drug interactions involving antipsychotics. Psychiatric Services (Washington, DC) 63(11): 1080–1088. https://doi.org/10.1176/appi.ps.201100443 [PubMed]
- Hahn M, Reiff J, Hiemke C, Braus D (2013) Drug-drug-interactions in psychiatry. Psychiatrische Praxis 40(03): 154–158. https://doi.org/10.1055/s-0032-1332831 [PubMed]
- Hiemke C, Bergemann N, Clement H, Conca A, Deckert J, Domschke K, Eckermann G, Egberts K, Gerlach M, Greiner C, Gründer G, Haen E, Havemann-Reinecke U, Hefner G, Helmer R, Janssen G, Jaquenoud E, Laux G, Messer T, Mössner R, Müller M, Paulzen M, Pfuhlmann B, Riederer P, Saria A, Schoppek B, Schoretsanitis G, Schwarz M, Gracia M, Stegmann B, Steimer W, Stingl J, Uhr M, Ulrich S, Unterecker S, Waschgler R, Zernig G, Zurek G, Baumann P (2018) Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. Pharmacopsychiatry 51(01/02): 9–62. https://doi.org/10.1055/s-0043-116492 [PubMed]
- de Leon J (2019) Why do you keep telling me that drug-drug interactions are important in psychopharmacology when I do not see them in my clinical practice?: My failure to convince clinicians. Journal of Clinical Psychopharmacology 39(1): 1–4. https://doi.org/10.1097/JCP.0000000000000924 [PubMed]
- de Leon J, Spina E (2018) Possible pharmacodynamic and pharmacokinetic drug-drug interactions that are likely to be clinically relevant and/or frequent in bipolar disorder. Current Psychiatry Reports 20: 17. https://doi.org/10.1007/s11920-018-0881-3 [PubMed]
- Misawa F, Shimizu K, Fujii Y, Miyata R, Koshiishi F, Kobayashi M, Shida H, Oguchi Y, Okumura Y, Ito H, Kayama M, Kashima H (2011) Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects?: a cross-sectional study. BMC Psychiatry 11: 118. https://doi.org/10.1186/1471-244X-11-118 [PubMed] [PMC]
- Murtaza G, Khan MYG, Azhar S, Khan SA, Khan TM (2015) Assessment of potential drug-drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharmaceutical Journal 24(2): 220–225. https://doi.org/10.1016/j.jsps.2015.03.009 [PubMed] [PMC]
- Oertle M (2012) Frequency and nature of drug-drug interactions in a Swiss primary and secondary acute care hospital. Swiss Medical Weekly 142: w13522. https://doi.org/10.4414/smw.2012.13522 [PubMed]
- Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ (Clinical research ed.) 329: 15–19. https://doi.org/10.1136/bmj.329.7456.15 [PubMed] [PMC]
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal 37(27): 2129–2200. https://doi.org/10.1093/eurheartj/ehw128 [PubMed]
- Spina E, Hiemke C, de Leon J (2016) Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. Expert Opinion on Drug Metabolism & Toxicology 12(4): 407–422. https://doi.org/10.1517/17425255.2016.1154043 [PubMed]
- Tranulis C, Skalli L, Lalonde P, Nicole L, Stip E (2008) Benefits and risks of antipsychotic polypharmacy. Drug Safety 31(1): 7–20. https://doi.org/10.2165/00002018-200831010-00002 [PubMed]

Author contributions

- **Oleg O. Kirilochev**, PhD of Medical Sciences, Associate Professor of the Department of Clinical Pharmacology, e-mail: kirilochev@gmail.com, **ORCID:** 0000-0002-8788-8510. The author had a leading role in planning and performing the experiment, analyzing the data and literature and writing the article.

- **Inna P. Dorfman**, PhD of Medical Sciences, Associate Professor of the Department of Clinical Pharmacology, e-mail: inna1977@inbox.ru. The author participated in planning the experiments, analyzing the literature and interpreting the data.

- **Adelya R. Umerova**, Doctor of Medical Sciences, Head of the Department of Clinical Pharmacology, e-mail: adelya_umerova@mail.ru, **ORCID:** 0000-0002-3129-2443. The author participated in planning the experiments, analyzing the literature and interpreting the data.

- **Svetlana E. Bataeva**, PhD of Medical Sciences, Associate Professor of the Department of Clinical Pharmacology, e-mail: klinfarm_agma@mail.ru. The author participated in planning the experiments, analyzing the literature and interpreting the data.