Drug-induced parkinsonism

Ostroumova T.M.[1], Ostroumova O.D.[2, 3], Soloveva A.S.[3]
[1]Department of Nervous System Diseases and Neurosurgery, N.V. Sklifosovsky Institute of Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia, Moscow;
[2]Department of therapy and polymorbid pathology, Russian Medical Academy of Continuous Professional Education, Ministry of Health of Russia, Moscow;
[3]N.V. Sklifosovsky Institute of Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia, Moscow
[1]11, Rossolimo St., Build. 1, Moscow 119021, Russia;
[2]2/1, Barrikadnaya St., Build. 1, Moscow 125993, Russia;
[3]11, Rossolimo St., Build. 2, Moscow 119021, Russia

Drug-induced parkinsonism (DIP) is the most common drug-induced movement disorder and is most commonly associated with antipsychotic drugs, monoamine reuptake inhibitors, and calcium channel blockers. DIP manifests as a typical movement disorder, which makes it practically indistinguishable from idiopathic Parkinson's disease (PD) and requires differential diagnosis. DIP symptoms develop fairly quickly (hours to weeks) after the antipsychotic is started or after the dose is increased. Therefore, DIP is predominantly a clinical diagnosis that must be kept in mind when a patient develops typical symptoms during treatment onset or increasing the dose of drugs that most often lead to such an adverse reaction (ADR). DIP evaluation includes using the Naranjo algorithm, which helps assess a causal relationship between drug intake and the development of parkinsonism symptoms. The primary DIP treatment is the reduction of the dose of the inducer drug, or its cancellation, or replacement with another drug. In patients with schizophrenia and antipsychotic-induced DIP, dose reduction, replacement with another medication, or prescription of a drug with anticholinergic activity may be possible. The awareness of the doctor and the patient about the possibility of developing this ADR is crucial in the prevention of DIP. Therefore, choosing a drug with the lowest risk of developing DIP is necessary for pharmacotherapy.

Keywords: *parkinsonism; drug-induced parkinsonism; drugs; adverse drug reactions.*
Contact: *Tatiana Maksimovna Ostroumova;* ***t.ostroumova3@gmail.com***
For reference: *Ostroumova TM, Ostroumova OD, Soloveva AS. Drug-induced parkinsonism. Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2021;13(6):91–97. DOI: 10.14412/2074-2711-2021-6-91-97*

Extrapyramidal (movement) disorders caused by the side effects of certain medications include drug-induced parkinsonism (DIP), tardive dyskinesia and dystonia, akathisia, myoclonus, and tremor [1, 2]. DIP is the most common drug-induced movement disorder among them and is most often associated with drugs that affect dopamine receptors [2]. However, the risk of DIP related to other drug classes is not well known to both neurologists and psychiatrists, and doctors of different specialties.

Many drugs from different groups are associated with DIP (table) [1, 3–48]. DIP frequently develops in patients receiving antipsychotics, monoamine reuptake inhibitors, and calcium channel blockers (CCBs).

Epidemiology

Currently, there is a lack of data on the prevalence of DIP due to the variety of drugs that can lead to its development. In patients with schizophrenia receiving antipsychotics, its prevalence is 25–35% and increases with age [49, 50]. In cross-sectional studies, the prevalence of DIP is lower – 10–20% [51]. On the other hand, according to the analysis of the pharmacovigilance database of the World Health Organization (WHO) [52], the frequency of DIP is only 0.05%.

Pathophysiology

The pathophysiology of DIP is based on the interruption of dopaminergic transmission. The most common mechanism is structural or functional blockade of D2-like dopamine receptors in the striatum due to drugs affecting dopamine receptors [2]. When D2-like dopamine receptors are blocked, neurons containing GABA and enkephalin are activated in the striatum, which affects the indirect pathway of the basal ganglia and ultimately leads to a relative decrease in the activity of the thalamocortical pathways [50]. In addition, violation of dopamine release can also occur when tetrabenazine is administered, as it inhibits the monoamine reuptake in the presynaptic neurons [14]. Drugs whose primary mechanism does not directly affect dopamine concentration (for example, valproic acid, CCBs) can cause DIP through other means – modulation of GABA activity or mitochondrial dysfunction [50]. Probably, there are additional pathophysiological mechanisms of DIP that have not yet been studied since the spectrum of medications associated with DIP is quite broad. In contrast, these drugs have no pronounced effect on dopamine receptors. The mechanisms of DIP in various medications are presented in the table.

Risk factors

Several predisposing factors increase DIP risk. These include older age, female sex, long-term use of antipsychotics and / or their administration in high doses, HIV infection, traumatic brain injury, stroke, history of movement disorders [1, 3, 4, 50].

Clinical presentation, evaluation and differential diagnosis

Clinical presentation. DIP manifests as parkinsonism syndrome, which makes it, in some cases, clinically similar to PD and other diseases that cause parkinsonism. DIP symptoms can develop both relatively quickly (hours – days – weeks) after the antipsychotic initiation or after increasing its dose [50], and during the first six months after the treatment onset; the time of symptoms onset depends on the specific inducer drug [4]. It is considered that DIP manifests with symmetrical symptoms [3, 4], which may help in the differential diagnosis of DIP and PD, but in two recent studies, asymmetric symptoms were detected in 20% of patients with DIP [53, 54]. DIP is also characterized by acute or subacute onset with a relatively rapid increase in symptoms severity, the presence of pronounced postural or postural-kinetic tremor (involving the extremities and the lower jaw, lips, and tongue), comorbidity with other movement disorders. In addition, the severity of the DIP symptoms can be different depending on the causative agent. Thus, R.P. Munhoz et al. [55] analyzed the motor symptoms of DIP in patients receiving typical and atypical antipsychotics, as well as CCBs. Akinetic-rigid syndrome was observed in a larger number of patients with DIP treated with antipsychotics compared with participants treated with CCBs. In addition, resting tremor was significantly more common in typical antipsychotics users, compared to CCBs, while in patients receiving CCBs and atypical antipsychotics, its frequency did not differ significantly. Two cohort studies [56, 57] also reported an increased risk of PD in patients with DIP caused by antipsychotics and CCBs.

The mechanism of PD development in the above cases hasn't been fully studied. Antipsychotics may increase the risk of PD due to their potentially toxic effect on dopaminergic neurons, inhibition of the mitochondrial respiratory chain, increased dopamine turnover (the ratio between dopamine metabolites and dopamine itself) and increased production of free radicals [58]. It is assumed that in people with a genetic predisposition to parkinsonism, the neurotoxic effects of prolonged use of antipsychotics may be irreversible. However, this genetic predisposition is currently not proven. It is also logical to assume that these drugs may contribute to the onset of clinical symptoms at the preclinical stage of PD [56, 57].

Evaluation and differential diagnosis. DIP is primarily a clinical diagnosis that should be kept in mind when a patient

Drugs associated with DIP [1, 3–48]

Drug/drug class	Incidence, %	Mechanism	Level of evidence
Antipsychotics (neuroleptics)			
First generation (typical)			
Chlorpromazine	21,1	Dopamine D2-like receptors blockade	*A*
Haloperidol	22,6		
Second generation (atypical)			
Clozapine	3,7	Dopamine D2-like receptors blockade	*A*
Quetiapine	8,8		
Olanzapine	8,1		
Risperidone	12,1		
Asenapine	2,4		
Levosulpiride	29,3		
Amisulpride	10,3		
Aripiprazole	7,2		
Sulpiride	29,3		
Ziprasidone	10,0		
Paliperidone	No data		
Monoamine reuptake inhibitors			
Tetrabenazine	2,5–28,5	Inhibition of monoamines reuptake in the presynaptic neurons within central nervous system, which leads to a decrease in the amount of monoamines, including dopamine	*A*
Calcium channel blockers			
Flunarizine	2,8–2,9	Blockade of postsynaptic D2-like receptors due to inhibition of voltage-gated calcium channels, which leads to a slowdown in vesicular dopamine transport	*B*
Cinnarizine			*A*
Verapamil	No data		*B*
Diltiazem			*C*
Antidepressants			
Selective serotonin reuptake inhibitors			
Citalopram	No data	Small ability to bind to dopamine D1-like and D2-like receptors. Not fully known. The serotonergic system is involved in the modulation of basal ganglia activity and in the pathogenesis of PD, which may be associated with the development of DIP	*C*
Escitalopram			
Paroxetine			
Fluoxetine			
Sertraline			
Other antidepressants			
Duloxetine	No data	The potential inhibitory effect of 5-HT receptor blockers and the inhibitory effect of norepinephrine on dopaminergic neurons of the ventral region of the tegmentum are discussed	*C*
Mirtazapine		The potential inhibitory effect of 5-HT receptor blockers on dopaminergic neurons is discussed	*B*
Amitriptyline		Unknown	*B*
Clomipramine		Unknown	*B*
Trazodone		Antagonism of 5-HT2A receptors with increasing dose may potentially lead to inhibition of dopaminergic neurotransmission	*C*
Venlafaxine		Unknown	*B*

Continuing of table

Drug/drug class	Incidence, %	Mechanism	Level of evidence
Anticonvulsants			
Valproic acid	1,37–75	Inhibition of dopamine transport in the basal ganglia by GABA is discussed	
Pregabalin Gabapentin	No data	Potentially reduce the release of dopamine when binding to L-type calcium channels. Complex interactions with dopaminergic pathways cannot be excluded due to the well-known abuse and misuse of these drugs.	*B*
Carbamazepine Oxcarbazepine		Unknown	*C*
Prokinetics			
Metoclopramide	3,5	Blockade of the striatum postsynaptic D2 receptors	*A*
Domperidone	No data		*B*
Other drugs			
Amiodarone Tacrolimus Cyclosporine Amphotericin B Captopril Lithium	0,2 No data	Unknown	*C*

Notes. PD – Parkinson's disease; 5-HT - 5-hydroxytryptamine; GABA – gamma-aminobutyric acid. *Уровень доказательности: A* – one or more randomized, controlled clinical trials; *B* – nonrandomized clinical trials, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analyses and/or postmarketing surveillance studies; *C* – case-reports or case series [1].

develops typical symptoms during the treatment initiation or the increase of the dose of drugs commonly associated with such adverse reaction (AR). American Psychiatric Association recommends monitoring acute extrapyramidal ARs in patients with schizophrenia receiving antipsychotics at the start of the therapy and during each follow-up; however, it is also emphasized that the exact time of onset of DIP in each patient is individual [59].

Since DIP can be clinically indistinguishable from PD, it is essential to assess concomitant drug-induced movement disorders, such as akathisia and orofacial dyskinesia. They are more likely to develop in patients with DIP than in PD [4]. Thorough neurological examination is also necessary to exclude the subclinical stage of PD [2, 4]. The presence of the earliest non-motor symptoms is typical for such patients. Hyposmia [60], constipation, impotence, urination disorders, attention, sleep, and wakefulness disorders (daytime drowsiness, restless legs syndrome) [51] are much more common in PD than in DIP. The most specific non-motor phenomenon of PD (and other synucleinopathies) is parasomnia – rapid eye movement sleep behavior disorder.

As in any other drug-induced disorder, DIP evaluation should include the identification of a causal relationship between the drug and parkinsonism onset; the Naranjo algorithm is used for this purpose [61]. However, in some cases, symptoms may persist for many months after the withdrawal of a possible inducer drug [1, 2, 4], which necessitates the use of complex imaging techniques to exclude PD. In addition, since DIP is associated with a sufficiently large number of drugs of different classes, careful collection of pharmacological history is crucial; special algorithms are used for this purpose [1, 62].

In the absolute majority of cases, differential diagnosis between DIP and PD is required. Differences in clinical manifestations of DIP and PD are described above. Recently, the possibilities of single-photon emission computed tomography to assess the amount of dopamine transporter in the synaptic cleft with ^{123}I-FP-CIT (DaTscan) have been actively studied as a method to differentiate DIP with PD, especially in cases when the drug cannot be discontinued or when the symptoms of parkinsonism persist several months after drug discontinuation. 18F-fluorodopa positron emission tomography is also used [63]. In 2020, the European Association of Nuclear Medicine (EANM) published clinical guidelines [64], which emphasize that these methods can also be used for differential diagnosis between DIP and PD. In PD, there is a reduced absorption of the radiopharmaceutical agent in the basal ganglia, while in patients with DIP it remains within the normal range [63, 64]. 2021 meta-analysis [65] showed that the use of DaTscan led to a change in the clinical diagnosis in 34% of patients with parkinsonism, and management tactics were changed in slightly more than one-half of the patients.

^{123}I-metaiodbenzylguanidine (mIBG) scintigraphy, which allows assessing preganglionic cardiac parasympathetic innervation, is also studied in clinical trials. In a small study [66], ^{123}I-mIBG uptake was significantly reduced in PD and remained normal in patients with DIP. Another study [67] using DaTscan and ^{123}I-mIBG scintigraphy demonstrated the potential of combining these methods in evaluating the earliest PD stage, the symptoms of which may increase when antipsychotics are administered.

However, it should be emphasized that the possibilities of the above methods in the differential diagnosis of parkinsonism require further investigation, and it is not yet possible to conclude their sensitivity and specificity.

Also, in some cases, it may be necessary to differentiate DIP from other diseases (Lewy body dementia, corticobasal degeneration, multisystem atrophy, progressive supranuclear palsy, etc.) and to exclude other conditions that cause secondary parkinsonism (vascular, toxic parkinsonism, etc.) [3, 68].

Treatment

The primary treatment strategy in DIP and other drug-induced diseases includes reducing the dose of the causative drug or its discontinuation/replacement with another agent [1]. However, if it is impossible to stop the antipsychotic completely, it is preferable to choose medications with minimal DIP risk, for

example, clozapine and quetiapine, which the International Movement Disorder Society recommends for the treatment of psychosis in patients with PD [57].

In patients with schizophrenia and DIP caused by antipsychotics, American Psychiatric Association [59] suggests reducing their dose, replacing them with another drug, or prescribing medications with anticholinergic activity (level of evidence 2C). In particular, it is recommended to prescribe trihexyphenidyl and benztropine (not registered in Russia at the time of the article preparation), diphenhydramine (H1-receptor blocker), and amantadine (N-methyl-D-aspartate receptor blocker). At the same time, it is preferable to use a minimal dose of drugs and administer them for a short period [49, 59]. The effectiveness of these drugs in treating DIP, including in patients who do not have schizophrenia, is relatively low. Thus, anticholinergics administration was analyzed only in a few small trials. At the same time, anticholinergics can cause numerous AR, including urinary retention, angle-closure glaucoma, cognitive impairment, tachycardia, constipation, and an increased delirium risk [51]. The efficacy of drugs from other groups (dopamine, exogenous melatonin, dopamine and melatonin receptor agonists, etc.) in the management of DIP associated with antipsychotics is also being studied. However, not all of these drugs are registered in Russia, most of them do not yet have direct indications for use in patients with DIP caused by antipsychotics, and the obtained results are inconclusive and/or contradictory. Therefore, this problem needs further investigation. Levodopa and dopamine receptor agonists do not have such indications as DIP in their instructions, and studies on their effectiveness were conducted more than 20 years ago in small cohorts of patients with schizophrenia.

Symptoms of DIP usually resolve within a few weeks or months after dose reduction or withdrawal of drugs [2], but in some patients, they may regress for a year or even longer [4]. In such cases, the patient is most likely to have a subclinical stage of PD or Lewy body dementia, which dictates the need for a thorough examination and monitoring [4, 57].

Prevention

The main method of preventing DIP is to increase the awareness of medical practitioners about this AR in many drugs. Before prescribing medications with extrapyramidal AR, it is necessary to assess the DIP risks (for example, elderly age) and avoid prescribing medications associated with DIP, especially in cases where it is not obligatory or when they can be replaced with drugs with a better safety profile. It should also be kept in mind that depression and anxiety in middle and older age can be early non-motor symptoms of PD, and psychotic disorders could indicate the presence of Lewy body dementia. Antipsychotic administration can cause severe movement disorders, which can be life-threatening in Lewy body dementia.

Conclusion

An increase in life expectancy, in the number of elderly and senile patients with a large number of comorbid diseases, the problems of polypharmacy, drug-drug interactions, and the active development of the pharmaceutical market cause an increase in the risk of drug-induced diseases, including DIP. Therefore, raising awareness of medical practitioners, primarily neurologists, psychiatrists, and general practitioners, about drugs that can cause DIP will help reduce the risk of AR, which could decrease morbidity, improve patients' quality of life, and reduce healthcare costs for the treatment of drug-induced diseases.

REFERENCES

1. Tisdale JE, Miller DA, eds. Drug-induced diseases: prevention, detection, and management 3rd edition. Bethesda, Md: American Society of Health-System Pharmacists; 2018.

2. Shin HW, Chung SJ. Drug-induced parkinsonism. *J Clin Neurol*. 2012 Mar;8(1):15-21. doi: 10.3988/jcn.2012.8.1.15

3. Левин ОС, Шиндряева НН, Аникина МА. Лекарственный паркинсонизм. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2012;112(8):76-81. [Levin OS, Shindryaeva NN, Anikina MA Drug-induced parkinsonism. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova*. 2012;112(8):76-81 (In Russ.)].

4. Нодель МР. Лекарственный паркинсонизм: возможности минимизации риска. *Нервные болезни*. 2015;(3):18-22. [Nodel MR. Drug-induced parkinsonism:opportunities to minimize risk. *Nervnye bolezni*.2015;(3):18-22 (In Russ.)].

5. Kumsa A, Girma S, Alemu B, Agenagnew L. Psychotropic medications-induced tardive dyskinesia and associated factors among patients with mental illness in Ethiopia. *Clin Pharmacol*. 2020 Dec 1;12:179-87. doi: 10.2147/CPAA.S285585. eCollection 2020.

6. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013 Sep 14;382(9896):951-62. doi: 10.1016/S0140-6736(13)60733-3. Epub 2013 Jun 27.

7. Chyou TY, Nishtala R, Nishtala PS. Comparative risk of Parkinsonism associated with olanzapine, risperidone and quetiapine in older adults – a propensity score matched cohort study. *Pharmacoepidemiol Drug Saf*. 2020 Jun;29(6):692-700. doi: 10.1002/pds.5007. Epub 2020 Apr 16.

8. Bondon-Guitton E, Perez-Lloret S, Bagheri H, et al. Drug-induced parkinsonism: a review of 17 years' experience in a regional pharmacovigilance center in France. *Mov Disord*. 2011 Oct;26(12):2226-31. doi: 10.1002/mds.23828. Epub 2011 Jun 14.

9. Tsai SC, Sheu SY, Chien LN, et al. High exposure compared with standard exposure to metoclopramide associated with a higher risk of parkinsonism: a nationwide population-based cohort study. *Br J Clin Pharmacol*. 2018 Sep;84(9):2000-9. doi: 10.1111/bcp.13630. Epub 2018 Jun 19.

10. Lai CH, Yeh YC, Chen YY. Metoclopramide as a prokinetic agent for diabetic gastroparesis: revisiting the risk of Parkinsonism. *Ther Adv Drug Saf*. 2019 Jun 20;10:2042098619854007. doi: 10.1177/2042098619854007. eCollection 2019.

11. Leung JG, Breden EL. Tetrabenazine for the treatment of tardive dyskinesia. *Ann Pharmacother*. 2011 Apr;45(4):525-31. doi: 10.1345/aph.1P312. Epub 2011 Apr 12.

12. Sahin T, Yilmaz R, Akbostanci MC. Predictive factors for tolerability of tetrabenazine in patients with hyperkinetic movement disorders. *Parkinsonism Relat Disord*. 2020 May;74:36-7. doi: 10.1016/j.parkreldis.2020.04.007. Epub 2020 Apr 14.

13. Guay DR. Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinetic movement disorders. *Am J Geriatr Pharmacother*. 2010 Aug;8(4):331-73. doi: 10.1016/j.amjopharm.2010.08.006

14. Kenney C, Hunter C, Jankovic J. Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. *Mov Disord*. 2007 Jan 15;22(2):193-7. doi: 10.1002/mds.21222

15. Teive HA, Troiano AR, Germiniani FM, Werneck LC. Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord*. 2004 Jun;10(4):243-5. doi: 10.1016/j.parkreldis.2003.12.004

16. Lin HL, Lin HC, Tseng YF, et al. Risk of parkinsonism induced by flunarizine or cinnarizine: a population-based study. *Eur J Clin Pharmacol*. 2017 Mar;73(3):365-71. doi: 10.1007/s00228-016-2181-3

17. Miguel R, Correia AS, Bugalho P. Iatrogenic parkinsonism: the role of flunarizine and cinnarizine. *J Parkinsons Dis*. 2014;4(4):645-9. doi: 10.3233/JPD-140414

18. Kim S, Cheon SM, Suh HS. Association between drug exposure and occurrence of parkinsonism in Korea: a population-based case-control study. *Ann Pharmacother*. 2019 Nov;53(11):1102-10. doi: 10.1177/1060028019859543. Epub 2019 Jun 19.

19. Jhang KM, Huang JY, Nfor ON, et al. Flunarizine related movement disorders: a nationwide population-based study. *Sci Rep*. 2019 Feb 8;9(1):1705. doi: 10.1038/s41598-018-37901-z

20. Liang CY, Yeh YC, Lee CJ, Chen YY. Flunarizine and the risk of parkinsonism in a newly diagnosed type 2 diabetic population in Taiwan: A nested case-control study. *J Clin Neurosci*. 2018 Apr;50:281-6. doi: 10.1016/j.jocn.2018.01.017. Epub 2018 Feb 1.

21. Padrell MD, Navarro M, Faura CC, Horga JF. Verapamil-induced parkinsonism. *Am J Med*. 1995 Oct;99(4):436. doi: 10.1016/s0002-9343(99)80195-8

22. Revet A, Montastruc F, Roussin A, et al. Antidepressants and movement disorders: a postmarketing study in the world pharmacovigilance database. *BMC Psychiatry*. 2020 Jun 16;20(1):308. doi: 10.1186/s12888-020-02711-z

23. Miletic V, Relja M. Citalopram-induced parkinsonian syndrome: case report. *Clin Neuropharmacol*. Mar-Apr 2011;34(2):92-3. doi: 10.1097/WNF.0b013e318210ea3e

24. Ak S, Anil Yagcioglu AE. Escitalopram-induced Parkinsonism. *Gen Hosp Psychiatry*. Jan-Feb 2014;36(1):126.e1-2. doi: 10.1016/j.genhosppsych.2013.09.010. Epub 2013 Oct 5.

25. Kuloglu M, Caykoylu A, Ekinci O, et al. Successful management of depression with reboxetine in a patient who developed Parkinsonism related to paroxetine use. *J Psychopharmacol*. 2010 Apr;24(4):623-4. doi: 10.1177/0269881108099962. Epub 2008 Dec 12.

26. Christodoulou C, Papadopoulou A, Rizos E, et al. Extrapyramidal side effects and suicidal ideation under fluoxetine treatment: a case report. *Ann Gen Psychiatry*. 2010 Jan 18;9:5. doi: 10.1186/1744-859X-9-5

27. Gray JA. Parkinsonism and rabbit syndrome after discontinuation of low-dose ziprasidone and concomitant initiation of sertraline. *J Clin Psychopharmacol*. 2012 Feb;32(1):142-3. doi: 10.1097/JCP.0b013e31823f912a

28. Pina Latorre MA, Modrego PJ, Rodilla F, et al. Parkinsonism and Parkinson's disease associated with long-term administration of sertraline. *J Clin Pharm Ther*. 2001 Apr;26(2):111-2. doi: 10.1046/j.1365-2710.2001.00307.x

29. Bayrak A, Cetin B, Meteris H, Kesebir S. Parkinsonism secondary to duloxetine use: a case report. *North Clin Istanb*. 2015 Dec 25;2(3):243-6. doi: 10.14744/nci.2015.63634. eCollection 2015.

30. Hong JY, Sunwoo MK, Oh JS, et al. Persistent drug-induced parkinsonism in patients with normal dopamine transporter imaging. *PLoS One*. 2016 Jun 13;11(6):e0157410. doi: 10.1371/journal.pone.0157410. eCollection 2016.

31. Sarwar AI. Trazodone and parkinsonism: the link strengthens. *Clin Neuropharmacol*. May/Jun 2018;41(3):106-8. doi: 10.1097/WNF.0000000000000278

32. Brugger F, Bhatia KP, Besag FM. Valproate-associated parkinsonism: a critical review of the literature. *CNS Drugs*. 2016 Jun;30(6):527-40. doi: 10.1007/s40263-016-0341-8

33. Yomtoob J, Koloms K, Bega D. DAT-SPECT imaging in cases of drug-induced parkinsonism in a specialty movement disorders practice. *Parkinsonism Relat Disord*. 2018 Aug;53:37-41. doi: 10.1016/j.parkreldis.2018.04.037. Epub 2018 May 5.

34. Ristic AJ, Vojvodic N, Jankovic S, et al. The frequency of reversible parkinsonism and cognitive decline associated with valproate treatment: a study of 364 patients with different types of epilepsy. *Epilepsia*. 2006 Dec;47(12):2183-5. doi: 10.1111/j.1528-1167.2006.00711.x

35. Muralidharan A, Rahman J, Banerjee D, et al. Parkinsonism: a rare adverse effect of val-

proic acid. *Cureus*. 2020 Jun 23;12(6):e8782. doi: 10.7759/cureus.8782

36. Pacheco-Paez T, Montastruc F, Rousseau V, et al. Parkinsonism associated with gabapentinoid drugs: A pharmacoepidemiologic study. *Mov Disord*. 2020 Jan;35(1):176-80. doi: 10.1002/mds.27876. Epub 2019 Oct 21.

37. Rissardo JP, Caprara ALF. Carbamazepine-, oxcarbazepine-, eslicarbazepine-associated movement disorder: a literature review. *Clin Neuropharmacol.* May/Jun 2020;43(3):66-80. doi: 10.1097/WNF.0000000000000387

38. Marras C, Herrmann N, Fischer HD, et al. Lithium use in older adults is associated with increased prescribing of parkinson medications. *Am J Geriatr Psychiatry.* 2016 Apr;24(4):301-9. doi: 10.1016/j.jagp.2015.11.004. Epub 2015 Dec 10.

39. Gmitterova K, Minar M, Zigrai M, et al. Tacrolimus-induced parkinsonism in a patient after liver transplantation – case report. *BMC Neurol.* 2018 Apr 20;18(1):44. doi: 10.1186/s12883-018-1052-1

40. Ling H, Bhidayasiri R. Reversible Parkinsonism after chronic cyclosporin treatment in renal transplantation. *Mov Disord.* 2009 Sep 15;24(12):1848-9. doi: 10.1002/mds.22530

41. Montastruc JL, Durrieu G. Amiodarone and Parkinsonism: a pharmacovigilance study. *Fundam Clin Pharmacol.* 2021 Aug;35(4):781-4. doi: 10.1111/fcp.12618. Epub 2020 Nov 9.

42. Dotti MT, Federico A. Amiodarone-induced parkinsonism: a case report and pathogenetic discussion. *Mov Disorders.* 1995 Mar;10(2):233-4. doi: 10.1002/mds.870100223

43. Malaterre HR, Renou C, Kallee K, Gauthier A. Akinesia and amiodarone therapy. *Int J Cardiol.* 1997 Mar;59(1):107-8. doi: 10.1016/s0167-5273(96)02891-4

44. Ishida S, Sugino M, Hosokawa T, et al. Amiodarone-induced liver cirrhosis and parkinsonism: a case report. *Clin Neuropathol.* Mar-Apr 2010;29(2):84-8. doi: 10.5414/npp29084

45. Sandyk R. Parkinsonism induced by captopril. *Clin Neuropharmacol.* 1985;8(2):197-8. doi: 10.1097/00002826-198506000-00013

46. Fisher JF, Dewald J. Parkinsonism associated with intraventricular amphotericin B. *J Antimicrob Chemother.* 1983 Jul;12(1):97-9. doi: 10.1093/jac/12.1.97

47. Miguelez C, Morera-Herreras T, Torrecilla M, et al. Interaction between the 5-HT system and the basal ganglia: functional implication and therapeutic perspective in Parkinson's disease. *Front Neural Circuits.* 2014 Mar 17;8:21. doi: 10.3389/fncir.2014.00021. eCollection 2014.

48. Guiard BP, El Mansari M, Merali Z, Blier P. Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. *Int J Neuropsychopharmacol.* 2008 Aug;11(5):625-39. doi: 10.1017/S1461145707008383. Epub 2008 Jan 21.

49. Вайман ЕЭ, Шнайдер НА, Незнанов НГ, Насырова РФ. Лечение антипсихотик-индуцированного паркинсонизма у пациентов с шизофренией. *Неврология, нейропсихиатрия, психосоматика*. 2021;13(4):4-11. doi: 10.14412/2074-2711-20214-4-11 [Vaiman EE, Shnayder NA, Neznanov NG, Nasyrova RF. Treatment of antipsychotic-induced parkinsonism in schizophrenic patients. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2021;13(4):4-11. doi: 10.14412/2074-2711-20214-4-11 (In Russ.)].

50. Ward KM, Citrome L. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther.* 2018 Dec;7(2):233-248. doi: 10.1007/s40120-018-0105-0. Epub 2018 Jul 19.

51. Wisidagama S, Selladurai A, Wu P, et al. Recognition and management of antipsychotic-induced parkinsonism in older adults: a narrative review. *Medicines (Basel)*. 2021 May 26;8(6):24. doi: 10.3390/medicines8060024

52. De Germay S, Montastruc F, Carvajal A, et al. Drug-induced parkinsonism: Revisiting the epidemiology using the WHO pharmacovigilance database. *Parkinsonism Relat Disord.* 2020 Jan;70:55-9. doi: 10.1016/j.parkreldis.2019.12.011. Epub 2019 Dec 17.

53. Pieters LE, Bakker PR, van Harten PN. Asymmetric drug-induced parkinsonism and psychopathology: a prospective naturalistic study in long-stay psychiatric patients. *Front Psychiatry.* 2018 Feb 5;9:18. doi: 10.3389/fpsyt.2018.00018. eCollection 2018.

54. Savica R, Grossardt BR, Bower JH, et al. Incidence and time trends of drug-induced parkinsonism: A 30-year population-based study. *Mov Disord.* 2017 Feb;32(2):227-34. doi: 10.1002/mds.26839. Epub 2016 Oct 25.

55. Munhoz RP, Bertucci Filho D, Teive HA. Not all drug-induced parkinsonism are the same: the effect of drug class on motor phenotype. *Neurol Sci.* 2017 Feb;38(2):319-24. doi: 10.1007/s10072-016-2771-y. Epub 2016 Nov 16.

56. Foubert-Samier A, Helmer C, Perez F, et al. Past exposure to neuroleptic drugs and risk of Parkinson disease in an elderly cohort. *Neurology*. 2012 Oct 9;79(15):1615-21. doi: 10.1212/WNL.0b013e31826e25ce. Epub 2012 Sep 26.

57. Jeong S, Cho H, Kim YJ, et al. Drug-induced Parkinsonism: A strong predictor of idiopathic Parkinson's disease. *PLoS One*. 2021 Mar 1;16(3):e0247354. doi: 10.1371/journal.pone.0247354. eCollection 2021.

58. Erro R, Bhatia KP, Tinazzi M. Parkinsonism following neuroleptic exposure: A double-hit hypothesis? *Mov Disord.* 2015 May;30(6):780-5. doi: 10.1002/mds.26209. Epub 2015 Mar 18.

59. The American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 3rd ed. Washington, DC: American Psychiatric Association; 2021. doi: 10.1176/appi.books.9780890424841

60. Morley JF, Duda JE. Use of hyposmia and other non-motor symptoms to distinguish between drug-induced parkinsonism and Parkinson's disease. *J Parkinsons Dis.* 2014;4(2):169-73. doi: 10.3233/JPD-130299

61. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154

62. Сычев ДА, Остроумова ОД, Переверзев АП и др. Лекарственно-индуцированные заболевания: подходы к диагностике, коррекции и профилактике. *Фармаконадзор. Фарматека*. 2020;(6):113-26. doi: 10.18565/pharmateca.2020.6.113-126 [Sychev DA, Ostroumova OD, Pereverzev AP, et al. Drug-induced diseases: approaches to diagnosis, correction and prevention. *Farmakonadzor. Farmateka*. 2020;(6):113-26. doi: 10.18565/pharmateca.2020.6.113-126 (In Russ.)].

63. Сапронова МР, Дмитренко ДВ, Шнайдер НА, Молгачев АА. Диагностика болезни Паркинсона. Часть 1. Возможности функциональной нейровизуализации. *Доктор.Ру*. 2020;19(9):6-12. doi: 10.31550/1727-2378-2020-19-9-6-12 [Sapronova MR, Dmitrenko DV, Schnaider NA, Molgachev AA. Diagnosis of Parkinson's Disease. Part 1. The Potential of Functional Neuroimaging. *Doctor.Ru*. 2020;19(9):6-12. doi: 10.31550/1727-2378-2020-19-9-6-12 (In Russ.)].

64. Morbelli S, Esposito G, Arbizu J, et al. EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0. *Eur J Nucl Med Mol Imaging.* 2020 Jul;47(8):1885-912. doi: 10.1007/s00259-020-04817-8. Epub 2020 May 9.

65. Bega D, Kuo PH, Chalkidou A, et al. Clinical utility of DaTscan in patients with suspected Parkinsonian syndrome: a systematic review and meta-analysis. *NPJ Parkinsons Dis.* 2021 May 24;7(1):43. doi: 10.1038/s41531-021-00185-8

66. Lee PH, Kim JS, Shin DH, et al. Cardiac ^{123}I-MIBG scintigraphy in patients with drug induced parkinsonism. *J Neurol Neurosurg Psychiatry.* 2006 Mar;77(3):372-4. doi: 10.1136/jnnp.2005.073999. Epub 2005 Aug 15.

67. Tachibana K, Matsuura K, Shindo A, et al. Symptomatic characteristics of parkinson's disease induced by neuroleptic drugs, based on a functional neuroimaging diagnosis. *Intern Med.* 2020;59(4):485-90. doi: 10.2169/internalmedicine.2553-18. Epub 2020 Feb 15.

68. Caproni S, Colosimo C. Diagnosis and differential diagnosis of parkinson disease. *Clin Geriatr Med.* 2020 Feb;36(1):13-24. doi: 10.1016/j.cger.2019.09.014. Epub 2019 Sep 17.

Received/Reviewed/Accepted
24.07.2021/02.09.2021/19.09.2021

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Ostroumova T.M. https://orcid.org/0000-0003-1499-247x
Ostroumova O.D. https://orcid.org/0000-0002- 0795-8225
Soloveva A.S. https://orcid.org/0000-0001-6647-2260