# Off-label antipsychotics prescription to adolescents with acute psychotic episodes does not cause adverse drug reactions

**Ivashchenko D.V.[1, 2], Buromskaya N.I.[3], Malakhova A.D.[4], Tsarkova N.A.[5], Savchenko L.M.[1], Shevchenko Yu.S.[1], Sychev D.A.[1]**

*[1]Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Moscow; [2]Institute for Further Training of Physicians — Penza Branch, Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Penza; [3]G.E. Sukhareva Scientific and Practical Center for Mental Health of Children and Adolescents, Moscow Healthcare Department, Moscow; [4]I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia, Moscow; [5]National Research University Higher School of Economics, Ministry of Education and Science of Russia, Moscow*

*[1]2, Barrikadnaya St., Build. 1, Moscow 125993, Russia; [2]8A, Stasova St., Penza 440060, Russia; [3]21A, 5th Donskoy Dr., Moscow 119334, Russia; [4]8, Trubetskaya St., Build. 2, Moscow 119991, Russia; [5]20, Myasnitskaya St., Moscow 101000, Russia*

*Antipsychotics are often used to treat children and adolescents. Because of their age, there are a lot of off-label prescribed antipsychotics in that population. However, the off-label use of medications is considered to be potentially unsafe.*

***Objective:*** *to evaluate whether the off-label prescription of antipsychotics outside of the approved age group increased the risk of adverse drug reactions in adolescents experiencing an acute psychotic episode.*

***Patients and methods.*** *We analyzed 450 charts of adolescents hospitalized due to an acute psychotic episode (only completed cases). In addition, we evaluated adverse drug reactions adjusted by off-label antipsychotics prescription outside the approved age group using the Global Trigger Tool (GTT). We also registered prescriptions with duplicates drug classes and potentially dangerous drug interactions.*

***Results and discussion.*** *Off-label antipsychotics prescription outside the approved age group was less frequently associated with adverse drug reactions (3.2% vs. 10.5%; p=0.013). The logistic regression analysis did not show any significant associations between the off-label antipsychotic use and increased risk of adverse drug reactions (Odds ratio=0.994 (95% confidence interval 0.572-1.726), p=0.982). Although, patients with off-label use of antipsychotics were more likely to have potentially dangerous drug interactions (35.2% vs. 16.15%; p=0.0001) and prescriptions with duplicates drug classes (39.6% vs. 15.43%; p=0.0001).*

***Conclusion.*** *Off-label antipsychotic prescription outside the approved age group in adolescents with acute psychotic episode does not increase the risk of adverse drug reactions. However, an increase in potentially dangerous drug interactions and prescriptions with duplicates drug classes frequency could be considered red flags. Therefore, we have concluded that the concerns about off-label antipsychotics prescription outside of approved age groups in adolescents with acute psychotic episodes were overrated.*

***Keywords:*** *antipsychotics; adolescents; off-label prescription; acute psychotic episode; safety.*

***Contact:*** *Dmitriy Vladimirovich Ivashchenko;* ***dvi1991@yandex.ru***

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Schizophrenia is a disabling mental disorder, which is often manifested as an acute psychotic episode, treatment of which is the first stage of treating the underlying disease [1]. Antipsychotics are the first line of treatment for patients with an acute psychotic episode [1].

Antipsychotics are a class of drugs whose action is realized by blocking dopamine receptors [2]. There are two main groups of antipsychotics: first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs). FGAs cause extrapyramidal adverse reactions due to a pronounced blockage of dopamine receptors [3]. SGAs, due to serotonin receptor blockade, do not lead to marked extrapyramidal symptoms, but can induce metabolic and hormonal disorders [4]. Antipsychotics are widely used in children for various indications: psychotic disorders, schizophrenia spectrum disorders, schizoaffective disorder, bipolar disorder, conduct disorders [5], [6]. Antipsychotics have a high risk of adverse side effects (ADEs), and children are more prone to them than adults [7]. Use of antipsychotics in children has been steadily increasing for the past 30 years [8], [9]. According to Varimo et al. (2020), between 2008 and 2017, the use of antipsychotics increased 1.5-fold among children aged 7–12, and 2.2-fold among adolescents aged 13–17 [10]. In the U.S., the use of FGAs is quite limited, while in European countries they remain important [9], [11]. In Russia, the use of FGAs in schizophrenia accounts for more than a half of all cases of antipsychotics use [12].

Prescription of antipsychotics to children quite often involves off-label use. This mainly concerns SGAs, as this class of drugs is relatively new on the market, and indications for use in children are limited compared with FGAs [8].

Off-label use of antipsychotics among children is most often due to a lack of indications in the instructions for use. According to Sohn et al. (2016), in the U.S., up to 66% of antipsychotic drug prescriptions for children do not meet FDA guidelines [8]. A similar problem of antipsychotics off-label use for children exists in European countries: off-label prescriptions account for up to 92% of cases, most prescriptions are for quetiapine and olanzapine [13], [14]. Also, the study by Korno et al. (2018) touched upon an important issue – the off-label use of antipsychotics outside the approved age group, which amounted to 63%[13].

According to FDA, many antipsychotics are not recommended for use before the age of 18 [8], and this is relevant to most countries in the world [13]. However, off-label use of antipsychotics is quite common among children and adolescents [13], [15]. In Russia, according to Government Registry of Drugs [16], only some SGAs and almost all FGAs can be prescribed for patients under 18 years old , although there are restrictions for use in children under 15 years old (Table 1).

Prescribing medicines off-label for children is considered unsafe [8], [17], [18]. At the same time, there has been insufficient research into the off-label prescription of antipsychotics outside the approved age group [13]. There were no differences in the safety of antipsychotics depending on their use on- or off-label in the study of Schröder et al. (2017)l [15]. Considering a limited choice of antipsychotics and the risk of resistance development, more information is needed on possible risks of off-label use of antipsychotics outside the approved age groups. In Russia, almost all FGAs can be prescribed for patients under 18 years old. But more difficulties arise when prescribing SGAs with a better safety profile [4].

Table 1. *Antipsychotics prescribed during hospitalization. Proportion of off-label antipsychotics prescription outside the approved age group is shown separately*

| Drug name | Approved for use from the age | First | | Second | | Third | |
|---|---|---|---|---|---|---|---|
| | | Total number of prescriptions | Off label use n (%) | Total number of prescriptions | Off label use n (%) | Total number of prescriptions | Off label use n (%) |
| All antipsychotics | N/A | 450 | 38 (8.44%) | 155 | 31 (20%) | 175 | 42 (24%) |
| Haloperidol | 3 | 193 | 0 (0%) | 20 | 0 (0%) | 25 | 0 (0%) |
| Trifluoperazine | 3 | 58 | 0 (0%) | 14 | 0 (0%) | 25 | 0 (0%) |
| Risperidone | 15 | 61 | 11 (18%) | 12 | 0 (0%) | 41 | 4 (9.8%) |
| Alimemazine | 7 | 22 | 0 (0%) | 13 | 0 (0%) | 5 | 0 (0%) |
| Clozapine | 5 | 31 | 14 (45.2%) | 45 | 24 (53.3%) | 34 | 21 (61.8%) |
| Zuklopentixole | Under 18 – with caution | 14 | 0 (0%) | 5 | 0 (0%) | 8 | 0 (0%) |
| Sulpiride | 14 | 4 | 0 (0%) | 4 | 0 (0%) | 2 | 0 (0%) |
| Perphenazine | 12 | 15 | 1 (6.7%) | 6 | 1 (16.7%) | 8 | 0 (0%) |
| Periciazine | 3 | 8 | 0 (0%) | 10 | 0 (0%) | 2 | 0 (0%) |
| Chlorprotixene | 6 | 18 | 0 (0%) | 14 | 0 (0%) | 2 | 0 (0%) |
| Quetiapine | 18 | 0 | 0 (0%) | 2 | 2 (100%) | 1 | 1 (100%) |
| Fluphenazine | 12 | 1 | 0 (0%) | 0 | 0 (0%) | 1 | 0 (0%) |
| Olanzapine | 18 | 11 | 11 (100%) | 2 | 2 (100%) | 15 | 15 (100%) |
| Flupentixole | Under 18 – with caution | 1 | 0 (0%) | 1 | 0 (0%) | 1 | 0 (0%) |
| Tioridazine | 2 | 7 | 0 (0%) | 5 | 0 (0%) | 0 | 0 (0%) |
| Amisulpride | 15 | 1 | 1 (100%) | 1 | 1 (100%) | 0 | 0 (0%) |
| Promazine | 12 | 2 | 0 (0%) | 0 | 0 (0%) | 1 | 0 (0%) |
| Paliperidone | 12 | 0 | 0 (0%) | 1 | 1 (100%) | 3 | 1 (33.3%) |
| Chlorpromazine | 3 | 1 | 0 (0%) | 0 | 0 (0%) | 0 | 0 (0%) |
| Levomepromazine | 12 | 2 | 0 (0%) | 0 | 0 (0%) | 0 | 0 (0%) |

***Note:*** N/A – not applicable

There is no unified register of patients who are prescribed psychotropic drugs in Russia. This makes it difficult to conduct major studies such as those conducted in other countries [9], [10], [13], [15], [18]. Thus, the only way to assess the safety of off-label drug use is to directly analyze medical records. At present, no studies have been published to assess the safety of off-label drug use in children with acute psychotic episodes.

**The purpose** of this study is to determine whether off-label prescribing antipsychotics outside the approved age group is less safe for adolescents with acute psychotic episodes.

**Materials and methods.** The study was approved by the local ethics committees of the Russian Medical Academy of Continuous Professional Education (Minutes No. 3 of 06 June 2018) and Scientific-Practical Children's and Adolescents Mental Health Center n.a. G.E. Sukhareva (Minutes No. 2 of 14 June 2018).

We carried out a retrospective analysis of completed clinical cases over the period 01.01.2008–01.06.2018. The selection process of case histories was impersonal; we did not use personal data of patients in this study. The research was conducted in Scientific-Practical Children's and Adolescents Mental Health Center n.a. G.E. Sukhareva (Moscow, Russia).

We analyzed 450 case histories of patients hospitalized in a child psychiatric clinic with an acute psychotic episode. The diagnosis on admission was acute polymorphic psychotic disorder F23.0–23.9 according to ICD-10. A more accurate diagnosis was made when the patient was discharged. Thus, the final diagnoses were: acute polymorphic psychotic disorder (F23; n=143; 31.8%), schizophrenia (F20; n=105; 23.3%), delusional disorders (F22; n=5; 1.1%), schizotypal disorder (F21; n=39; 8.7%), bipolar affective disorder (F31–F34; n=18; 4%), and other non-psychotic disorders (n=40; 8.9%).

The following information was extracted from each case history:

- Sex;
- Age;
- Length of stay in hospital;
- Duration of mental illness;
- Total number of admissions (including the current one);
- Prescribed antipsychotics;
- Other prescribed drugs;
- Information about drug-drug interactions and drug duplications;
- Information about adverse drug effects.

**Off-label antipsychotic use analysis.** The main objective of this study was to analyze associations of off-label prescription of antipsychotics with treatment safety. Each patient received an antipsychotic during hospitalization. In the course of treatment antipsychotics could be replaced, sometimes more than once. Therefore, all antipsychotics prescribed to a patient were divided into the first, second and third ones in the order of use. The first antipsychotic was administered as the main drug to a patient after hospitalization. The second antipsychotic was added to improve the effectiveness of the therapy, it was used in conjunction with the first one. The third antipsychotic was administered to replace the first one. Thus, not all patients in the sample had a second or third antipsychotic.

Each prescribed antipsychotic was checked for its off-label use outside the approved age group. We compared the patients' age at the time of hospitalization with the acceptable age for antipsychotics according to the national labels [16]. The results are shown in Table 1. All patients were divided into two groups according to the fact of off-label prescription of antipsychotics outside the approved age group.

Doses of antipsychotics were converted to chlorpromazine equivalents (by International Consensus Study of Antipsychotic Dosing [19]). For each antipsychotic there was a starting dose, a maximum dose prescribed during staying in hospital and a maintenance dose (the dose that was fixed when the patient was discharged from hospital).

**Drug interactions and duplications.** When assessing the pharmacotherapy, two parameters were taken into account: drug duplications and «major» drug-drug interactions. We regarded as drug duplications cases where two antipsychotics were administered simultaneously to one patient. We searched for «major» drug-drug interactions using the online tool «Drugs Interactions Checker» [20]. For this purpose, we always checked the entire prescription list of the patient, not only antipsychotics. The presence of potentially dangerous drug-drug interactions of «major» category was regarded as a positive result.

**Searching for adverse drug effects.** To search for adverse drug effects we used the Global Trigger Tool (GTT) algorithm in the GAPPS modification [21]. This method was chosen because of its high efficiency in detecting ADEs when analyzing completed cases [22]. Each clinical case was analyzed using the standard GTT algorithm (see Figure 1) [22]. The GTT involves a retrospective analysis of completed case histories to identify «triggers». A «trigger» indirectly indicates the occurrence of an ADE; for example, a change in the dose of a drug, sudden withdrawal of a drug, prescription of a drug to treat an adverse event, or additional examinations (see Classen et al. (2011) [22]. One

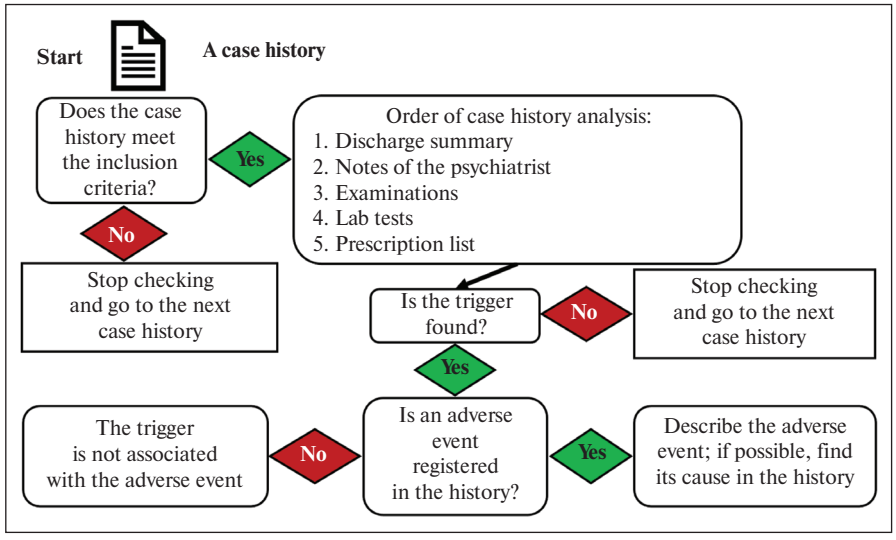


**Fig. 1.** *Unwanted events search algorithm using GTT. Each patient chart was analyzed according to the algorithm. It is not recommended to associate a single unwanted even with multiple triggers. Adapted from [22]*

Table 2. *Baseline characteristics of the study participants considering off-label antipsychotics prescription*

| Variables | All | | Off-label use | | No off-label use | | p |
|---|---|---|---|---|---|---|---|
| | N of patients | Mean±SD | N of patients | Mean±SD | N of patients | Mean±SD | |
| Age (years) | 450 | 14.52±2.21 | 103 | 13.48±2.62 | 347 | 14.82±1.97 | 0.00001 |
| Length of stay (days) | 450 | 59.36±31.09 | 103 | 71.05±39.17 | 347 | 55.9±27.37 | 0.001 |
| Lifetime number of hospital admissions | 450 | 1.59±1.06 | 103 | 62±1.05 | 347 | 1.58±1.06 | 0.488 |
| Duration of mental illness (months) | 276 | 9.67±11.11 | 62 | 8.91±11.16 | 214 | 9.89±11.11 | 0.555 |

***Note:*** SD – standard deviation

case report was given 20 minutes. In case of a «trigger» detection, the ADE search was performed. The number of ADEs in one patient was not summed up. As a result, all patients were divided into those who had ADE detected and those who had no ADE detected.

*Statistical analysis.* Data analysis was carried out using the statistical package IBM SPSS Statistics 21.0. For the subsequent analysis of quantitative variables, nonparametric Mann–Whitney test and Pearson Chi-square test were applied (Shapiro–Wilk test: $Z<1.0$; $p<0.0001$).

The patients were divided into two groups: those who received off-label antipsychotics, and those who did not.

The Mann–Whitney test was utilized for comparison of antipsychotic doses, patients' age, length of hospital stay and other continuous variables between the groups. Comparison of frequencies of categorical variables was carried out by means of Pearson's Chi-square. Using this test we compared drug duplications, «major» drug-drug interactions, fact of ADE, sex.

We used Bonferroni correction for multiple comparisons.

We performed binominal logistic regression to evaluate the prognostic value of off-label antipsychotic use for ADE occurrence. We also included in the model the patients' age, length of stay, the fact of first-time hospitalization, the fact of drug duplication, the fact of «major» drug-drug interaction. The backward inclusion method (Wald) was used. Results of regression analysis were shown as odds ratio with 95% confidence intervals.

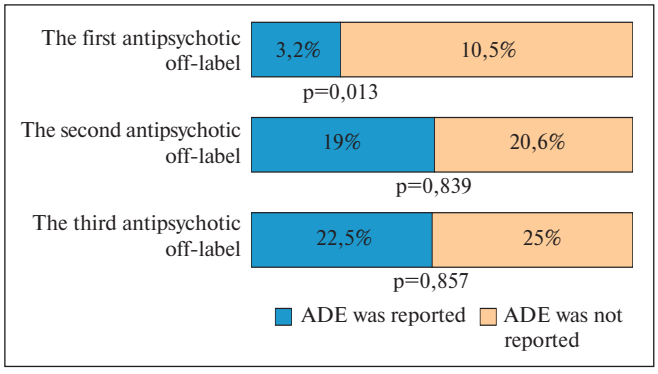


**Fig. 2.** *Off-label antipsychotics prescription association with ADR. Pearson's chi-squared test ($\chi^2$) was used. The graphs show the proportion of off-label antipsychotic prescriptions among patients with and without ADR. Significant differences were obtained only for the first antipsychotic; otherwise, off-label use was less likely to be associated with ADR*

**Results.** The Table 1 shows all prescribed antipsychotics.

Clinical and demographic characteristics of patients are presented in Table 2.

Mean age was 14.52±2.21 years old, 49,6% were males (n=223), mean length of stay in hospital was 59.36±31.09 days. The comparison showed that patients with off-label use of antipsychotic had a longer hospital stay (71.05±39.17 days vs 55.9±27.37 days; p=0.001) and were younger (13.48±2.62 years old vs. 14.82±1.97; p=0.0001). We also found that boys had off-label prescribed antipsychotics more often than girls (27.8% vs 18.1%; p=0.018) We did not discover significant differences in lifetime number of admissions or duration of mental illness.

We analysed the frequency of off-label use of antipsychotics. The first antipsychotic was prescribed off-label only in 8.44% (n=38) of cases, but off-label drug use was more often noted for the second (20%; n=31) and the third prescribed antipsychotics (22.7%; n=42). Comparison of antipsychotics doses, depending on whether they were prescribed off-label, revealed the difference only for the first antipsychotic maintenance (final) dose. Particularly, patients who were prescribed the first antipsychotic off-label had a higher maintenance dose compared with patients without off-label use (202.47±197.39 vs. 151.12±221.65 mg/day; p=0.048). When comparing the dosages of the second and third antipsychotics, no significant differences were found. The frequencies of antipsychotics off-label use are presented in Table 1. The most frequently prescribed off-label antipsychotics included risperidone, clozapine, and olanzapine. FGAs were almost always prescribed on-label.

***Adverse drug effects among patients with off-label use of antipsychotics.*** Among 450 analyzed cases, ADEs were found in 126 patients. There were different types of ADEs, but in most cases (n=90) they were antipsychotic-induced extrapyramidal symptoms (EPS).

We analyzed the frequency of detection of ADEs depending on the prescription of antipsychotics off-label (Figure 2). Significant differences were identified only for the first prescribed antipsychotic (p=0.013). But among patients with ADEs, off-label antipsychotics were prescribed only in 3.2% of cases, the proportion of off-label prescriptions among patients without ADEs was significantly higher (10.5% cases).

***Appropriateness of pharmacotherapy depending on off-label use of antipsychotics.*** It was found that patients with off-label use of antipsychotics were more likely to have drug-drug interactions of the «major» category and duplications of drugs of the same class (Figure 3).

***Risk evaluation of adverse drug effects depending on off-label use of antipsychotics.*** The result of logistic regression analysis did not confirm the role of off-label use of antipsychotic as a significant risk factor for ADEs (OR=0.994; 95%CI 0.572–1.726; p=0.982). The most significant risk factors were older age (OR=1.143 (95%CI 1.029–1.271) p=0.013), the fact of the first-time hospitalization (OR=2.315; 95%CI 1.437–3.729; p=0.001), and the presence of drug-drug interactions of the «major» category (OR=1.759 (95%CI 1.142–2.708) p=0.01). Similar results were observed in regression analysis using antipsychotic-induced extrapyramidal symptoms as a dependent variable. For details see Table 3.

**Discussion.** As a result of our study, we found that off-label prescribing of antipsychotics does not increase the risk of ADEs in adolescents experiencing an acute psychotic episode.

However, off-label prescriptions were associated with significant differences in some parameters, and that needs to be explained.

Antipsychotics were prescribed off-label more often in younger adolescents. This is logical, because our study took into account the off-label prescription outside the approved age group. Consequently, older patients were less likely to be subject to the restrictions in the instructions for use of a drug. We doubt that the younger age of the patient was the cause of more frequent off-label use of antipsychotics. An interesting fact is that boys were more likely to be given off-label antipsychotics. This finding can be explained by the fact that male patients were less suspicious of side effects, but this is our assumption, the real motives cannot be established.

The length of stay was higher in patients with off-label drugs prescribed. This could have been caused by the switching of the initially prescribed medication to another one. After drug switching, efficacy and safety monitoring is required, which results in longer hospital stays. After drug changing, off-label drugs were more common: one out of four new antipsychotics administered was off-label. Another feature of patients with off-label drug use is a high MAI score. Inappropriate use of drugs in this case indicates the presence of potentially dangerous drug-drug interactions of the «major» category and duplication of drugs of the same class. Consequently, the off-label use of antipsychotics in our study was combined with inappropriate medication prescribing. Duplication of antipsychotics can be explained by the fact that an off-label antipsychotic was more often used as the second drug (it meant simultaneous prescription of two antipsychotics). But potentially dangerous drug-drug interactions cannot be explained in this way. Off-label antipsychotics were typically prescribed for adolescents who had ineffective first-line therapy. In such cases, combinations of drugs are used more often, and the risk of irrational combinations on the prescription list is higher.

Dose analysis showed that a higher maintenance dose of the first prescribed antipsychotic was usual for antipsychotics prescribed off-label. The maintenance dose is usually significantly lower with poor drug tolerance. Therefore, it is possible to suggest better tolerance of antipsychotics administered off-label. This observation supports the main conclusion of our study: the use of psychotropic drugs off-label outside the approved age group does not worsen treatment outcomes.

Regression analysis did not confirm the role of off-label use of antipsychotics as a risk factor for ADEs, including EPS. This is due to the fact that FGAs are more often administered on-label, but they are more likely to cause EPS. In our study, EPS were the most commonly observed ADEs, so the proportion of SGAs as a cause of ADEs is relatively lower. As it follows from our research, SGAs as the second and third antipsychotics were administered relatively more frequently, while the proportion of off-label used antipsychotics increased. Thus, the risk of ADEs in patients with an acute psychotic episode was higher when prescribing an antipsychotic on-label compared with off-label one.

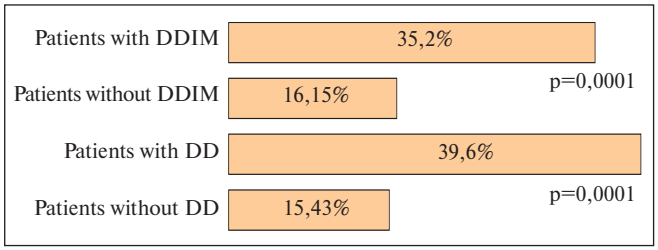


**Fig. 3.** *Off-label antipsychotics prescription association with «major» potentially dangerous drug interactions and prescriptions with duplicates drug classes. Pearson's chi-squared test ($\chi^2$) was used. The analysis included only patients with off-label antipsychotics prescription with or without «major» potentially dangerous drug interactions or prescriptions with duplicates drug classes*

Table 3. *Logistic regression analysis of adverse drug reactions (ADR) risk factors*

| Covariates | OR | 95% CI | | p |
|---|---|---|---|---|
| | | Lower | Upper | |
| *Any adverse drug effect* | | | | |
| Age 1.143 | 1.029 | 1.270 | 0.013 | |
| First time hospitalized | 2.314 | 1.436 | 3.729 | 0.001 |
| Drug-drug interactions of the «major» category | 1.758 | 1.142 | 2.708 | 0.01 |
| Off-label use of antipsychotics | 0.993 | 0.572 | 1.726 | 0.982 |
| *Antipsychotic-induced extrapyramidal symptoms* | | | | |
| Age 1.127 | 1.000 | 1.271 | 0.05 | |
| First time hospitalized | 3.073 | 1.721 | 5.487 | 0.0001 |
| Drug-drug interactions of the «major» category | 2.121 | 1.311 | 3.430 | 0.002 |
| Off-label use of antipsychotic | 0.973 | 0.53 | 1.788 | 0.931 |

***Note:*** OR – odds ratio

We can compare our results with similar studies. It should be noted that the comparison is rather tentative, as our study presents only one clinical group – adolescents with an acute psychotic episode. Among adolescents with an acute psychotic episode off-label drug use was low compared with previous pharmacoepidemiological studies. In the study of Korno et al. (2018) up to 88% of antipsychotics were prescribed to children off-label outside the approved age group. It is difficult to compare our results with other studies, because off-label use of antipsychotics was studied depending on the diagnosis of the patient [8], [10], [14]. All patients in our study had indications for antipsychotics, and only age could be a restriction for on-label drug use. A similar feature of our and previous studies is that off-label drugs are more often SGAs. At the same time, our study includes analysis of FGA applications, which is almost absent in other studies [8], [10], [14]. The use of FGAs is relevant in Russia and some other European countries. The advantage of FGAs is precisely the low age restrictions for use in children [16].

Our study showed the regional characteristics and traditions of prescribing antipsychotics to adolescents in a psychiatric hospital setting. The first line of therapy, as shown by the analysis, was FGAs. The off-label prescription of antipsychotics more often occurred after ineffective or poorly tolerated first-line therapy. Thus, in this group of patients, prescription of off-label antipsychotics was not potentially dangerous.

*Limitations*. In this study, we did not evaluate the relationship between the prescription of a specific antipsychotic and the development of ADEs due to a retrospective design. We demonstrated the incidence of ADEs depending on the presence or absence of off-label use of antipsychotics. Medical records did not always provide details on the presence of ADEs, so there are probably more cases of intolerance among patients than we observed. No weight monitoring of patients was conducted in medical records, which excludes retrospective assessment of metabolic disorders.

**Conclusion.** In this study, we did not find that off-label use of antipsychotics could increase the risk of ADEs in adolescents with acute psychotic episodes. In contrast, the use of FGAs more often resulted in the development of ADEs, although these antipsychotics were prescribed on-label. Thus, in adolescents with an acute psychotic episode, prescribing antipsychotics off-label outside the approved age groups was not a risk factor for ADEs.

But at the same time, the off-label use of antipsychotics was associated with an increase in duplications of drugs of the same class and potentially dangerous drug-drug interactions. We have concluded that the danger of prescribing antipsychotics off-label outside the approved age groups in adolescents with acute psychotic episodes was overrated.

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Ivashchenko D.V. https://orcid.org/0000-0002-2295-7167
Buromskaya N.I. https://orcid.org/0000-0003-0991-4960
Malakhova A.D. https://orcid.org/0000-0002-8103-8312
Savchenko L.M. https://orcid.org/0000-0002-2411-3494
Shevchenko Yu.S. https://orcid.org/0000-0001-7790-9595
Sychev D.A. http://orcid.org/0000-0002-4496-3680