The polymorphic variants DRD2 rs1800497 and ABCB1 3435C>T are associated with antipsychotic safety parameters in adolescents with an acute psychotic episode: the results of a pilot study

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Children and adolescents are more likely than adults to experience adverse side effects when taking antipsychotics. Pharmacogenetic testing allows one to more accurately choose the initial dose of a drug. The genes of pharmacokinetic factors have been shown to be of high prognostic value for the safety of antipsychotics in adults.

Patients and methods. *The study enrolled 36 adolescents (58.3% male) (mean age, 14.83±1.84 years). All the patients took an antipsychotic. The follow-up lasted 28 days. On 14 and 28 days of treatment, its efficiency and safety were evaluated using the Children's Global Assessment Scale (CGAS), the Positive and Negative Syndrome Scale (PANSS), the Udvalg for Kliniske Undersьgelser Side Effects Rating Scale (UKU-SERS), the Simpson-Angus Scale (SAS), and the Barnes Akathisia Rating Scale (BARS). The patients were genotyped for CYP3A4*22, CYP3A5*3, CYP2D6*4, *9, *10, ABCB1 1236C>T, 2677G>T/A, 3435C>T, DRD2 rs1800497, DRD4 rs1800955, and HTR2A rs6313.*

Results and discussion. *The decrease in the mean score of the PANSS subscale "Productive symptoms" was more pronounced in carriers of the DRD2 rs1800497 polymorphic variant (-6.5 [-10.25; -3.75] vs -3 [-6.5; -2] on 14 day (p=0.028) and (-11 [-13; -9.5] vs -5 [-9; -3.5] on 28 day (p=0.001) compared to baseline. The carriage of ABCB1 3435CT+TT was associated with worse tolerance to pharmacotherapy on 14 day (the total score of the UKU-SERS M, 8 [3; 11.75] vs M, 2 [1; 6]; p=0.034). The carriers of DRD2 rs1800497 reported a greater severity of antipsychotic-induced neurological disorders (UKU-SERS subscale score M, 1 [0; 2.25] vs M 0 [0; 1]; p=0.029).*

Conclusion. *The polymorphic variants DRD2 rs1800497 and ABCB1 3435C>T were established to be significantly associated with the efficacy and safety of antipsychotics in adolescents with an acute psychotic episode.*

Keywords: *pharmacogenetics; antipsychotics; adolescents; acute psychotic episode; safety; efficacy.*

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

Children and adolescents are more likely to have adverse adverse side effects (ADEs) of antipsychotics than adults. It was shown that types of ADEs in response to antipsychotics in children were generally similar in adults with the first psychotic episode, but children are more prone to metabolic disorders [2, 3].

All of that determines the importance of personalized choice of antipsychotics in the treatment of acute psychotic episode in children and adolescents. Nowadays, there are no clinical guidelines on the use of pharmacogenetic testing for prescribing of antipsychotics in patients with an acute psychotic episode. But a certain evidence base, mainly for adult patients, confirms the importance of genes of pharmacokinetic factors – in particular, *CYP2D6. CYP2D6* polymorphisms change the activity of the corresponding isoenzyme, which may affect the safety of antipsychotics [4]. The role of other genes encoding isoenzymes of cytochrome P450 family are less important in selection of antipsychotics [4]. But their effect on serum levels of antipsychotics was confirmed by the studies done on Asians [5, 6]. Another important pharmacogenetic marker studied as an antipsychotic safety predictor is the ABCB1 gene encoding the transport protein P-glycoprotein (P-gp). *ABCB1* polymorphisms lead to a decreasing of P-gp activity, which in turn affects the higher toxicity of drugs taken [7]. There were studies confirmed

the role of ABCB1 polymorphisms in the safety of antipsychotics in adults [8, 9]. Studies of pharmacodynamic genetic factors, in particular dopamine and serotonin receptor genes, have shown inconsistent results [10, 11].

To date, quite a number of pharmacogenetic studies on the efficacy and safety of antipsychotics in children and adolescents have been conducted. But among them, there were not enough studies that include patients with an acute psychotic episode [12]. Other studies which confirmed the role of *CYP2D6* in the safety of antipsychotics predominantly included adult patients with schizophrenia [13, 14].

Given the lack of work involving adolescents experiencing acute psychotic episodes who were prescribed antipsychotics, new data are required. In our study, we aimed to study the predictive role of polymorphic variants of pharmacokinetic factor genes for early signs of ineffectiveness and intolerance of antipsychotics in adolescents with an acute psychotic episodes.

Purpose:

To establish possible associations of pharmacokinetic and pharmacodynamic factors' genes with effectiveness and safety of antipsychotics in adolescents experiencing acute psychotic episodes during 28 days of treatment.

Materials and methods

The study was approved by the local Ethics Committees of 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). Study was complied with the World Medical Association Declaration of Helsinki.

Research design: prospective observational with post-hoc analysis of associations of genetic polymorphisms with safety parameters and effectiveness of antipsychotic therapy. The current part of the study was being done from 20 June 2018 to 20 June 2019 in Scientific-Practical Children's and Adolescents Mental Health Center n.a. G.E. Sukhareva (Moscow, Russia).

Study sample

We included 36 adolescents in the study and monitored the participants' condition for 28 days. Patients were included in the study within 1 to 3 days after admission to a hospital. Each patient and his parent(s) signed the informed consent to be involved in the study. Informed consent included permission to publish results of the study. Personal information or identifiers of study participants were not included in database. All patients were Russian by self-identification.

Inclusion criteria:

1. Age from 10 to 18 years;
2. Clinically verified acute psychotic episode;
3. Antipsychotic as the main drug of pharmacotherapy;
4. Consent of the patient and parent (legal representative) to participate in the study;

Non-inclusion criteria:

1. The presence of a physical or infectious disease in a state of decompensation;
2. Positive test result for substance use, which indicates the exogenic psychotic disorder;
3. Contraindications for taking antipsychotics;
4. Refusal of the patient or his/her parent (legal representative) to participatein the study.

Follow up

We did not influenced on psychopharmacotherapy which was administered by physician. The leading syndrome in most cases was a hallucinatory-paranoid syndrome (n=24), and the sample also contained paranoid (n=4), depressive-paranoid (n=4), maniacal-paranoid (n=3) and catatonic (n=1) syndromes. The diagnoses according to ICD-10 are: brief psychotic disorder – F23 (n=16), paranoid schizophrenia – F20 (n=17), schizoaffective disorder – F25 (n=3).

All patients received antipsychotics as their main therapy. Some patients had antipsychotic's change during 28 days of observation. In the first 14 days, antipsychotics were replaced in 6 patients due to lack of efficacy. Between the 14th and 28th days, the main antipsychotics were replaced in 8 patients: in 4 cases due to poor tolerance, in 4 cases due to inefficacy. We had no influence on the changes in psychopharmacotherapy.

As the main antipsychotic, first-generation antipsychotics (FGA) were used more often. In addition, additional antipsychotics were added in several cases. Twenty-five patients took trihexyphenydil during 14 days and 24 patients took it between 14 and 28 days.

Doses of antipsychotics were converted to the chlorpromazine equivalent to unify further analysis. __ [15].

To assess the effectiveness of antipsychotics in dynamics, special scales were used: Children's Global Assessment Scale (CGAS) [16], Positive and Negative Symptoms Scale (PANSS) [17]. The mental state was assessed 3 times: when the patient was included in the study, on the 14th and 28th days of observation.

The safety of psychopharmacotherapy was assessed with UKU Side Effects Rating Scale (UKU SERS) [18], Sympson–Angus Scale (SAS) [19], Barnes Akathisia rating scale (BARS) [20].

Laboratory part

A buccal epithelium scrape was collected from each patient on the day of inclusion in the study to genotype. The biomaterial was transported to the laboratory and stored at -77 degrees Celsius. DNA from buccal epithelium was performed by sorbent method. The isolated DNA was stored at -77 degrees Celsius.

Single nucleotide polymorphism *CYP3A4*22* (rs2740574), *CYP3A5*3* (6986A>G, rs7776746), *CYP2D6*4*, *9, *10 (rs3892097, rs1065852), *ABCB1* 1236C>T (rs1128503), 2677G>T/A (rs2032582), 3435C>T (rs1045642), *DRD2* (rs1800497), *DRD4* (rs1800955), *HTR2A* (rs6313) were detected by the real-time polymerase chain reaction (RT-PCR) with the use of commercial kits of reagents («Syntol») on CFX96 TouchTM Real-Time PCR Detection System (Bio-Rad, USA). Genotyping was done for the entire patient sample at once. Processing of research results was carried out after obtaining genotyping results for all patients.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 21.0. Given the small sample size, we used non-parametric criteria (Mann–Whitney, Kruskal–Wallis) to compare continuous variables between groups. We compared the frequencies of the categorical variables with each other by Pearson's Chi-square, and the exact Fisher's criterion (for 2x2 comparisons). Bonferroni's correction of multiple comparisons was introduced. The limit of significance was set to 0.05.

In our analysis, we did not exclude patients with concurrent drugs used besides the main antipsychotic. But the concurrent use of psychopharmacotherapy was taken into account during analysis to prevent a bias.

Table 1. Clinical and demographic characteristics of patients

Parameters		N	Mean	Standard deviation
Age (years)		36	14,83	1,84
Height (sm)		30	166,60	9,19
Weight (kg)		30	59,43	16,94
Body mass index		30	21,43	6,23
Lifetime number of admissions (including the current)		36	1,89	1,63
Age of mental disorder's appearance (years)		36	13,44	2,32
Lifetime number of exacerbations		36	1,89	1,49
Duration of mental illness (months)		36	14,81	19,06
Antipsychotics daily dose at 1-3rd days (chlorpromazine equivalent, mg/day)		36	200,31	153,11
Antipsychotics daily dose at 7-9th days (chlorpromazine equivalent, mg/day)		36	319,18	195,53
Antipsychotics daily dose at 14-15th days (chlorpromazine equivalent, mg/day)		36	297,93	200,72
Antipsychotics daily dose at 21-23th days (chlorpromazine equivalent, mg/day)		36	297,71	183,95
Antipsychotics daily dose at 28th day (chlorpromazine equivalent, mg/day)		36	298,40	189,71
Nominative variables				
Parameter			**n**	**%**
Sex	Male		21	58,3
	Female		15	41,7
Mental disorders among relatives	No		21	58,3
	Yes		10	27,8
	No information		5	13,9
Hospitalizations in psychiatric hospital among relatives	No		24	66,7
	Yes		3	8,3
	No information		9	25,0
Fact of taking psychopharmacotherapy among relatives	No		24	66,7
	Yes		3	8,3
	No information		9	25,0
Type of antipsychotic during 1-14 days of observation	First generation antipsychotic		20	55,6
	Second generation antipsychotic		16	44,4
Type of antipsychotic during 14-28 days of observation	First generation antipsychotic		23	63,9
	Second generation antipsychotic		13	36,1
Main antipsychotic during 1-14 days of observation	Haloperidol		18	50,0
	Trifluoperazine		1	2,8
	Risperidone		6	16,7
	Clozapine		5	13,9
	Zuklopentixole		1	2,8
	Olanzapine		5	13,9
Main antipsychotic during 14-28 days of observation	Haloperidol		19	52,8
	Trifluoperazine		1	2,8
	Risperidone		3	8,3
	Clozapine		5	13,9
	Zuklopentixole		1	2,8
	Olanzapine		5	13,9
	Tioridazine		1	2,8
	Levomepromazine		1	2,8

Results

Clinical and demographic characteristics of the patients included in the study are presented in Table 1.

There were no associations of clinical and demographic characteristics of patients with effectiveness of psychopharmacotherapy.

The further analysis concerned the pharmacogenetic part of the research: establishment of possible associations of genetic polymorphisms with the psychopharmacotherapy effectiveness and safety.

Table 2. The distribution of genetic polymorphisms among study participants

Genetic polymorphism	Genotype	n	%	Chi-square	p-value
CYP3A4*22 C>T intron 6 rs35599367	CC	35	97,2	0.01	P>0.05
	CT	1	2,8		
CYP3A5*3 (A6986G)	GG	34	94,4	0.03	p>0.05
	AG	2	5,6		
CYP2D6*4 (G1846A)	GG	31	86,1	0.2	p>0.05
	GA	5	13,9		
CYP2D6*10 C100T rs1065852	CC	28	77,8	0.56	p>0.05
	CT	8	22,2		
ABCB1 1236C>T rs1128503	CC	11	30,6	0.09	P>0.05
	CT	17	47,2		
	TT	8	22,2		
ABCB1 2677G>T/A rs2032582	GG	12	33,3	0.03	P>0.05
	GT	18	50,0		
	TT	6	16,7		
ABCB1 C3435T rs1045642	CC	7	19,4	0.47	P>0.05
	CT	20	55,6		
	TT	9	25,0		
DRD2 C2137T rs1800497	CC	26	72,2	0.04	P>0.05
	CT	9	25,0		
	TT	1	2,8		
DRD4 C-521T rs1800955	CC	10	27,8	0.56	p>0.05
	CT	20	55,6		
	TT	6	16,7		
HTR2A T102C rs6313	TT	11	30,6	0.42	p>0.05
	TC	16	44,4		
	CC	9	25,0		

The distribution of genotypes of all polymorphisms corresponded to the distribution according to Hardy–Weinberg equilibrium. (p>0.05) (Table 2).

Clinical and demographic parameters were compared between carriers of different genotypes of genetic polymorphisms to determine their comparability.

Significant differences in the PANSS scale and some of its subscales scores between the carriers of *CYP2D6*4*, *HTR2A* rs6313 and *ABCB1 3435 C*>T were established (Table 3). There were no differences in CGAS score depending on genetic polymorphisms.

We did not revealed differences in first or second generation antipsychotics prescription between carriers of different genotypes of genetic polymorphisms.

Doses of antipsychotics between carriers of different genetic polymorphisms were analyzed. Statistically significant differences were obtained only for *CYP2D6*10* and *DRD2* rs1800497. The revealed associations are presented in Table 4.

The analysis of the concurrent pharmacotherapy revealed the following: 10 carriers of the C-allele of *HTR2A* rs6313 took mood stabilizer between 14 and 28 days, which significantly differed from carriers of TT homozygotes, none of which received mood stabilizer during this period (p=0.016).

Analysis of the effectiveness of antipsychotics depending on pharmacokinetic gene's polymorphisms

No significant differences were found in CGAS and PANSS scales' scores mean changes during the observation peri-

Table 3. Associations of PANSS mean scores at the moment of inclusion into the study with CYP2D6*4, HTR2A rs6313 and ABCB1 3435 C>T.

CYP2D6*10 (rs1065852)	CC (n=28)			CT (n=8)			p
	Median	Q 1	Q 3	Median	Q 1	Q 3	
PANSS Subscale "Negative symptoms" score	25	21	29,75	20	17,25	23,75	0,033
PANSS total score	86	77	96	73,5	66,75	83,5	0,033
HTR2A rs6313	TT (n=10)			CC+CT (n=25)			p
	Median	Q 1	Q 3	Median	Q 1	Q 3	
PANSS Subscale "Negative symptoms" score	26	24	31	23	18,5	27,5	0,022
PANSS Subscale "General symptoms" score	42	39	49	34	29,5	42,5	0,011
PANSS total score	94	82	97	80	67,5	88	0,015
ABCB1 3435 C>T	CC (n=7)			CT+TT (n=29)			p
	Median	Q 1	Q 3	Median	Q 1	Q 3	
PANSS Subscale "Positive symptoms" score	23	19	25	20	17	22	0,036

Note: Q - quartile

od depending on polymorphisms *CYP3A4*22, CYP3A5*3, CYP2D6*10, ABCB1 1236C>T, 2677G>T/A, 3435C>T.*

It has been established that the decrease in the total PANSS scale score for 28 days was significantly lower for the carriers *CYP2D6*4* GA (M=(-17) [-22; -9.5]) in comparison with homozygotes GG (M=(-24.5) [-35.25; -15.75]) of this polymorphic variant (p=0.048).

Analysis of the effectiveness of antipsychotics depending on pharmacodynamic gene's polymorphisms

No significant differences were found in the CGAS and PANSS scales' scores mean change during the observation period for *HTR2A* rs6313 and *DRD4* rs1800955 polymorphisms' carriers.

Significant differences in the PANSS "Positive Symptoms" on 14th and 28th days as well as the total PANSS score on day 28 for *DRD2* rs1800497 carriers were found (Figure).

Analysis of the effectiveness and safety of antipsychotics depending on pharmacokinetic and pharmacodynamic gene's polymorphisms

The carriage of *ABCB1 3435C>T* and *DRD2* rs1800497 was associated with a significant increased UKU SERS and it's several subscales scores (Table 5). Other polymorphisms included in the study did not demonstrate any significant associations with the average scores of UKU SERS, BARS and SAS scales.

The analysis of associations of genetic polymorphisms with frequency of individual adverse drug reactions showed negative results.

Table 4. Antipsychotics daily doses which were different between carriers and not carriers of CYP2D6*10 and DRD2 rs1800497.

CYP2D6*10 (rs1065852)	CC (n=28)			CT (n=8)			p
	Median	Q 1	Q 3	Median	Q 1	Q 3	
Antipsychotics daily dose at 21-23th days (chlorpromazine equivalent, mg/day)	300	200	447,5	220	100	246,25	0,036
DRD2 (rs1800497)	CC (n=26)			CT+TT (n=10)			p
	Median	Q 1	Q 3	Median	Q 1	Q 3	
Antipsychotics daily dose at 1-3rd days (chlorpromazine equivalent, mg/day)	141,25	50	170	325	157,5	350	0,008

Note: Q - quartile

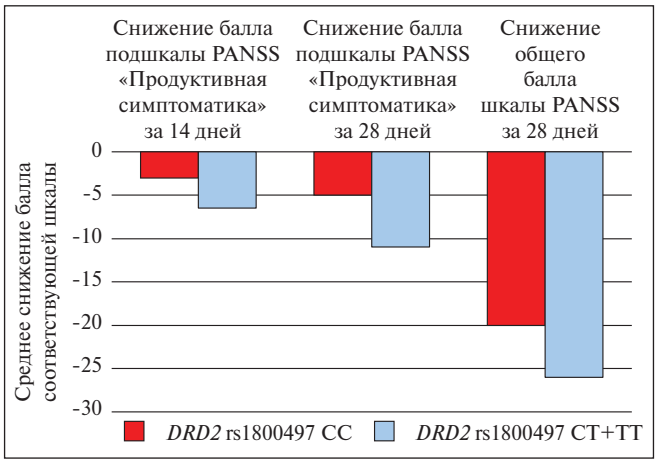

Figure 1. *PANSS scale and Subscale «Positive symptoms» mean score changes depending of DRD2 rs1800497.*

Notes: *Patients with DRD2 rs1800497 polymorphism demostrated substantial decreasing of PANSS subscale «Positive symptoms» score by the 14th day (-6,5) [-10,25; -3,75] vs (-3) [-6,5;-2]; p=0,028) and the 28th day (-11) [-13; -9,5] vs (-5) [-9; -3,5]; p=0,001) compared to the initial state. Also those patients with DRD2 rs1800497 had more prominent decreasing of PANSS total score on the 28th day of therapy (-26) [-37,25; -24] vs [-27,5;-11,5]; p=0,025) compared to wild-type genotype of that polymorphism.*

PANNS – Positive and Negative Symptoms Scale.

Discussion

Differences of initial PANSS scores between carriers of genetic polymorphisms did not influence on mental state changes during treatment. The objectives of the study did not include an interpretation of possible reasons why PANSS scores were initially higher in carriers of certain genotypes.

It was found that only *CYP2D6*4* and *DRD2* rs1800497 showed significant associations with the effectiveness of the treatment of adolescents experiencing acute psychotic episode. *CYP2D6*4* which is associated with slower metabolism of the CYP2D6 isoenzyme, associated with poorer treatment outcomes. That is a controversial result, because reducing the rate of antipsychotics' metabolism should increase their serum levels. At the same time, patients with *CYP2D6*4* have a higher risk to

Table 5. UKU SERS and its' subscales scores on 14th day depending on ABCB1 3435C>T and DRD2 rs1800497 polymorphisms.

Parameters	*ABCB1* C3435T (rs1045642) genotype						p
	CC (n=7)			CT + TT (n=29)			
	Median	Q 1	Q 3	Median	Q 1	Q 3	
UKU SERS Subscale "Autonomous nervous system disturbances" score	0	0	1	2	0,25	5	0,01
UKU SERS total score	2	1	6	8	3	11,75	0,034
Параметр	*DRD2* rs1800497 genotype						p
	CC (n=26)			CT + TT (n=10)			
	Median	Q 1	Q 3	Median	Q 1	Q 3	
UKU SERS Subscale "Neurological disturbances" score	0	0	1	1	0	2,25	0,029

Notes: UKU SERS – UKU Side Effects Rating Scale; Q - quartile

develop schizophrenia than the general population [21]. Consequently, a less pronounced decreasing of the PANSS scores may be due to the increased resistance of symptoms to treatment by *CYP2D6*4*.

Carriers of *DRD2* rs1800497 had better response to psychopharmacotherapy. It was known that *DRD2* rs1800497 leads to decreased density of dopamine receptors in the striatum area, as well as to a deterioration of ligand binding [22]. Positive psychotic symptoms are associated with dopaminergic activity. Increased activity of striatum dopaminergic neurons is one of the pathophysiological mechanisms of psychosis [22]. Thus, the *DRD2* rs1800497 carriage can facilitate the reduction of positive psychotic symptoms by antipsychotics. It should be separately noted that the degree of initial expression of psychosis was not influenced by the carrying of *DRD2* rs1800497. Our findings were consistent with other studies confirming the effect of *DRD2* rs1800497 on improving the response to antipsychotics [23, 24]. But not all studies have found positive results. Escamilla et al. (2018) did not revealed of significant associations *DRD2* rs1800497 with a response to antipsychotics in adult schizophrenics [25], The negative result was also shown by Kang et al. (2015) for amisulphride [26], and by Vehof et al. (2012) for second-generation antipsychotics [27]. But carriers of *DRD2* rs1800497 in our study initially received much higher doses of antipsychotics. However, differences in dosages disappeared after the first week of therapy. This fact may question the isolated effect of the *DRD2* rs1800497 carrier on the reduction of positive symptoms at 14th day: it may have been due to a more aggressive start of psychopharmacotherapy. It is doubtful that the high initial dose had an effect on the reduction of psychotic symptoms on the 28th day of observation. There were no objective reasons why *DRD2* rs1800497 carriers were initially prescribed a higher dose of antipsychotics.

We found significant associations of *ABCB1 3435C>T* and DRD2 rs1800497 with the safety of antipsychotics on 14th day. By 28th day, the average scores of UKU SERS, SAS and BARS scales were not significantly associated with the carriage of genetic polymorphisms.

Presence of *ABCB1 3435C>T* can lead to reduced P-gp activity, which leads to increased concentration of protein-transporter's substrates in blood. Thus, the deteriorating tolerance of antipsychotics in *ABCB1 3435C>T* carriers looks reasonable.

The results obtained in our study are consistent with earlier published data on the impact of *CYP2D6* and *ABCB1* on the safety of antipsychotics in children [8] and adults [28]. The polymorphism *ABCB1 3435C>T* was also previously shown to be substantial for riperidone safety [8]. In our study, that polymorphism was also associated with decreased tolerance of psychopharmacotherapy. Indirect confirmation of the significance of the selected polymorphisms was also the fact that *CYP2D6*10* and *ABCB1* led to an increase in serum levels of some antipsychotics, in particular, riperidone, aripiprasol, clozapine [29–31].

The association *DRD2* rs1800497 with increased score of UKU subscale «Neurological disturbances» obtained in our study looks logical, as extrapyramid symptoms on antipsychotics depend on the activity of dopamine receptors. Reduced expression of dopamine receptors related to *DRD2* rs1800497 polymorphism may lead to excessive blockage of the nigrostriar pathway by antipsychotics, increasing the risk of extrapyramidal symptoms. The predictive role of pharmacodynamic factor's genes for antipsychotic safety has previously been demonstrated in adult patients [32, 33].

Most of research studied the pharmacogenetics of antipsychotics in children was done not on patients with acute psychotic episodes [12]. Consequently, those studies will differ in terms of both doses and delivery times compared to ours. Given the small number of published studies with similar designs, comparison of current research with other pediatric samples was not possible. But few studies done on patients experiencing first psychotic episodes (youths) confirmed the importance of *CYP2D6* and *ABCB1* genes to predict the safety of antipsychotics [34, 35].

The design of our study did not allow us to assess the long-term side effects of antipsychotics: in particular, weight gain. We did not measure the level of prolactin, which can also be attributed to study limitations. But at the same time, our research focuses on a very important problem – the prediction of the effectiveness and safety of antipsychotics during the acute treatment stage of psychosis. The results presented are preliminary, as the study is ongoing and the sample of patients is getting larger. The associations identified are significant for replication on a larger sample of patients.

Conclusion. As a result of the study it was found that *CYP2D6*4* was associated with less reduction of positive psychotic symptoms during treatment with antipsychotics in adolescents with acute psychotic episodes. In contrast, *DRD2* rs1800497 led to a more significant decrease in the severity of total psychotic symptoms on 28th day and positive symptoms – on 14th and 28th days as compared to the initial state.

Polymorphisms *ABCB1 3435C>T* and *DRD2* rs1800497 were significant predictors of antipsychotics' unsafety during the first 14 days of treatment.

It is planned to continue the study and to increase the sample of patients as well as the panel of genetic polymorphisms.

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