ORIGINAL ARTICLE

ANTIPSYCHOTIC TREATMENT EMERGENT ADVERSE EVENTS IN CORRELATION WITH THE PHARMACOGENETIC TESTING AND DRUG INTERACTIONS IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Manuscript received: January 2016

Abstract

Even though a shift toward the use of second generation of modern atypical antipsychotics was partly justified by their lower risk of extrapyramidal symptoms, their serious adverse effects include high risk of weight gain, hyperinsulinemia, metabolic syndrome, type 2 diabetes mellitus. Especially in children and adolescents, the choice of antipsychotic medication should be driven by the safety and side effects profiles. The present study is part of an extensive research on pharmacological treatment in child and adolescent psychoses, performed between 2007 and 2015, focused especially on safety aspects, treatment emergent adverse events (TEAE) and pharmacogenetic correlations. The study group consisted of 90 patients, children and adolescents with psychosis (schizophrenia and bipolar disorder). The primary objective of our study was to evaluate the safety and the adverse events of aripiprazole compared with risperidone in the studied paediatric population. Also a major objective was to establish some correlations between the pharmacogenetic profile of the subjects and the presence of treatment emergent adverse events. We investigated also variables like BMI (Body Mass Index), blood insulin increase in different time points after the long duration administration of the antipsychotic treatment. The obtained results proved a high safety profile, especially for aripiprazole and high correlations of the emergence of the adverse events with the pharmacogenetic profile of the subjects.

Rezumat

Utilizarea antipsihoticelor atipice modern, de generația a doua, a fost justificată parțial de riscul lor scăzut pentru simptome extrapiramidale, însă efectele lor adverse includ un risc ridicat de creștere în greutate, hiperinsulinemie, sindrom metabolic, diabet zaharat de tip 2. În special la copii și adolescenți, alegerea medicației antipsihotice ar trebui să fie ghidată de profilul de siguranță și de profilul efectelor secundare. Studiul de față face parte dintr-o cercetare amplă asupra tratamentului farmacologic al psihozelor la copii și adolescenți, fiind efectuat între anii 2007 și 2015 și s-a axat în special pe aspectele legate de siguranță, evenimentele adverse emergente ale tratamentului și pe corelațiile farmacogenetice. Grupul de studiu a fost format din 90 de pacienți, copii și adolescenți cu psihoze (schizofrenie și tulburare bipolară). Obiectivul principal al studiului a fost de a evalua siguranța și evenimentele adverse ale aripiprazolului, comparativ cu cele ale risperidonei, la populația pediatrică studiată. De asemenea, un obiectiv major a fost acela de a realiza unele corelații între profilul farmacogenetic al subiecților și prezența evenimentelor adverse emergente tratamentului. De asemenea, am investigat variabile cum ar fi IMC (indicele de masă corporală), creșterea insulinemiei în diferite momente de timp după administrarea de lungă durată a tratamentului cu antipsihotice. Rezultatele obținute au dovedit un profil ridicat de siguranță, în special pentru aripiprazol și corelații ridicate între emergența evenimentelor adverse și profilul farmacogenetic.

Keywords: antipsychotics, pharmacogenetic, CYP2D6, adverse events, aripiprazole, risperidone

Introduction

Over the past years, the use of antipsychotic medications has increased in the treatment of children and adolescents with psychosis and bipolar disorders [25, 27, 28]. Early onset schizophrenia represents one of the most severe psychiatric disorders, which can significantly interfere with the

global functioning and the quality of life. Bipolar disorder (BPD) is a serious, challenging psychiatric disorder, characterized by maniac and depressive mood switches and a remitting and relapsing course. This is why, the cornerstone of the clinical and pharmacologic management is the stabilization and preventive interventions using mood-stabilizing medications to reduce both maniac and depressive symptoms but also the use of antipsychotics targeted for the psychotic dimension of BPD, but not limited to this [5, 6]. Several different types of mood stabilizers are available: anticonvulsants such as valproate, carbamazepine, lamotrigine, and on the other side, lithium [14]. Atypical antipsychotic drugs such as olanzapine, risperidone, aripiprazole, quetiapine, lurasidone also have demonstrated their efficacy as mood stabilizers [6, 9]. The use of the first generation of typical antipsychotics can trigger serious side effects like extrapyramidal symptoms, sedation, tardive dyskinesia, neuroleptic malignant syndrome [12, 18]. A shift toward the use of second generation of modern atypical antipsychotics was partly justified by their lower risk of extrapyramidal symptoms, but their serious adverse effects include the high risk of weight gain, hyperinsulinemia, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, elevated prolactin and lipid levels [1, 2, 7, 9, 11, 13, 16]. The atypical antipsychotics carry FDA „black box" warning regarding suicidality, if indicated for depression. Aripiprazole and risperidone oral tablets are approved by FDA for the treatment of adults and adolescents with the indication schizophrenia and for the acute/-maintenance treatment of bipolar mania in adults and paediatric patients, monotherapy or as adjunct to lithium or valproate. Aripiprazole is a dopamine D_2 receptors partial agonist, weak 5-HT_{1A} receptors partial agonist and 5-HT_{2A} receptor antagonist. Risperidone is a dopamine D2, 5-HT_{2A}, α1-adrenoceptor and histamine-1 receptor antagonist [3, 9, 15, 21, 23]. Some of the existing studies showed that concerning the metabolic adverse effects, olanzapine was correlated with high weight gain, iloperidone, quetiapine, risperidone with moderate weight gain and aripiprazole, asenapine, lurasidone, paliperidone, ziprasidone with low weight gain. Concerning the electrocardiography QT interval (ECG QT) prolongation, all the atypical antipsychotics showed high correlations, with few exceptions [20, 30].

Despite these evidences, it is very interesting that receiving the same antipsychotic or mood stabilizing and antidepressive treatment only some patients showed serious adverse effects and others not. This phenomenon could be in correlation with their pharmacogenetic profile. The pharmacogenetic testing allows understanding the role of the genetic component in the response to a particular medication. The variability in the response to pharmacological treatment could be significantly related to the drug metabolism polymorphisms. The cytochrome P450 (CYP450) enzymes are significantly involved in the metabolism of many categories of psychiatric drugs. When choosing the pharmacological treatment we must take also these aspects into account, in order to achieve drug response, in order to avoid adverse events and undesirable drug interactions [3, 17, 19, 24, 31, 32]. Prescribing practices have been under ongoing review due to the marked increase of the "off-label" use and to concerns regarding the medication safety and tolerability. Especially in children and adolescents, the choice of medication should be driven by the safety, side effects profiles, that might affect growth, development, the cognitive domains, the school functioning, the health-related quality of life and the medication adherence and compliance. Great attention should be given also to the drug interactions. There is lack of data and evidence for choices especially between antipsychotics for the paediatric population with psychosis (schizophrenia and other psychotic disorders) and also for mood stabilizers or anti-depressive medication in bipolar disorders. The prescription of pharmacologic treatment/ antipsychotic treatment has to be preceded by a thoughtful risk/benefit evaluation [12, 22, 25].

The primary objective of our study was to evaluate the safety, the adverse events and tolerability of aripiprazole (10 to 30 mg/day) compared with risperidone (2 -4 mg). Also a major objective of our study was to correlate the pharmacogenetic profile of the subjects with the presence of treatment emergent adverse events (TEAE).

Materials and Methods

The present study complied with the Ethical Committee regulations of the University of Medicine and Pharmacy "Victor Babeș", Timișoara, Romania, with the ICH-GCP (Good Clinical Practice) regulations and guidelines and with the Paediatric Investigational Plan.

The present study is part of an extended research on the pharmacological treatment in child and adolescent psychoses performed at the University Hospital for Child and Adolescent Psychiatry and Neurology Timişoara, Romania, between 2007 and 2015 and it was focused especially on aspects of safety, treatment emergent adverse events (TEAE) and pharmacogenetic correlations.

The study group consisted of 90 patients, children and adolescents with psychosis (schizophrenia and bipolar disorder), for whom, the diagnostic was reconfirmed by a Child and Adolescent Psychiatrist, through K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version).The 90 patients included in

the study, were aged between 13 and 20 years (median age 16 ± 3.4). The sex ratio in the study was 1.14:1 male to females (48 male and 42 females). We obtained for each patient under 18 years old, the informed consent from the parents/ legal guardians and also the personal consent for patients over 18 years old. Everybody signed the informed consent before enrolling in the study.

The patients with schizophrenia (n = 44) were randomly assigned, in a 1:1 ratio, into 2 pharmacologic treatment groups: first group (G1) receiving aripiprazole and the second group (G2) risperidone. Also the subjects with bipolar disorder (n = 46) were randomly assigned in two groups and followed the same treatment. We applied the following Rating Scales, in order to evaluate the safety of the antipsychotic medication administered: CSSRS (Columbia Suicide Severity Rating Scale), UKU Side Effects Rating Scale, Extrapyramidal Symptoms Rating Scales – SAS (The Simpson-Angus Scale), AIMS (Abnormal Involuntary Movement Scale), BARS (Barnes Akathisia Rating Scale). We evaluated the safety of the chosen antipsychotic treatment, through: the frequency and severity of adverse events (clinical and laboratory tests); the analysis of potential suicide events recorded on the CSSRS; mean change from baseline and clinically significant values of the laboratory tests (fasting blood lipids and glucose, insulin concentrations), the vital signs and ECG parameters; the mean change from baseline of the z-scores for height and body weight and of the BMI (Body Mass Index); the mean change on the Extrapyramidal Movement Scales.

We assessed the body mass index (BMI) and the blood insulin levels for different time points - at baseline, T1 after 3 months, T2 after 6 months, T3 after 12 months, T4 after 18 months, T5 after 24 months.

Knowing that aripiprazole and risperidone are key CYP2D6 metabolized atypical antipsychotics, we performed the pharmacogenetic testing, through the CYP2D6 genotyping. The CYP2D6 genotyping was performed close to the endpoint of the study, the laboratory staff being blinded to the patient's data. CYP2D6 genotyping was performed using Reverse transcription-polymerase chain reaction (RT-PCR) or Polymerase chain reaction (PCR), followed by electrophoresis. For DNA isolation QIAamp96 DNA Blood Kit (Qiagen) was used and the samples were stored at -80°C. CYP2D6 variant identification was carried out on 7900 HT Fast Real-Time PCR instrument (Applied Biosystems, Foster City, CA) by using TaqMan Drug Metabolism Genotyping Assay for Allelic Discrimination, for the following variants: CYP2D6*3,*4. For CYP2D6*5 a 50-µL long PCR reaction was performed followed by PCR products analysis by 0.8% agarose gel electrophoresis. Two controls were used: AL-1 corresponding to the wild-type (WT) and AL-2 (CYP2D6*3,*4) corresponding to the mutant type (*3,*4). Genotypes were determined by measuring allele-specific fluorescence using the software for allelic discrimination (Applied Biosystems, Foster City, CA).

Knowing that the genotype, the mutant allelic type – (*) of the patients could be responsible for the high percentage of adverse events when taking the specific antipsychotic treatment, at the end, we classified the patients receiving aripiprazole and those taking risperidone (schizophrenia and bipolar subjects) included in this study, in three groups based on the genotype identified: extensive metabolizers (EM) was the most numerous group including subjects carrying the functional allele, normal metabolizers, AL-1 (wt – "wild type") and missing the non-functional allele AL-2 (*3,*4,*5); intermediate metabolizers (IM) were included, being subjects carrying one functional (wt) and one non-functional allele (*3,*4,*5); poor metabolizers (PM) included subjects that exhibit the presence of the non-functional/low functional alleles AL-2 (*3,*4,*5) and were not carrying the functional allele AL-1 (wt).

Efficacy Statistical Analyses. The statistical comparison of the safety/presence of adverse events was performed by the log-rank test comparing the 2 treatment groups (aripiprazole *versus* risperidone) at a significance level of 0.05 and by the Friedman non-parametric test for pair values. We also used the log-rank test for assessing the statistical significance of the differences between the 2 studied groups (with aripiprazole *versus* risperidone) and concerning the adverse events in correlation with the pharmacogenetic profiles. For comparing the weight gain and insulin blood level variation/ increase between groups, we applied the non-parametric test Mann-Whitney. For comparing the median of BMI and the plasma insulin level at two different time points, the nonparametric test Wilcoxon signed Ranks was used.

Results and Discussion

Evaluating the safety profile of the chosen antipsychotics administered in the study groups, we obtained the following results: 32% of the patients taking aripiprazole and 68% of the subjects receiving risperidone showed adverse effects. In the aripiprazole group most adverse events were mild to moderate in severity and only 24% of the total adverse events were considered as TEAE, having a causal relationship with the administered drug. In the risperidone group, 60% of the total AE's (adverse events) were considered TEAE's.

We compared the groups of patients receiving aripiprazole with the group receiving risperidone treatment (schizophrenia as well as bipolar disorder patients), and we reported the incidence of adverse events results represented in Table I.

Table I

Incidence of adverse events in treatment groups with aripiprazole and risperidone (45 subjects receiving aripiprazole, 45 taking risperidone)

Incidence of the main adverse events occurring (%) in patients		
System	**Aripiprazole treatment group (%)**	**Risperidone treatment group (%)**
Gastrointestinal Disorders		
Vomiting, nausea, constipation, diarrhoea	8.8	15.5
Reproductive system		
Dysmenorrhoea, amenoreea	4.4	17.7
Investigations. Laboratory abnormal values with clinical relevance		
Insulin, fasting	13.3	35.5
HDL Cholesterol	7.4	18
Total Bilirubin high	4.4	8.88
Triglycerides	7.5	31.1
Blood glucose increased	8.8	26.6
Nervous System Disorders		
Headache	16.9	21
Somnolence	6.3	15
Tremor	6.6	17
Akathisia	8.8	11
Dyskinesia	4	19
Extrapyramidal symptoms	4.4	16
Psychiatric Disorders		
Anxiety	8.8	26.6
Insomnia	4.7	11
Agitation	8.8	15.5
Aggression	4.4	4
Suicidal ideation - CSSRS	4.4	22.2
Cognitive side effects UKU-scale	8.8	24
Cardiac. Vascular disorders		
Arrhythmia, tachycardia	4.5	11
Orthostatic hypotension	8.8	21
ECG QT prolongation	4.4	17.7
Metabolic effects		
Weight gain ≥ 7 %	11.11	33.3
Weight loss ≥ 7 %	8.8	4.4
BMI (Body Mass Index) increased	13.3	40
Skin and Subcutaneous Tissue Disorders		
Rash	4.4	6.6

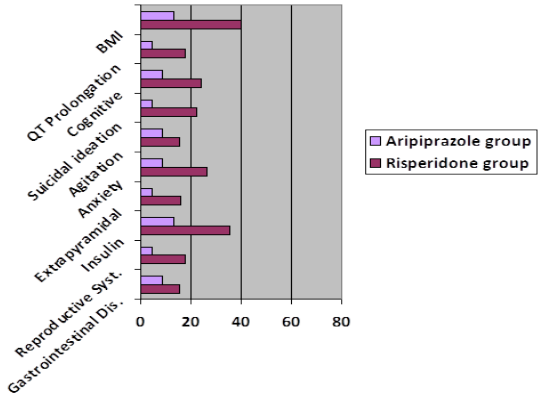

Figure 1.
Incidence of the main adverse effects (%) for study groups treated with aripiprazole *versus* risperidone - in percentages

We summarized the incidence of the main adverse effects for both groups in Figure 1.

In order to evaluate the safety profile of the chosen antipsychotics in the studied groups, we analysed the relevant variables like the mean change from baseline of the BMI and blood insulin levels, which are correlated with the metabolic syndrome, the weight gain and the potential of developing type 2 diabetes mellitus of the psychotic patients under treatment with atypical antipsychotics. We analysed these parameters, with actual values and the mean change from baseline in the aripiprazole treatment group (Table II).

The same parameters concerning the safety profile were analysed in the risperidone treatment group (Table III).

Table II

The mean change from baseline of the BMI and insulin values in the aripiprazole (G1) treatment group

		BMI				Insulin values (uIU/mL)			
Time	**N**	**Actual value Mean (Std. deviation)**	**Change from baseline Mean (SD)**	**Min.**	**Max.**	**Actual value Mean (SD)**	**Change from baseline Mean (SD)**	**Min.**	**Max.**
BASELINE	45	20.73 (2.44)	-	16.00	29.00	11.40 (3.53)	-	4.40	17.70
3 Months	45	21.23 (2.51)	0.5 (0.94)	16.30	29.30	12.01 (3.74)	0.61 (0.97)	4.60	18.10
6 Months	45	22.49 (2.67)	1.76 (0.92)	17.00	29.90	12.21 (3.76)	0.81 (0.99)	4.80	20.30
1 Year	44	22.89 (2.71)	2.16 (0.98)	17.10	30.90	13.87 (5.26)	2.47 (0.96)	4.90	21.10
18 Months	43	23.00 (3.13)	2.27 (0.95)	17.30	36.00	12.44 (3.94)	1.04 (0.98)	4.90	19.70
24 Months	43	24.70 (3.41)	3.97 (0.91)	18.20	36.40	13.79 (4.74)	2.39 (1.04)	5.10	20.10

Table III

The mean change from baseline of the BMI and insulin values in the risperidone (G2) treatment group

		BMI				Insulin values (uIU/mL)			
Time	**N**	**Actual value Mean (Std. deviation)**	**Change from baseline Mean (SD)**	**Min.**	**Max.**	**Actual value Mean (SD))**	**Change from baseline Mean (SD)**	**Min.**	**Max.**
BASELINE	45	21.18 (2.92)	-	17.00	28.00	6.40 (2.11)	-	4.40	12.60
3 Months	44	23.53 (2.78)	2.35 (0.95)	17.30	28.70	9.56 (2.45)	3.16 (0.97)	5.70	13.30
6 Months	41	25.05 (1.99)	3.87 (0.93)	21.70	29.90	15.55 (3.76)	9.15 (0.98)	7.90	24.90
1 Year	37	27.53 (1.93)	6.35 (0.97)	23.80	32.00	26.69 (1.20)	20.29 (0.99)	10.30	41.90
18 Months	36	29.30 (2.14)	8.12 (0.92)	24.70	35.00	32.24 (1.78)	25.84 (1.02)	11.30	52.00
24 Months	35	30.16 (1.99)	8.98 (1.02)	17.50	36.50	34.57 (2.01)	28.10 (1.04)	10.90	56.70

Firstly, we must notice, that more patients in the risperidone treatment group discontinued the study because of their emergent adverse effects.

In order to compare the BMI and insulin values for the 6 time points, for the studied samples of patients, in the aripiprazole treatment group respectively the risperidone group, we applied the Friedman non-parametric test for pair values and comparing the time points each 2 by 2, using the Wilcoxon signed Ranks nonparametric test, we searched in each of the 10 comparisons for statistically significant differences [1, 9, 11, 13, 15-17].

So that, for the aripiprazole treatment group: the BMI increase from the start moment until 24 months, analysing each time point, this increase was not statistically significant. Statistical significance with predictive power was obtained only for time point 4 (after 18 months) and for time point 5 (after 24 months). Concerning the insulin values increase, the registered differences from baseline till the endpoint were not statistically significant in this sample. Comparing the time points each 2 by 2, using the Wilcoxon signed Ranks nonparametric test, we didn't obtain in each of the 12 comparisons statistically significant differences. So that, the registered increase of BMI and insulin values, concerning the mean scores, from baseline till endpoint, was not statistically significant in the aripiprazole treatment group.

In the risperidone treatment group, when comparing the BMI values between the 6 time points, through the Friedman nonparametric test for pair values, we obtained statistically significant differences ($p < 0.001$), the increase of the BMI values from baseline till endpoint being statistically significant. We also obtained high threshold of significance

results and statistically significant differences in each of the 12 comparisons ($\alpha = 0.001$, $p < 0.001$) when comparing the BMI increase values each 2 by 2, using the Wilcoxon signed Ranks nonparametric test. In this study group, the mean patients' scores expressed high BMI increase and weight gain. Also, the registered increase of the insulin values, from baseline till endpoint, was statistically significant in the risperidone treatment group ($\alpha = 0.001$, $p < 0.001$) [21, 23]. We also compared the differences between the aripiprazole and the risperidone treatment group, regarding the evolution of the BMI and insulin level, the results being summarized in Table IV.

Table IV

Statistical differences between the aripiprazole (G1) and the risperidone (G2) treatment group regarding the BMI and insulin level for the 6 time points

Time point	BMI mean		BMI		Insulin mean uIU/mL		Insulin	
			$p^{significance}$	α level of significance			$p^{significance}$	α level of significance
BASELINE	G1	20.73	0.796^{ns}	0.05	G1	11.40	$< 0.001^{s}$	0.001
	G2	21.18			G2	6.40		
3 Months	G1	21.23	$< 0.114^{s}$	0.05	G1	12.01	$< 0.001^{s}$	0.001
	G2	23.53			G2	9.56		
6 Months	G1	22.49	$< 0.001^{s}$	0.001	G1	12.21	$< 0.001^{s}$	0.001
	G2	25.05			G2	15.55		
12 Months	G1	22.89	$< 0.001^{s}$	0.001	G1	13.87	$< 0.001^{s}$	0.001
	G2	27.53			G2	26.69		
18 Months	G1	23.00	$< 0.001^{s}$	0.001	G1	12.44	$< 0.0001^{s}$	0.001
	G2	29.30			G2	32.24		
24 Months	G1	24.70	$< 0.0001^{s}$	0.001	G1	13.79	$< 0.0001^{s}$	0.001
	G2	30.16			G2	34.57		

It is important to note that at the moment of treatment initiation, there were no statistically significant differences between the BMI of patients from G1-aripiprazole treatment and G2 - risperidone treatment group. Contrary, we found at baseline, statistically significant lower values for insulin in G2. We found that the differences of BMI are statistically significant, especially after 6 month of administration of atypical antipsychotics ($p < 0.001$). It was observed that patients from group 2 (G2) showed higher BMI as compared with patients from group 1 (G1). For insulin values, statistically significant differences were found for each time point ($p < 0.001$) and especially higher insulin was in group 2 - risperidone treatment group after 3 months till endpoint in every different time point. So, after antipsychotic treatment, we observed higher mean BMI and insulin levels in the risperidone treatment group [21, 23].

Concerning the pharmacogenetic testing and the CYP2D6 genotyping, in the whole sample of 90 patients with psychosis, we identified: 53 subjects EM (extensive metabolizers) - WT (wild type); 29 subjects IM (intermediate metabolizers) - (WT/*3,*4,*5); 8 subjects PM (poor metabolizers) - (*3,*4,*5).

The distribution of the subjects receiving aripiprazole respectively risperidone, based on their genotype is represented in Figure 2.

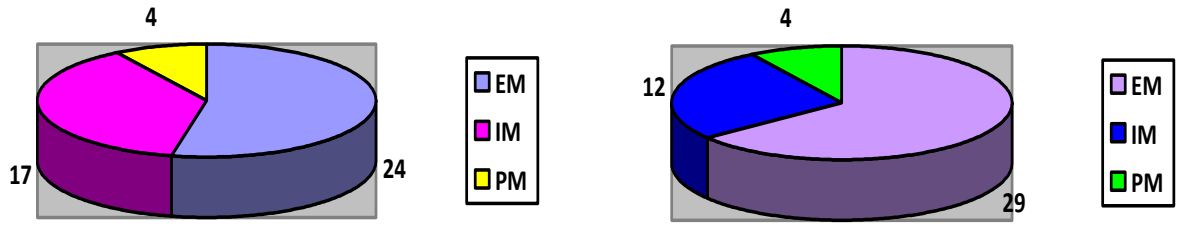

Figure 2.

Patients' distribution based on their genotype (left aripiprazole treatment, right risperidone treatment group)
EM = extensive metabolizers; IM = intermediate metabolizers; PM = poor metabolizers.

We analysed the differences between the genotyped established groups regarding the BMI and insulin level in the aripiprazole treatment group and we obtained statistically significant values ($p < 0.001$) (Table V).

Table V

Statistical differences between the genotyped established groups (the EM-extensive metabolizers and IM-intermediate metabolizers' patients) regarding the BMI and insulin level for the 6 time points in the aripiprazole treatment group

Time point	BMI mean		BMI		Insulin mean uIU/mL		Insulin	
			$p^{significance}$	α level of significance			$p^{significance}$	α level of significance
BASELINE	EM	20.43	0.896^{ns}	0.05	EM	10.80	$< 0.765^{ns}$	0.001
	IM	21.06			IM	12.00		
3 Months	EM	19.01	$< 0.001^{s}$	0.05	EM	11.00	$< 0.001^{s}$	0.05
	IM	23.45			IM	13.01		
6 Months	EM	20.45	$< 0.001^{s}$	0.001	EM	10.21	$< 0.001^{s}$	0.01
	IM	24.53			IM	14.21		
12 Months	EM	19.22	$< 0.001^{s}$	0.001	EM	11.74	$< 0.001^{s}$	0.001
	IM	26.56			IM	16.00		
18 Months	EM	19.02	$< 0.001^{s}$	0.001	EM	07.00	$< 0.0001^{s}$	0.001
	IM	26.98			IM	17.88		
24 Months	EM	22.20	$< 0.001^{s}$	0.001	EM	7.50	$< 0.0001^{s}$	0.001

So we observed in the aripiprazole treatment group, statistically significant differences depending on the CYP2D6 genotype of the patient ($p < 0.001$), meaning that subjects carrying non-functional alleles, showed weight gain, BMI increase, higher insulin levels, being more prone and exposed to the adverse effects of the atypical antipsychotics [15, 17, 19, 31]. On the other side, the global aripiprazole treatment group showed a good safety and low adverse effects profiles.

We also found the correlations between the CYP2D6 patient genotype and the presence of adverse effects like weight gain, high BMI and insulin levels increase, in the risperidone treatment group (Table VI).

Table VI

Statistical differences between the EM (extensive metabolizers) and IM (intermediate metabolizers) patients regarding the BMI and insulin level for the 6 time points in the risperidone treatment group

Time point	BMI mean		BMI		Insulin mean (uIU/mL)		Insulin	
			$p^{significance}$	α level of significance			$p^{significance}$	α level of significance
BASELINE	EM	20.18	0.696^{ns}	0.05	EM	5.80	0.756^{ns}	0.001
	IM	22.18			IM	7.00		
3 Months	EM	21.00	$< 0.001^{s}$	0.05	EM	8.00	$< 0.001^{s}$	0.01
	IM	26.06			IM	11.12		
6 Months	EM	23.00	$< 0.114^{s}$	0.001	EM	10.00	$< 0.001^{s}$	0.001
	IM	27.01			IM	21.10		
12 Months	EM	24.00	$< 0.001^{s}$	0.001	EM	12.38	$< 0.0001^{s}$	0.001
	IM	31.06			IM	41.00		
18 Months	EM	24.50	$< 0.001^{s}$	0.001	EM	15.30	$< 0.0001^{s}$	0.001
	IM	34.10			IM	49.18		
24 Months	EM	26.00	$< 0.001^{s}$	0.001	EM	17.64	$< 0.0001^{s}$	0.001
	IM	34.32			IM	51.50		

We observed in the risperidone treatment group, statistically significant differences in function of the CYP2D6 genotype of the patient ($p < 0.001$), meaning that subjects carrying non-functional alleles - (*3,*4,*5), showed significant weight gain, BMI increase, significant higher insulin levels, being most prone and exposed to the adverse effects of the atypical antipsychotics [21, 23, 31].

On the other side, in comparison with the aripiprazole treatment group, the risperidone group showed globally a higher percentage of adverse effects, in some cases independently of the individual pharmacogenetics profile [26].

In line with other reports, through the present study, we noticed that independently of the antipsychotic medication doses, the pharmacokinetics of atypical antipsychotics (risperidone, aripiprazole) is not affected only by age, but its half-life varies depending on the activity of the CYP2D6 enzyme [19, 32].

Also concerning the medication interactions, we have to be very careful, to know the pharmacogenetic metabolizing pathways of every chosen medication, in order to prevent some unwanted reactions [4, 8, 10, 18, 29]. So, when administering atypical anti-psychotics like aripiprazole and risperidone, we must avoid the strong CYP2D6 inhibitors, the

strong CYP3A4 inhibitors and enzyme inducers from the following drug categories (antipsychotics, antidepressants, mood stabilizers).

Conclusions

There is no first-line antipsychotic drug, which is suitable for all children, so the choice should be driven by the pharmacogenetic profile, correlated with the risks of developing adverse effects, by the medication history and the presence of predominant negative symptoms. Nowadays, in accordance with the PIP - Paediatric Investigational Plan, the drug safety must be investigated, especially in the case of psychotic patients being children and adolescents. From the two atypical antipsychotics, used in our study, aripiprazole proved a better safety profile but both antipsychotics are in the area of safety concerning the major treatment emergent adverse events. Our research is a proof that aripiprazole and risperidone could be safe treatment options in the paediatric population, if we investigate the patient's clinical and pharmacogenetic profile carefully.

The implementation of the pharmacogenetic testing to this category of patients, before choosing the suitable antipsychotics, in the clinical practice, could avoid the severe side effects, like morbid weight gain, metabolic syndrome and suicide. Especially in the paediatric population, it is ethical and cost-effective to prevent the adverse events, the permanent antipsychotic switching, through choosing a proper, tailored antipsychotic treatment.

The therapeutic protocols need to be properly adjusted and improved, in order to correspond to the real needs of the paediatric population with mental disorders. There is lack of data regarding the impact of the pharmacogenetic profile on the incidence of adverse effects, in the case of paediatric patients using atypical antipsychotic drugs, further research being needed.

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