

PHARMACOLOGICAL AND CLINICAL ASPECTS OF EFFICACY, SAFETY AND TOLERABILITY OF ATYPICAL ANTIPSYCHOTIC MEDICATION IN CHILD AND ADOLESCENT PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS

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Abstract

The treatment plan in child psychosis must be carefully managed. Despite of the increasing use of modern, second generation antipsychotics in paediatric patients, data on the efficacy, safety and tolerability of these drugs in the paediatric population are limited. The present research was performed between 2007 and 2015 and includes 90 children and adolescents with a diagnosis of psychosis - schizophrenia or bipolar disorder. Our primary objective was to evaluate the efficacy and safety of aripiprazole compared with risperidone. The efficacy of the pharmacotherapy was evaluated through the mean change in the PANSS (Positive and Negative Syndromes Scale) total scores and the CGI-S (Clinical Global Impression of Severity) from baseline. Our results, showing statistically significant differences, prove the efficacy of the 2 atypical antipsychotics in the paediatric population. Especially aripiprazole showed a high efficacy and safety profile, risperidone being correlated with more adverse events. The present study represents a step forward, although further research was being needed. The paediatric psychiatry therapeutic protocols need to be properly adjusted and improved, in order to correspond to the real needs.

Rezumat

Planul de tratament în psihoza copilului trebuie să fie gestionat cu atenție. În ciuda utilizării tot mai mari a antipsihoticelor moderne, de a doua generație, la pacienții pediatrici, datele privind eficacitatea, siguranța și tolerabilitatea acestor medicamente la populația pediatrică sunt limitate. Prezența cercetare a fost realizată între 2007 și 2015 și include 90 de copii și adolescenți cu un diagnostic de psihoză - schizofrenie sau de tulburare bipolară. Obiectivul nostru principal a fost de a evalua eficacitatea și siguranța aripirazolului comparativ cu risperidona. Eficacitatea farmacoterapiei a fost evaluată prin modificarea scorurilor medii totale ale PANSS (Scala Sindroamelor Pozitive și Negative) și CGI-S (Scala Impresiei Clinice Globale a Severității) de la momentul inițial. Rezultatele noastre, care arată diferențe semnificative statistic, dovedesc eficacitatea celor 2 antipsihotice atipice la populația pediatrică. Aripirazolul a demonstrat un profil înalt al eficacității și siguranței, risperidona fiind corelată cu mai multe efecte adverse. Protocoalele terapeutice în psihiatria pediatrică trebuie să fie ajustate și îmbunătățite în mod corespunzător, pentru a se adresa necesităților reale.

Keywords: schizophrenia, bipolar disorder, paediatric, pharmacological therapy, atypical antipsychotics

Introduction

The present study is very important for the field of pharmaceutical research, making a valuable connection between the experimental and clinical pharmacology. It targets to optimize the Romanian pharmaceutical research, promoting the latest international pharmaceutical news. It is in line with the Pharmacological Paediatric Investigational of EMA

(European Medicines Agency), bringing in the same time in the forefront, the significant role of multi-disciplinary, interdisciplinary working and research. The current study tries to bridge the gap between the pharmacological research and its practical, clinical applicability and resonance.

Child and adolescent psychoses, especially schizophrenia and bipolar disorder represent complex diagnostic

categories and dimensions, being some of the most severe, challenging psychiatric disorders, which can significantly interfere with the global functioning and the quality of life of the patient and of his whole family [12]. Especially in the paediatric population, if improperly treated and managed, the diagnosis has a huge negative impact on the life trajectory and the global development [9, 14]. The treatment plan in child psychosis must be carefully managed, with great attention on aspects of medication safety, tolerability and efficacy [5, 12]. Atypical antipsychotics, although widely used, being effective against both positive and negative symptoms of schizophrenia and the psychotic dimension of bipolar disorder, still need further research for the paediatric population [1, 6]. So, despite of the increasing use of modern, second generation antipsychotics in paediatric patients, data on the efficacy, safety and tolerability of these drugs in the vulnerable paediatric population are limited [8, 16].

We approached some pharmacological and clinical aspects of great interest, nowadays, because there is a lack of data concerning the efficacy and safety of proper pharmacologic treatment in the paediatric population with psychosis [20-24]. Our research addresses actual needs according to the actual Paediatric Investigational Plan and intends to bring new data for the clinicians. According to the Guides to Psychiatric Therapeutics, there are some important issues to consider with both the typical and atypical antipsychotics. The typical antipsychotics tend to cause more extrapyramidal effects and carry a higher risk of tardive dyskinesia, because of the D2 receptor blockade. Psychomotor slowing, tremor, cognitive slowing and avolition are associated with this type of medication. The atypical antipsychotics generally present a partial D2 receptor blockade and a more pronounced 5HT1 antagonism [2, 3]. They carry fewer risks for extrapyramidal symptoms and tardive dyskinesia. On the other hand, they bring the risk of weight gain, diabetes and metabolic syndrome [4]. In the symptomatic management of psychotic disorders, low-doses of risperidone (0.95 to 2 mg/day), aripiprazole (5 to 15 mg/day), olanzapine (2.5 to 5 mg/day) are recommended for paediatric protocols. Assuming fewer risks of metabolic syndrome or diabetes in the psychotic patient, we could start with an atypical agent, using risperidone (0.25 or 0.5 mg/day and slowly increasing the dose upward to 2 - 4 mg/day) or aripiprazole (especially when metabolic syndrome signs emerge we should cross-taper to aripiprazole) - 5 mg/day and slowly increasing the dose to 15 mg as tolerated [10, 15].

Materials and Methods

The present research, being an open-label, prospective study, was performed between 2007 and 2015 and

included children and adolescents with a diagnosis of schizophrenia or bipolar disorder. The research was performed at the University Hospital for Child and Adolescent Psychiatry and Neurology Timișoara, Romania.

During the enrolment period of 5 years, 90 patients with psychosis (schizophrenia and bipolar disorder) were found eligible for entrance in the research study. Criteria for inclusion in this study were: male and female, inpatients or outpatients, with an established diagnosis of schizophrenia or bipolar disorder, according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV), which was reconfirmed by a Child and Adolescent Psychiatrist, certified rater, through K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version); the age < 18 years or under 21 years if the patients were still studying in school; patients with psychotic exacerbation, needing antipsychotic treatment; a baseline PANSS (Positive and Negative Syndrome Scale) score ≥ 70 and a CGI-S (Clinical Global Impression of Severity) > 4 (4 = moderately ill); Exclusion criteria were: other psychiatric comorbidities needing sustained treatment; mental retardation; known medical conditions and abnormal laboratory findings. 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 (48) to females (42).

We obtained for each patient under 18 years, the informed consent from the parents/legal guardians and the assent from the child and for the patients over 18 years we obtained the informed consent signed by them. Our study is in accordance with the Ethical Committee regulations of the "Victor Babeș" University of Medicine and Pharmacy Timisoara, with the ICH-GCP (Good Clinical Practice) regulations and guidelines and with the Paediatric Investigational Plan.

The patients (44 with schizophrenia) were randomly assigned, in a 1:1 ratio, into 2 pharmacologic treatment groups: first group receiving aripiprazole and second group risperidone, the same algorithm being used for the 46 subjects with bipolar disorder. The study had an Antipsychotic Medication Conversion/Titration, Stabilization and Maintenance phase.

The primary objective of our study was to evaluate the efficacy, safety and tolerability of aripiprazole (10 to 20 mg/day) compared with risperidone (2mg) for the 2 diagnostic groups. We applied the following Rating Scales: PANSS, CGI-S, CGI-I (Clinical Global Impression of Improvement), CSSRS (Columbia Suicide Severity Rating Scale), CGAS (Children's Global Assessment of Functioning Scale). The PANSS-Positive and Negative Syndrome Scale was applied by an authorized rater, in order to offer an objective measure for the psychiatric symptoms, to evaluate the psychopathology, the positive, negative

and general symptoms. We assessed the *efficacy* through the drug response to the atypical antipsychotic pharmacologic treatment and the clinical outcome, measured through the PANSS scores. The efficacy of the pharmacotherapy (aripiprazole *versus* risperidone) was evaluated through the mean change in the PANSS total scores and the CGI-S (Clinical Global Impression of Severity) from baseline - T0, through every timepoint - T1 = after 3 months, T2 = after 6 months, T3 = after 12 months, T4 = after 18 months, till endpoint - T5 = after 24, the mean CGI-I (Clinical Global Impression of Improvement) at endpoint and the mean CGAS change from baseline to endpoint. We took into account the fact that high PANSS scores mean a poor clinical evolution in schizophrenia and bipolar disorder and decreased scores are correlated with a clinical improvement. We quantified a good drug response if an improvement with $\geq 35\%$ of the PANSS score from baseline was noted. The efficacy of the treatment was also evaluated through the number of responders, meaning the patients who had psychosis stability criteria (PANSS scores < 70 - for the schizophrenia patients and < 60 for the bipolar disorder patients, CGI-S under 4 and CGI-I under 3 = minimally improved). We evaluated the *safety* of the chosen antipsychotic treatment, through: the frequency and severity of adverse events (clinical and laboratory) and the analysis of potential suicide events recorded on the CSSRS. We also assessed the treatment compliance of the patients, by counting the used tablets between the visits, comparing the values with the expected number of taken tablets. Also noncompliant patients (compliance under 80%) were properly counselled.

Efficacy Statistical Analyses. The statistical comparison of the efficacy main endpoint was performed by the log-rank test comparing the 2 treatment groups (aripiprazole *versus* risperidone) at a significance level of 0.05. We also used the log-rank test for testing the statistical significance of the differences between the 2 studied groups (with aripiprazole *versus* risperidone).

Results and Discussion

The obtained results concerning the antipsychotic medication efficacy assessments are presented in the present study, mainly through: PANSS consisting

of 3 subscales containing a total of 30 symptom dimensions, 3 subscales (Positive Symptoms Subscale - delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, and hostility; Negative Symptoms Subscale - blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking; General Psychopathology Subscale - somatic concern, anxiety, guilt feelings, tension, mannerism and posturing, depression, motor retardation, uncooperative, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance) [7, 14]. For each symptom dimension, severity was rated on a 7 - point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms; CGI-S - Clinical Global Impression Severity (1 = normal, 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients; CGI-I - Clinical Global Impression - Improvement (1 = very much improved, 2 = much improved, 5 = minimally worse, 6 = much worse, 7 = very much worse); CGAS - Children's Global Assessment Scale - a 100 - point rating scale measuring the global, psychological, social, and school functioning of the children and their evolution in correlation with the administered antipsychotic medication. Our study samples consisted of the group of subjects with schizophrenia (G1 = 22 patients with aripiprazole antipsychotic treatment and G2 = 22 subjects taking risperidone) and the subjects with bipolar disorder (G3 = 23 patients taking aripiprazole and G4 = 23 subjects taking risperidone). For the schizophrenia lot, at baseline, the total mean PANSS score was 96.03 ± 19.1 , the positive symptoms score 33.8 ± 6.5 and the negative symptoms score 30.02 ± 8.8 . We applied Friedman nonparametric test for pair values in order to compare the PANSS mean total scores values for 6 time points (T0 = Baseline, T1 = after 3 months, T2 = after 6, T3 = after 12 months, T4 = after 18, T5 = after 24), for the 4 study groups identified, in the whole sample of patients with schizophrenia and bipolar disorder (Table I).

Table I

Comparison between the mean total PANSS scores for the 6 time points for the 2 study groups with schizophrenia

Time point	No. cases	PANSS Mean	Std. Deviation	Minimum	Maximum
Group 1 (Schizophrenia patients taking aripiprazole)					
T0	22	135.7	16.89	92	192
T1	22	123.3	15.72	89	178
T2	22	102.3	14.86	68	156
T3	22	95.2	14.95	66	128
T4	22	87.3	15.29	64	120
T5	22	80	10.21	59	107

Time point	No. cases	PANSS Mean	Std. Deviation	Minimum	Maximum
Group 2 (Schizophrenia patients taking risperidone)					
T0	22	134.8	15.19	91	190
T1	22	122.2	12.62	85	175
T2	21	115.4	10.37	80	160
T3	19	110.9	10.84	77	143
T4	18	96.2	16.14	69	128
T5	18	92.3	10.24	67	119

We have obtained statistical significant differences concerning the PANSS results on the 5 timepoints, as well as at endpoint, in the sample with schizophrenia patients, between group 1 of patients treated with aripiprazole and group 2 treated with risperidone ($p < 0.001$, the significance level $\alpha = 0.001$) [13]. The PANSS mean total scores registered a statistically significant decrease, meaning an improvement concerning the clinical evolution especially for the patients in group 1, treated with aripiprazole, who were considered treatment responders, achieving in a high percentage of the patients the stability criteria [1]. Also the group of patients treated with risperidone registered clinical improvement expressed through the decrease in the PANSS mean total scores but not at the same level of significance, so that not so many patients in this group 2 have been responders achieving the stability criteria. Comparing the total PANSS scores for group 1 (patients treated with aripiprazole) in each 2 with 2 time points with

the Wilcoxon signed Ranks non-parametric test, we obtained statistically significant differences ($p < 0.001$), for the group 2, the differences being not so significant, especially between baseline and endpoint T5 PANSS results ($p = 0.109$, $\alpha = 0.05$). We also noticed that in both patient groups 1 and 2, the PANSS results for the Positive Subscale decreased substantially, meaning clinical improvement but concerning the PANSS Negative Symptoms Subscale and the Cognitive Subscale, the group 1, taking aripiprazole as antipsychotic medication registered a stronger, significant decrease of the scores, correlated with better clinical evolution on the dimension of social interaction and on the cognitive one [2, 19]. In the sample of bipolar disorder patients, the differences between G3, treated with aripiprazole and G4, taking risperidone, were not so significant, but we noticed the decrease in PANSS scores and clinical improvement in both studied groups (Table II).

Table II

Comparison between the mean total PANSS scores for the 6 time points for the 2 study groups with bipolar disorder

Time point	No. cases	PANSS Mean	Std. Deviation	Minimum	Maximum
Group 3 (Bipolar disorder patients taking aripiprazole)					
T0	23	88.2	18.16	77	99
T1	23	85.4	13.60	72	93
T2	23	83.8	19.40	67	88
T3	22	80.8	14.48	62	83
T4	21	71.7	12.29	56	79
T5	21	66.3	10.16	53	75
Group 4 (Bipolar disorder patients taking risperidone)					
T0	23	87.4	16.16	75	98
T1	22	80.4	10.60	67	89
T2	20	74.8	15.40	62	81
T3	18	66.8	13.48	60	78
T4	18	62.3	12.59	53	72
T5	17	55.3	11.17	49	70

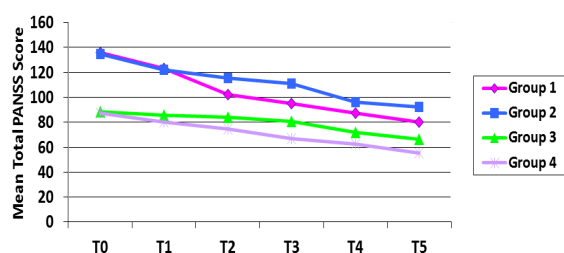


Figure 1.

Mean total PANSS scores evolution for the 4 groups (T0-T5)

The best clinical improvement, depicted through the decrease in PANSS scores between baseline and endpoint was registered in group 4. These results are proving the fact that the patients achieved in higher percentage the clinical stability criteria and better drug response in the bipolar patients group taking risperidone [5, 9]. For each of the 4 groups, a decrease of the mean total PANSS scores was found, indicating an amelioration of the symptoms and clinical improvement [17]. The 2 atypical antipsychotics proved both their efficacy in the paediatric population with schizophrenia respectively with bipolar

disorder - higher drug efficacy being described for aripiprazole in the schizophrenia patients and for risperidone in the bipolar disorder sample (Figure 1). In our study population, we found for the patients in group 1, the best drug efficacy and response, with a decrease $\geq 35\%$ in the PANSS scores from baseline. So, we correlated the obtained results with

a higher clinical improvement for the schizophrenia patients treated with aripiprazole, as a positive response to the atypical antipsychotic. An analysis of the mean change from baseline in CGI-S Score, capturing the clinical evolution of the sample with schizophrenia for group 1 and 2 is represented in Table III.

Table III

Comparison between the mean total CGI-S scores for the 6 time points for the 2 study groups of patients with schizophrenia

Time point	No. cases	Actual value CGI-S (SD)	Change from baseline CGI-S (SD)	Minimum	Maximum
Group 1 (Schizophrenia patients taking aripiprazole)					
T0	22	5.2 (0.94)	-	4.26	6.14
T1	22	4.5 (1.08)	-0.7 (0.97)	3.42	5.58
T2	22	4.0 (1.12)	-1.2 (0.94)	2.88	5.12
T3	22	3.8 (1.14)	-1.4 (0.95)	2.66	4.94
T4	22	3.5 (1.07)	-1.7 (0.98)	2.43	4.57
T5	22	3.3 (1.5)	-1.9 (1.04)	1.8	4.8
Group 2 (Schizophrenia patients taking risperidone)					
T0	22	5.1 (0.95)	-	4.15	6.05
T1	22	4.9 (1.05)	-0.2 (0.95)	3.85	5.95
T2	21	4.8 (0.97)	-0.3 (0.93)	3.83	5.77
T3	19	4.6 (1.15)	-0.5 (0.97)	3.45	5.75
T4	18	4.4 (1.2)	-0.7 (1.02)	3.2	5.6
T5	18	4.3 (0.96)	-0.8 (0.92)	3.34	5.26

So we observed improvements in the CGI-S scores in both groups, the clinical improvement being more significant for the group 1 schizophrenia patients treated with Aripiprazole. The patients in group 1 also achieved in higher percentage the clinical stability criteria after the antipsychotic

treatment, through CGI-S scores under 4 and CGI-I scores under 3. For the sample of patients with bipolar disorder, we obtained clinical improvements through the decrease of the CGI-S scores, for both groups 3 and 4, with lower scores and a more significant clinical improvement for group 4 (Table IV).

Table IV

Comparison between the mean total CGI-S scores for the 6 time points for the 2 study groups of patients with bipolar disorder

Time point	No. cases	Actual value CGI-S (SD)	Change from baseline CGI-S (SD)	Minimum	Maximum
Group 3 (Bipolar disorder patients-taking aripiprazole)					
T0	23	4.2 (1.29)	-	2.91	5.49
T1	23	3.6 (1.08)	-0.7 (0.97)	2.52	4.68
T2	23	3.3 (1.12)	-1.2 (0.94)	2.18	4.42
T3	22	2.9 (1.14)	-1.4 (0.95)	1.76	4.04
T4	21	2.5 (1.07)	-1.7 (0.98)	1.43	3.57
T5	21	2.3 (1.5)	-1.9 (1.04)	0.8	3.8

Time point	No. cases	Actual value CGI-S (SD)	Change from baseline CGI-S (SD)	Minimum	Maximum
Group 4 (Bipolar disorder patients taking risperidone)					
T0	23	4.1 (1.25)	-	2.85	5.35
T1	22	3.4 (1.15)	-0.2 (0.95)	2.25	4.55
T2	20	3.2 (0.97)	-0.3 (0.93)	2.23	4.17
T3	18	2.7 (1.13)	-0.5 (0.97)	1.57	3.83
T4	18	2.3 (1.2)	-0.7 (1.02)	1.1	3.5
T5	17	1.8 (0.96)	-0.8 (0.92)	0.84	2.76

An analysis of the mean change from baseline in CGAS Scores proves statistically significant results ($p < 0.001$): the patients in group 1 with schizophrenia receiving treatment with aripiprazole registered higher improvements of the global state, with increased, higher CGAS scores in comparison with the patients treated with risperidone from group 2 (Table V).

Table V
CGAS Scores - Mean Change from Baseline for the 4 groups of patients

Group	Actual Value		Change from Baseline
	Baseline	Endpoint	Mean (SD)
G1	40.4 (13.0)	75.9 (12.3)	35.5
G2	43.2 (12.8)	61.5 (10.2)	18.3
G3	61.3 (11.6)	77.5 (11.7)	16.2
G4	63.5 (10.9)	78.7 (11.5)	15.2

For the group of patients with bipolar disorder, the differences of the endpoint CGAS scores and concerning the improvement of the global functioning are less significant, when comparing group 3 and 4. Also, for all the studied samples, through the median scores, improvement of global functioning on both the atypical antipsychotics has been registered [20-24]. Concerning the treatment compliance, 98.3% of the patients receiving antipsychotic treatment with aripiprazole reported $\geq 90\%$ aripiprazole oral tablet compliance and only 75% in the group of patients taking risperidone.

Observing the medication discontinuation rate, 18% of the schizophrenia patients discontinued the treatment, no patient with schizophrenia receiving aripiprazole, 8.6% from the bipolar patients taking aripiprazole and 26% from the subjects receiving risperidone [16, 21-24].

The main reasons for discontinuation, for the patients receiving risperidone were adverse events

(41%), treatment emergent adverse events (TEAE - 29%), lack of compliance (12%), lack of medication efficacy (12%) and withdrawal of consent (6%) and for the only 8% of subjects taking aripiprazole, who dropped out the study, the discontinuation reasons were the adverse events respectively the lack of compliance (Figure 2).

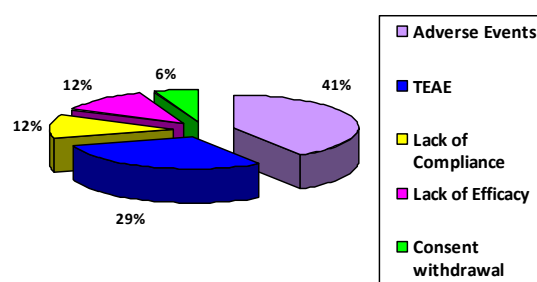


Figure 2.
Main reasons for discontinuation of the treatment for patients taking risperidone

So the most significant reasons for discontinuation of the treatment with risperidone were by far the adverse events (41%) and TEAE (29%), the most relevant adverse events being – weight gain, agitation, anxiety, extrapyramidal symptoms, akathisia, hyperglycaemia, hyperinsulinemia, orthostatic hypotension, ECG QTc interval prolongation, which is in accordance with other studies [11, 18]. So, the primary efficacy variables showed that aripiprazole was superior to risperidone in the schizophrenia group ($p < 0.001$). On the other side, both atypical antipsychotics proved efficacy in the studied paediatric population. Aripiprazole had an advantage for negative symptoms, possibly reflecting an overall activation effect. Risperidone administration was correlated with more adverse events and TEAE, respectively a statistically significant greater percentage of subjects discontinued the study and treatment [13]. Aripiprazole proved a very good efficacy and safety profile, the obtained results being in line with data from the existing literature [17, 21-24].

Conclusions

We can conclude that through this study, the chosen atypical antipsychotics proved a high efficacy and safety profile in the paediatric population.

In child and adolescent subjects with schizophrenia and bipolar disorder, with manic or mixed episodes, with or without psychotic features, both aripiprazole and risperidone treatment, proved their efficacy and especially aripiprazole was well tolerated without significant adverse effects or cognitive side effects. The research results are valuable because the treatment period was of long duration. The subjects showed clinical improvements of the global functioning, proving that through proper pharmacologic intervention strategies, the quality of life of the patients and their families can significantly increase. The pharmacologic efficacy, safety and tolerability of atypical antipsychotics have been studied in some studies in adults, but there is a scarcity of research studies involving children and adolescents, although these medication is extensively used, sometimes "off label" in this population, so that our present study represents a step forward, further research being needed.

The therapeutic protocols need to be properly adjusted and improved, in order to correspond to the real needs of the paediatric population with psychiatric disorders.

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