Key Words: adolescents; antipsychotics; early onset; schizophrenia; adverse effects; extrapyramidal side-effects; efficacy

Antipsychotic Medication in Adolescents Suffering from Schizophrenia: A Meta-Analysis of Randomized Controlled Trials

By Ignazio Ardizzone, Francesca Nardecchia, Arianna Marconi, Teresa I. Carratelli, Mauro Ferrara

ABSTRACT ~ **Background:** *The aim was to perform a meta-analysis on the efficacy, safety and tolerability of antipsychotic drugs in adolescents aged between 13 and 17 suffering from Schizophrenia.* **Methods:** *Enclosed studies*

– were multicentric, randomized, double-blind clinical trials;
– included only adolescents (aged 13–17) with DSM-IV diagnosis of Schizophrenia;
– used standardized scales to assess efficacy, safety and tolerability of antipsychotics.

Results: *All treatments resulted in significant improvements in Positive and Negative Syndrome Scale (PANSS) total score ($p < 0.001$), in PANSS positive subscale score ($p < 0.001$) and in Clinical Global Impression Scale-Severity of Illness score ($p < 0.001$) at the endpoint. Patients with a considerable weight gain were significantly higher in the Olanzapine-treated group. Data about extrapyramidal side-effects were not available for Olanzapine. Risperidone group was associated with a significantly major incidence of akathisia, tremor and dystonic events than controls. High dose of Aripiprazole was associated with a significant major incidence of tremor and Parkinsonism ($p < 0.01$) than controls.* **Conclusions:** *Results demonstrated that antipsychotic treatment with Risperidone, Olanzapine or Aripiprazole in adolescents affected by Schizophrenia led to significant improvements in symptomatology. A pharmacological treatment for adolescents suffering from Schizophrenia must fulfil several prerequisites, to grant the most favourable outcomes, avoiding acute and long term side-effects.*

Treatment with a 10 mg daily dose of Aripiprazole was associated with the lowest incidence of extrapyramidal symptoms and showed no significant weight gain. If a treatment with antipsychotic drugs associated with significant weight gain as Olanzapine or Risperidone is needed, compensative measures should be soon considered. Psychopharmacology Bulletin. *2010;43(2):41–62.*

Drs. Ardizzone, MD, PhD, Nardecchia, MD, Marconi, MD, Ferrara, MD, Department of Child and Adolescent Neurology, Psychiatry and Rehabilitation, SAPIENZA, University of Rome, Roma, Italy. Dr. Carratelli, Head Physician, Department of Child and Adolescent Neurology, Psychiatry and Rehabilitation, SAPIENZA, University of Rome, Roma, Italy.

To whom correspondence should be addressed: Dr. Arianna Marconi, MD, Department of Child and Adolescent Neurology, Psychiatry and Rehabilitation, SAPIENZA, University of Rome, via Doria 36, 00192 Roma, Italy. Phone: 00393495867383; Email: arimarc_83@yahoo.it

INTRODUCTION

Schizophrenia is a severe chronic neuropsychiatric disease, characterized by a massive individual, familiar and social burden.

Developmental events and antecedents of Schizophrenia may include a broad variety of dysfunctions and disorders as increased rates of soft neurological signs and obstetric complications, slow habituation and high baseline autonomic activity, elevated prevalence of developmental disorders of speech and/or language and overall and specific cognitive deficits.[1–3]

Early onset Schizophrenia was formerly defined as "Schizophrenia with onset prior the age of 18".[4]

No study specifically directed to the estimation of prevalence of very early onset Schizophrenia has been published, nevertheless it is assumed that only 0.1 to 1% of all schizophrenic psychoses manifest themselves before the age of 10 years, while the incidence rate increases remarkably during adolescence.[5] According to this data, two subtypes can be distinguished: Very Early Onset Schizophrenia (VEOS), with onset before 13, and Early Onset Schizophrenia (EOS), with onset between 13 and 17.[6,7]

The diagnosis can be made when the specific criteria of DSM-IV or ICD- 10 are satisfied.

If compared with adult-onset Schizophrenia, early onset Schizophrenia and very early onset Schizophrenia show specific features: insidious onset; more severe premorbid neurodevelopmental abnormalities; more frequent terrifying visual hallucinations; invariable inappropriate or flattened affects; higher rate of familial psychopathology; minor response to treatment; and worse prognosis.[6–8]

Treatment of Schizophrenia was revolutionized by the discovery of antipsychotic drugs since the 1950s and later by the development of atypical antipsychotics, started with the release of Clozapine in the US in 1989.

To start the treatment as soon as possible is fundamental for a better outcome[9,10] but the pharmacological management of younger psychotic patients remains controversial because of lack of evidences. There is a paucity of studies on early onset Schizophrenia treatment although the number of randomised controlled trials in which antipsychotic drugs are assessed is continually increasing.[11]

CLINICAL INDICATIONS OF ANTIPSYCHOTIC DRUGS IN DEVELOPMENTAL AGE: STATE OF THE ART

Atypical antipsychotics are used for a plenty of several childhood and adolescent psychiatric disorders[12] as Disruptive Behavioural Disorders,

Pervasive Developmental Disorders, Tic Disorders, Schizophrenia, and Bipolar Disorder.[13–15]

Despite, a large use of atypical drugs is not supported by available evidence for safety and tolerability: both in USA and in Europe, the largest part of outpatient prescriptions of psychotropics[16–19] are "off label".[20]

Although continuity and similarity with the adult form are often recognised, differences in neuroreceptor sensitivities are strongly postulated, especially in consequence of the demonstration of the peculiar child response to antidepressant medication. Moreover, animal experimentation and clinical experience suggested that this category of patients could be more sensitive to extrapyramidal adverse effects, sedation, prolactin increase and weight gain.[21–23]

Several studies highlighted changes in the dopaminergic system and other neurotransmitter systems in late adolescence especially in the prefrontal cortex.[24] These modifications concern dopamine cell density,[25] basal dopamine levels,[26] dopamine turnover,[27] dopaminergic prefrontal cortex input[28] and D_1 and D_2 receptor concentrations in the striatum.[29,30]

These changes may explain the increased incidence of Schizophrenia onsets during adolescence and early adulthood[31] and may be responsible of the peculiar incidence of side effects and of the specific clinical response to atypical antipsychotics in adolescence.

The peculiar characteristics of child and adolescent patients suffering from Schizophrenia require a particular caution in approving the prescription of an antipsychotic drug.

In the past years researchers investigated the use of antipsychotic medications in patients of this age, nevertheless the large part of the studies were short-term or showed substantial methodological limitations.[32–40]

Up to June 2009, US Food and Drug Administration (FDA) exclusively approved the use of Aripiprazole and Risperidone for paediatric indications. Although Olanzapine, Quietatine and Ziprasidone showed efficacy in early-onset Schizophrenia treatment, they did not received approval because of significative incidence or severity of side effects. However in December 2009 Olanzapine has been approved to treat Schizophrenic adolescents even if with Special Consideration because of the increased potential for weight gain and hyperlipidemia; besides, the FDA stated that clinicians have to consider prescribing other drugs in adolescent patients.

In Europe, EMEA approved the use of Aripiprazole for the treatment of Schizophrenia in adolescents older than 15 years while Olanzapine and Risperidone are not recommended, due to a lack of data on safety and efficacy.

Safety and tolerability are the most important characteristics in determining which antipsychotic agent would be better to prescribe to this

category of patients. This meta-analysis aims to assess which of these antipsychotic drugs has a better profile considering efficacy, safety and tolerability parameters and is intended to provide a tool for neuropsychiatrists, paediatricians and practitioners. Physicians must be aware of the experimental evidences regarding the use and management of different antipsychotics, in addition to their strengths and weaknesses, their side-effects profile and their monitoring requirements: the selection of appropriate agent, a correct timing and dosing, together with the early identification and treatment of side-effects, are fundamental to maximize therapeutic benefits.

DRUGS CHARACTERISTICS

Aripiprazole is a dopamine-serotonin system stabilizer with potent partial agonist activity at dopamine D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[41–44]

The FDA first approved Aripiprazole for the treatment of Schizophrenia in adults on November 2002, while the supplemental new drug application for the use in adolescents between 13 and 17 years was announced on November 2007. In adolescent patients with Schizophrenia, the recommended Aripiprazole oral target dose is 10 mg/day (with a starting dose of 2 mg/day which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days).

Risperidone is a benzisoxazole derivative with potent serotonin 5-HT_{2A} and dopamine D_2 receptor-blocking properties. The FDA approved the use of Risperidone in October 2006 for treating irritability associated with autistic disorders in children and adolescents aged 5 to 16 years and on August 2007 for treating children and adolescents suffering from Schizophrenia and mania or mixed episodes of bipolar I disorder: Risperidone was the first atypical antipsychotic drug approved for either disorder in young patients.

Olanzapine is an atypical antipsychotic with a broad spectrum of affinity for several receptors (serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and 5-HT_6 and dopamine $D_{1–5}$,α_1, histamine H_1, and muscarinic $M_{1–5}$). Olanzapine showed to be effective in treating symptoms of Schizophrenia.[45]

In December 2009 the FDA approved the use of Olanzapine for treating adolescents suffering from Schizophrenia but not as first-line treatment for the potential long-term risks associated with its use.

OBJECTIVES

We carried out an exploratory meta-analysis by identifying all recent investigations related to antipsychotic treatment of Schizophrenia in

adolescents to examine the evidence from randomized, double-blind comparison studies supporting the use of antipsychotics in Early Onset Schizophrenia. Our primary aim was to compare efficacy, safety and tolerability of such medications in order to give an evidence-based overview and to provide a tool for clinicians in the choice and in the monitoring of pharmacotherapy in these young patients.

METHODS

Literature Search and Data Extraction

A systematic literature search using the Medline and the Cochrane Library databases was performed to identify studies concerning the use of antipsychotic in adolescents suffering from Early Onset Schizophrenia. We started our search in May 2009 and searched up to September 2009. Key search terms included Antipsychotics and Schizophrenia. We limited our search for

– Randomized Control Trials carried out with
– double-blind method to increase the quality of pooling analysis; studies
– published or added to PubMed in the last 5 years;

Two readers (F.N. and A.M) independently reviewed all 171 abstract identified by the search and found 10 studies[46–55] meeting our inclusion criteria. Any disagreement was resolved by discussion. To have the maximum of homogeneity we choose stricter inclusion criteria: considering the high diversity between children and adolescents as well as the rarity of Childhood onset Schizophrenia in comparison with Early Onset Schizophrenia, we included only studies with an age range of 13–17 years. Seven studies,[46–49,51–53] though involving individuals of this age, showed a population characterized by a broader age range and didn't allow to extract only data concerning 13 to 17 year-old subjects. We included studies involving only patients with a diagnosis of Schizophrenia excluding those works with subjects suffering from other Schizophrenia Spectrum Disorders.[46–50] Moreover, we excluded works involving treatment resistant patients.[48,49,52] For these reasons, seven works were excluded from the meta-analysis.

Table 1 shows the main characteristics of excluded studies.

We assessed methodological quality of included trials in this meta-analysis using the criteria described in the Cochrane Handbook[56] and the Jadad Scale.[57] The former is based on the evidence of a strong relationship between allocation concealment and direction of effect.[58] The categories are defined below:

TABLE 1

Characteristics of Excluded Studies from the Meta-Analysis

Authors	Participants	Diagnosis	Type of Study	Drugs
Sikich et al., 2004	N = 50; aged 8–19 years	Psychosis NOS; Schizophreniform Disorder, Schizophrenia; Schizoaffective Disorder; Delusional Disorder; Major Depression with Psychotic Features; Bipolar Affective Disorder with Psychotic Features	Randomized, double-blind, flexible dose, parallel treatment trial	Risperidone; Olanzapine; Haloperidol
Mozes et al., 2006	N = 25; aged 9–14 years	Schizophreniform Disorder; Disorganized Schizophrenia; Paranoid Schizophrenia; Unspecified Schizophrenia	Comparative, randomized, prospective, flexible dose, open-label trial	Risperidone; Olanzapine
Shaw et al., 2006	N = 25; aged 7–16 years; treatment resistant	Schizophrenia (with onset before 13 years old)	Double-blind, randomized control study with a 2-year open-label follow-up	Clozapine; Olanzapine
Sporn et al., 2007	N = 54; aged 6–18 years; treatment resistant	Schizophrenia (with onset before 13 years old)	Double-blind (N = 22) or Open-label (N = 32) study	Clozapine; Haloperidol; Olanzapine
Jensen et al., 2008	N = 30; aged 10–18 years	Schizophrenia; Schizoaffective Disorder; Schizophreniform Disorder; Psychotic Disorder NOS	Pilot study, randomized, open-label, flexible-dose, parallel trial	Risperidone; Olanzapine; Quetiapine
Kumra et al., 2008	N = 39; aged 10–18 years treatment resistant	Schizophrenia, Schizoaffective Disorder	Double-blind, randomized clinical trial	Clozapine; high dose Olanzapine
Sikich et al., 2008	N = 116; aged 8–19 years	Schizophrenia; Schizoaffective Disorder; Schizophreniform Disorder	Double-blind, randomized, multisite, dosing flexible trial	Olanzapine; Risperidone; Molindone + benzotropine

Abbreviations: EOSS, Early Onset Schizophrenia Spectrum; NOS, not otherwise specified.

A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (some doubt about the results)
C. High risk of bias (inadequate allocation concealment).

Trials were included if they met the Cochrane Handbook criteria A: Leucht et al. (2009)[59] found that open-label and single-blind studies yielded significantly higher effect sizes than did double-blind studies in several domains of efficacy and tolerability.

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale includes three items:

1. Was the study described as randomized?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop outs?

Each item receives one point if the answer is positive. In addition, a point can be deducted if either the randomisation or the blinding/masking procedures described are inadequate. We used 3-points cut-off on the Jadad scale to check the assessment made by the Handbook criteria.

Through this very tight selection, investigated population had the same characteristics to be pooled together.

We identified three studies for inclusion[50–52] (Table 2). All studies:

- reported data on short-term follow-up (6 or 8 weeks);
- were multicentric, randomized, double-blind clinical trials;
- included only adolescents (aged 13–17) with DSM-IV diagnosis of Schizophrenia, assessed by using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime (K-SADS-PL);[60]
- excluded treatment resistant patients:
- used standardized scale to assess efficacy, safety and tolerability of antipsychotic drugs (i.e. Simpson Angus Scale, Barnes Akathisia Rating Scale and Abnormal Involuntary Movement Scale);
- had no more of 40% of discontinuation rate.

In all the studies, patients underwent a screening phase and a wash out period for psychotropic medications and substances of misuse. Both in Kryzhanovskaya et al., and in Findling et al., trials,[50,55] subjects were allowed to receive medications like Benzodiazepine (Lorezepam or equivalent) and Anticholinergic agents while, in Haas et al.,[54] Antiparkisonians and Propranolol were permitted during the trial while medications for agitation (Lorazepam, Diazepam, Hydroxyzine) or insomnia (zolpidem or zopiclone) were allowed during the wash out period and for the first 3 weeks of the trial.

TABLE 2

Characteristic of Studies Included in the Meta-Analysis

Authors	Arms	Duration	Participants at base-line	Participants at end-point	Efficacy assessment	Safety and tolerability assessment
Findling et al., 2008	Aripiprazole 10 mg (N = 100) Aripiprazole 30 mg (N = 102) Control group (placebo) (N = 100)	6 weeks	302	257 (85%)	PANSS; CGI; CGAS; Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire	Spontaneously reported Adverse Events; SAS; BRSDIA; AIMS; body weight; BMI; BP; trig.; HDL; glucose; ECG
Haas et al., 2009	Risperidone 1.5–6 mg (N = 125) Risperidone 0.15–0.6 mg as control group (N = 132)	8 weeks	257	172 (67%)	PANSS; CGI-S; CGI-I	EPS scales; AIMS; BRSDIA; SAS; hematology, serum chemistry, prolactin, urinalysis; body weight; ECG; drug screening
Kryzhanovskaya et al., 2009	Olanzapine (N = 72) Control group (placebo) (N = 35)	6 weeks	107	64 (60%)	BPRS-C; CGI-S; PANSS; OAS; CGI-I;	Body weight; ECG; EPS; electrolytes; lipid profile; PRL; urinalysis; hematology panels; ALT; SAS; BRSDIA; AIMS

Abbreviations: PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression Scale; CGI-I, Clinical Global Impression Scale-Improvement; CGI-S, Clinical Global Impression Scale-Severity; CGAS, Children's Global Assessment Scale; BPRS-C, Brief Psychiatric Rating Scale for Children; OAS, Overt Aggression Scale; SAS, Simpson Angus Scale; BRSDIA, Barnes Rating Scale for Drug-Induced Akathisia; AIMS, Abnormal Involuntary Movement Scale; BMI, Body Mass Index; BP, Blood Pressure; trig., fasting levels of serum trglycerides; HDL, High Density Lipoprotein Cholesterol; ECG, electrocardiogram; EPS, ExtraPyramidal Symptoms; ALT, alanine aminotransferase.

Considered our strict inclusion criteria, we could only found trials concerning three different second generation antipsychotics: Aripiprazole, Risperidone and Olanzapine.[50,54,55]

DATA ANALYSIS

Effect sizes were computed and aggregated using the Comprehensive Meta-Analysis software.[61]

The odds ratio (OR) and its 95% confidence interval (CI) were calculated as the effect size for the dichotomous outcome measure. SMD is the difference in means divided by the pooled standard deviation. SMD was calculated as Hedges'g, and its 95% CI were calculated for the continuous outcome measures. By convention, an SMD of 0.8 indicates large intervention effects, 0.5 a moderate effect, and 0.2 a small effect.

For both effect sizes, the OR and the SMD, a $P \leq 0.05$ (two-tailed) or a 95% CI not including the null point was regarded as statistically significant.

Separated analyses using a fixed-effects model were undertaken for both measurements. A fixed effects model was used to calculate differences between study design groups. The fixed-effects model assumes that all studies consider a common homogeneous population and that the effect size (OR or SMD) is not significantly different between the various trials. A significant Q-statistic indicates heterogeneity between groups that is greater than expected by chance. To aid in interpretation was calculated the I^2 statistic, which illustrates the degree of heterogeneity in terms of percentages. The I^2 value provides an estimate of the amount of variance across studies due to heterogeneity rather than chance. If the test for heterogeneity is significant ($p \leq 0.05$), the fixed-effects model may be invalid. In this case, the test for heterogeneity was never significant, the fixed-effects was appropriated for all cases.

BASELINE PATIENTS CHARACTERISTICS AND PARTICIPANTS DISPOSITION

A total of 766 patients were enrolled, 493 completed the studies (64%).

Five groups were created in consideration of five different regimens analyzed:

- a low dose treatment with Aripiprazole (10 mg per day)
- a high dose treatment with Aripiprazole (30 mg per day)
- treatment with Risperidone (1.5–6 mg per day)
- a flexible dose treatment with Olanzapine (mean dose 11.1 mg/day, dose range 2.5–20 mg/day)

– a control group (treatment with placebo or treatment with 0.15–0.60 mg/day of Risperidone)

We chose to include the treatment with 0.15–0.60 mg/day of Risperidone in the control group because authors themselves state that their work started before the Best Pharmaceuticals for Children Act (2002) and the Pediatric Research Equity Act (2003) and, given the reluctance to conduct a placebo-control trial in adolescents suffering from Schizophrenia, they judged to use two Risperidone dosing regimens: the higher dose range on the doses shown to be efficacious in adults and a tenfold lower dose as control.[54]

At baseline the four treatment groups and controls did not differ on any parameter (weight, EPS, PANSS and CGI scores) except for the case of the study concerning Risperidone, in which treated patients had a significant lower weight at the start. We decided to compare groups and controls considering a significant weight gain as a ≥7% increase in weight occurred in a period of 3 months and/or an increase of ≥0.5 in BMI z score.[23]

OUTCOMES

In order to define an appropriated antipsychotic therapy for adolescent patients, several outcome domains must be investigated for each medication taken into account. We analysed extrapyramidal symptoms and weight gain from base-line to the endpoint as indicators of tolerability. We also compared the reasons for discontinuation for the distinct drugs. Furthermore, SMD with the Hedges'g formulation were calculated at the endpoint for Positive and Negative Syndrome Scale total score, Positive and Negative Syndrome Scale positive and negative subscales and Children Global Impairment-Severity score as indicators of efficacy (see Table 2 Efficacy Assessment column).

Tolerability Measures

Young patients may be more susceptible to antipsychotic-induced extrapyramidal symptoms and weight gain, in order that a side-effect profile is needed to guide the medication of adolescents.[62,63]

Side effects as extrapyramidal symptoms (akathisia, tremor, dyskinesia, dystonic events, parkinsonism) and weight gain were considered and analyzed.

Extrapyramidal Symptoms

Extrapyramidal symptoms may occur with either second generation antipsychotics or traditional agents[64,65] and can be categorized as acute

(dystonia, akathisia and parkinsonism) and tardive (dyskinesia and tardive dystonia) syndromes. They have a substantial impact on subjective tolerability and adherence with antipsychotic therapy.

The extrapyramidal symptoms analyzed in the meta-analysis are described below:

- Parkinsonism: Antipsychotic agents can provoke symptoms as bradykinesia, tremors, and rigidity.
- Dystonia: A dystonic event can be defined as a sudden spastic contraction, often quite severe and distressing, of distinct muscle groups. It affects muscles of the neck, eyes (oculogyric crisis), larynx (laryngospasm) or torso. Risk factors include male sex, youthful age and the treatment with high potency drugs.
- Akathisia: This syndrome consists of subjective (a sense of severe inner restlessness that causes urge to move and emotional unease) and objective manifestations (rocking from foot to foot while standing, crossing and uncrossing the legs while sitting). Signs of motor restlessness can not be present in the mild cases: this situation can be referred to as subjective akathisia.
- Dyskinesia is an involuntary movement disorder, usually consisting of abnormal athetoid or choreic movements of the orofacial region (tongue, mouth), but may affect any part of the body (hands, fingers, trunk, toes).

In all these studies, side effects related to extrapyramidal system were assessed at each visit as clinically observed or as spontaneously reported adverse events and monitored by the most used extrapyramidal symptoms assessment scales (Simpson Angus Scale, Barnes Akathisia Rating Scale and Abnormal Involuntary Movement Scale).

Weight Gain

The prescription of second generation antipsychotic medication to young patients appeared to be associated with a significant weight gain and metabolic side effects. Substantial weight gain in children and adolescents has crucial repercussions on both personal and public health, considering the long-term risks for cardiovascular and endocrine disorders.[66] Weight gain due to therapy may result in an unfavourable effect on quality of life and on self-esteem.[67]

Efficacy Measures

We assessed the mean overall change in symptoms analyzing Positive and Negative Syndrome Scale total score, calculating standardized mean differences at the endpoint using the Hedges'g formulation.

We also compared separately the standardized mean differences at the endpoint in the Positive and Negative Syndrome Scale positive and negative subscales and Children Global Impairment severity scores at the endpoint. SMD were calculated for all these items.

RESULTS

Efficacy Measures

Compared with placebo-treated patients, the group of patients treated with antipsychotics had a greater clinical improvement in Clinical Global Impression Scale-Severity of Illness, in Positive and Negative Syndrome Scale total score, Positive and in Negative Symptoms subscales scores

Overall, across all interventions, there was a statistically significant change from baseline in all the group who received treatment comparing with controls.

Treatment with all the regimens taken into account resulted in significantly greater improvements in Positive and Negative Syndrome Scale total score ($p < 0.001$), in Positive and Negative Syndrome Scale positive subscale score ($p < 0.001$), in Children Global Impairment-Severity score at the endpoint ($p < 0.001$). The group who received active treatment showed improvements in PANSS negative subscale score at the endpoint, but only patients treated with the higher dose of Aripiprazole or with Ripseridone reported significant ameliorations ($p \leq 0.05$) (Figure 1).

Extrapyramidal Symptoms

Only 2 of the 3 selected studies presented data regarding the incidence of extrapyramidal side events. Kryzhanovskaya et al.,[55] did not presented data on EPS incidence during the treatment with Olanzapine: authors just stated that the two groups did not differ significantly in mean changes from baseline to endpoint on any of the three EPS measures (i.e. Simpson-Angus Scale total ($p = 0.260$), Barnes Akathisia Scale-global assessment of akathisia ($p = 0.747$), or the Involuntary Movement Scale non-global total (question 1–7, $p = 0.897$) scores).

Antipsychotic agents with greater dopamine antagonism (eg, haloperidol) tend to produce more extrapyramidal symptoms.[68–70] Second generation antipsychotics generally produce lower rates of extrapyramidal symptoms than traditional antipsychotics.

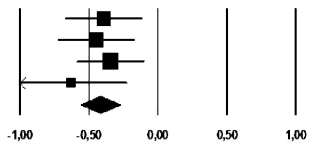
According to textbooks of pharmacology and previous findings, we found that each of the second generation antipsychotics taken into account was associated with a different incidence of side effects supporting the

FIGURE 1

EFFICACY MEASURES

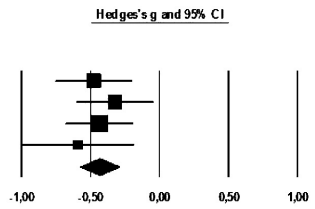
PANSS total score

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	-0,387	0,143	0,021	-0,668	-0,106	-2,701	0,007
Aripiprazole 30 mg	-0,442	0,144	0,021	-0,725	-0,159	-3,059	0,002
Risperidone	-0,340	0,126	0,016	-0,586	-0,093	-2,701	0,007
Olanzapine	-0,625	0,209	0,044	-1,035	-0,215	-2,991	0,003
	-0,415	0,074	0,005	-0,560	-0,270	-5,609	0,000



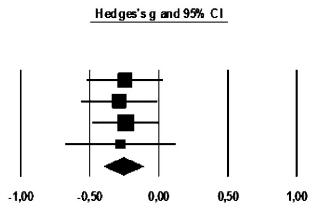
PANSS posivite subscale

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	-0,472	0,144	0,021	-0,754	-0,190	-3,281	0,001
Aripiprazole 30 mg	-0,320	0,144	0,021	-0,602	-0,039	-2,231	0,026
Risperidone	-0,432	0,126	0,016	-0,680	-0,185	-3,422	0,001
Olanzapine	-0,588	0,208	0,043	-0,997	-0,180	-2,821	0,005
	-0,433	0,074	0,005	-0,578	-0,288	-5,845	0,000



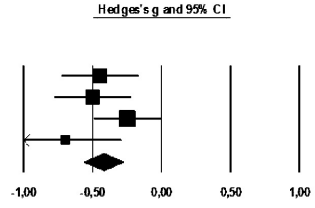
PANSS negative subscale

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	-0,241	0,142	0,020	-0,521	0,038	-1,695	0,090
Aripiprazole 30 mg	-0,282	0,143	0,021	-0,563	-0,001	-1,970	0,049
Risperidone	-0,236	0,125	0,016	-0,482	0,009	-1,885	0,059
Olanzapine	-0,272	0,205	0,042	-0,675	0,130	-1,325	0,185
	-0,254	0,073	0,005	-0,398	-0,110	-3,463	0,001



CGI

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	-0,443	0,144	0,021	-0,724	-0,161	-3,081	0,002
Aripiprazole 30 mg	-0,494	0,145	0,021	-0,778	-0,210	-3,410	0,001
Risperidone	-0,244	0,125	0,016	-0,490	0,002	-1,948	0,051
Olanzapine	-0,695	0,210	0,044	-1,107	-0,283	-3,309	0,001
	-0,418	0,074	0,005	-0,563	-0,273	-5,648	0,000



theory that considers second-generation antipsychotic drugs as too different to be considered as a homogeneous class.[59] Results are summarized in Figure 2.

Considered as a unique group, the arm who received active treatment presented a significantly higher incidence of EPS ($p < 0.05$).

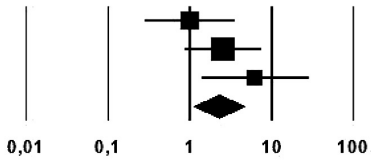
10 mg/day Aripiprazole was not associated with a significantly higher incidence of any EPS in comparison with control subjects; 30 mg/day of Aripiprazole was associated with a higher incidence of tremor and parkinsonism but not with dystonic events, dyskinesia nor akathisia. The group treated with 1.5–6.0 mg/day of Risperidone had major incidence of EPS than controls.

FIGURE 2

EXTRAPYRAMIDAL SIDE-EFFECTS

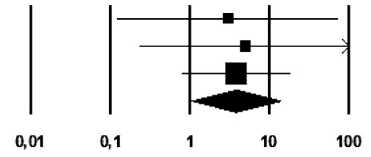
Akathisia

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	1,000	0,280	3,567	0,000	1,000
Aripiprazole 30 mg	2,533	0,858	7,478	1,683	0,092
Risperidone	6,272	1,362	28,892	2,356	0,018
	2,297	1,112	4,744	2,247	0,025



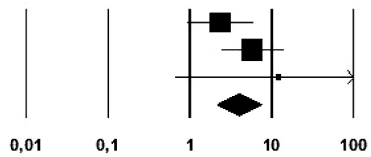
Diskinesia

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	3,030	0,122	75,279	0,676	0,499
Aripiprazole 30 mg	5,000	0,237	105,463	1,035	0,301
Risperidone	3,856	0,785	18,929	1,662	0,096
	3,886	1,068	14,138	2,060	0,039



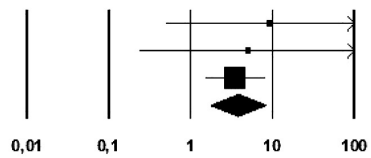
Parkinson

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	2,345	0,912	6,027	1,769	0,077
Aripiprazole 30 mg	5,801	2,415	13,935	3,931	0,000
Risperidone	12,095	0,662	221,048	1,682	0,093
	4,025	2,150	7,536	4,351	0,000



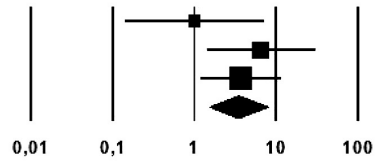
Dystonic events

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	9,373	0,498	176,426	1,494	0,135
Aripiprazole 30 mg	5,000	0,237	105,463	1,035	0,301
Risperidone	3,495	1,500	8,145	2,899	0,004
	3,841	1,751	8,426	3,368	0,001



Tremor

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Aripiprazole 10 mg	1,000	0,138	7,242	0,000	1,000
Aripiprazole 30 mg	6,533	1,423	29,993	2,414	0,016
Risperidone	3,714	1,177	11,719	2,238	0,025
	3,486	1,516	8,014	2,940	0,003



In a head to head comparison of each antipsychotic, we found no significant difference regarding akathisia.

Risperidone-treated patients reported significantly more dystonic events in comparison with patients treated with Aripiprazole 10 mg/day ($p = 0.001$) or Aripiprazole 30 mg/day ($p = 0.0001$). Treatment with Aripiprazole 10 mg/day caused less episodes of tremor than treatment with either Risperidone ($p = 0.01$) and Aripiprazole 30 mg/day ($p = 0.005$) did.

Treatment with Risperidone caused less events of parkinsonism in comparison with treatment with either Aripiprazole 10 mg/day ($p = 0.004$) or Aripiprazole 30 mg/day ($p < 0.0001$).

Weight Gain

Even though new generation antipsychotics are associated with improved extrapyramidal symptoms tolerability compared with first generation agents, it's important to consider the association of these medications with significant weight gain.

Significant weight gain is defined as a ≥7% increase in weight occurred in a period of 3 months and/or an increase of ≥0.5 in BMI z score. Mean change from baseline to endpoint was +3.2 kg for Risperidone, +4.3 for Olanzapine and +0.2 kg for Aripiprazole 30 mg while patients treated with Aripiprazole 10 mg had no overall change on average. From baseline to endpoint, treated patients who reported a significant weight gain with Olanzapine, Risperidone and both regimens with Aripiprazole were respectively 45,8%, 22% and 0%.

Weight gain was significantly more frequent and pronounced in Olanzapine-treated patients.

REASONS FOR DISCONTINUATION

Reasons for discontinuation are summarized in Table 3.

No statistically significant differences were observed between control group and drug-treated groups due to all reasons in Findling et al.,[50] and in Haas et al.,[54] works: both drugs and the three regimens were well tolerated, with a low rate of discontinuation due to adverse event (<5%) and a high completion rate.

Nevertheless in Kryzhanovskaya et al.:[55]

- control group discontinuation rate is significantly higher than patients treated with Olanzapine (23/72 vs 20/35 with a p-value of 0.01):

TABLE 3

Reasons for Discontinuation

		FINDLING ET AL., 2008		HAAS ET AL., 2009		KRYZHANOVSKAYA ET AL., 2009	
Discontinuation rate		44/302 (15%)		85/257 (33%)		43/107 (40%)	
Subgroups	10/100 (10%) placebo	16/100 (16%) Aripiprazole 10 mg/day	18/102 (18%) Aripiprazole 30 mg/day	35/125 (28%) Risperidone 1.5–6.0 mg/day	50/132 (38%) Risperidone 0.15–0.6 mg/day as control group	23/72 (31.9%) Olanzapine group	20/35 (57.1%) Control group
Lack of efficacy/ insufficient response		7 (2%)		19 (15%)	26 (20%)	10 (13%)	18 (51%)
Adverse events		13 (4%)		5 (4%)	6 (5%)	5 (6.9%)	–
Withdrew consent		21 (7%)		5 (4%)	8 (6%)	–	–
Lost to follow-up		1 (0.0%)		0	3 (2%)	1 (1.4%)	–
Not eligible to continue		–		2 (2%)	3 (2%)	–	–
Criteria not meet/ nonconpliance		–		–	–	2 (2.8%)	1 (2.8%)
Non-adherent		–		1 (1%)	0	–	–
Patient decision		–		–	–	4 (5.5%)	1 (2.8%)
Sponsor decision		–		–	–	1 (1.4%)	–
Other reasons		2 (1%)		3 (2%)	4 (3%)	–	–

– significantly more patients discontinue treatment because of lack of efficacy in placebo group than in Olanzapine treated group (10/23 vs 18/20 with a p-value of 0.01);
– significantly more Olanzapine-treated patient discontinue treatment than controls because of a adverse event (5/25 vs 0/20 with a p-value of 0.04).

No statistically significant differences in the discontinuation rates were observed between patients treated with Aripiprazole (4%), Risperidone (4%) and Olanzapine (6.9%).

LIMITATIONS

A major limitation of our meta-analysis is the paucity of the included studies due to the strict inclusion criteria we chose in order to select:

– a specific age range (i.e. 13–17 years old) that has the most higher incidence of Schizophrenic onset in paediatric patients;
– recent trials with the most high methodological quality.

Another limitation is that we considered subjects treated with 0.15–0.60 mg/day of Risperidone as a control group. Haas et al.,[54] explain how they preferred to use a tenfold lower dose respect to the efficacious adult dose as control. Risperidone FDA target dose for adolescent suffering from Schizophrenia is 3 mg/day with an effective dose range of 1–6 mg/day: authors expected the 0.15–0.60 mg/day regimen to be not efficacious. During the consent patients and their caregivers were informed that this dose might be an ineffective treatment.

Furthermore, it is an additional limitation of our study that one of the eligible trials[55] did not report the data regarding EPS.

Even though we tried to contact authors for having these data it was not possible without signing a consent with the pharmaceutical company. Finally, all trials were short-term and thus unlikely to report rare and long-term adverse events.

CONCLUSION

This meta-analysis provides data based on efficacy and side-effects that clinicians could consult to prescribe an appropriate treatment for adolescent patients suffering from Schizofrenia.

New generation antipsychotics could represent a useful tool in treating young patients as these medications were found to be efficacious in controlling psychotic symptoms and less associated with adverse events such extrapyramidal symptoms.[70–73]

However, a pharmacological treatment in children and adolescents suffering from Schizophrenia must fulfil different and broader prerequisites than the ones applied for adults, to grant the most favourable outcomes in terms of cognitive functioning, individual well-being and quality of life, social and educational skills, and disease suffering.

Our meta-analysis demonstrates that antipsychotic treatment with Risperidone, Olanzapine or Aripiprazole in adolescents affected by Schizophrenia led to significant improvements in clinical manifestations of illness as it is demonstrated by SMD calculated with Hedges'g at the endpoint for Positive and Negative Syndrome Scale and Children Global Impairment-Severity. In the negative scale of PANSS only patients treated with the higher dose of Aripiprazole or with Ripseridone reported significant imporvements ($p \leq 0.05$).

On the other hand, adolescents were previously found to have a higher risk than adults for experiencing adverse events such as extrapyramidal symptoms, prolactin elevation, weight gain effects when taking antipsychotics.[23,74,75] These results supported previous issues: Olanzapine treated adolescents gained 4.3 kg vs. 1.9 reported in a 6-week study in olanzapine-treated adults.[76]

No significant differences were observed between 10 mg/day and 30 mg/day Aripiprazole in determining efficacy improvements execpt for PANSS negative scale, while the higher-dose regimen was linked with a major incidence of extrapyramidal symptoms.

Treatment with a 10 mg daily dose of Aripiprazole was associated with the lowest incidence of extrapyramidal symptoms and weight gain. The percentages of patients who reported significant weight gain were considerably higher than controls for patients treated with Olanzapine ($p = 0.01$) while were not for the group treated with Risperidone ($p = 0.08$) both doses of Aripiprazole ($p > 0.8$).

A particular caution must be used for this issue. Weight gain is an unwelcome side effect in adolescents, affecting both body image and self-esteem. Obesity in children is observed to last in adulthood: 75% of overweight adolescents continuing to be overweight as adults.[77] This condition may favour the onset of severe long-term disorders such as insulin resistance, diabetes mellitus, hypertension and cardiovascular problems.[78] If a treatment with antipsychotic drugs associated with significant weight gain as Olanzapine is needed, compensative measures, a particular attention to create a healthy lifestyle and, in several cases pharmacological medications should be soon considered.[23,79] In the first place, reduction of sugar and saturated fats intake, frequent small meals rich in fibres and increase of physical activities must be strongly encouraged.

Furthermore, adolescents are more vulnerable both to weight gain to the negative impact of this effect on quality of life, body image, and self-esteem.[67]

Finally, clinical trials for the use of antipsychotic drugs in adolescent patients must consider long term effects and consequences of a long use of these medications on the developmental brain and body. On the other hand, developmental modifications may exert influence on treatment response and tolerability so that further studies on these issues are needed. However, early intervention with an effective and well-tolerated antipsychotic provide benefits and may modify the actual course of the disease in some paediatric mental disorders.[80] ✤

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