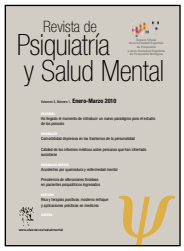
Rev Psiquiatr Salud Ment (Barc.) 2010;**3(4)**:152–167

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental



REVIEW

Differential characteristics of the efficacy and tolerability of second-generation antipsychotics in the treatment of psychotic disorders in children and adolescents

David Fraguas[a,c,*], Jessica Merchán-Naranjo[b,c], Celso Arango[b,c]

[a]*Servicio de Salud Mental, Complejo Hospitalario Universitario de Albacete, Albacete, Spain*
[b]*Unidad de Adolescentes, Departamento de Psiquiatría, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[c]*Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain*

Received de March 17, 2010; accepted August 27, 2010

KEYWORDS
Efficacy;
Tolerability;
Antipsychotic;
Psychosis;
Pediatric population

Abstract
Over the last few years, there has been a marked increase in the prescription of second-generation antipsychotics (SGA) for the treatment of psychotic disorders and other psychiatric conditions in children and adolescents. However, few reports compare the tolerability and efficacy of the different SGAs in this population. We review the literature on the differential characteristics of efficacy and tolerability of SGA in the pediatric population. Our results show that SGAs are not a homogeneous group, but that each drug has a distinct profile, particularly with respect to side effects, especially metabolic complications. Comparisons between SGAs have shown that treatment with olanzapine was associated with greater weight gain and increased cholesterol levels, and that treatment with risperidone was associated with a greater increase in prolactin levels. Therefore, the specific profile of an SGA should be taken into consideration when prescribing these drugs.

PALABRAS CLAVE
Eficacia;
Tolerabilidad;
Antipsicótico;
Psicosis;
Población pediátrica

Características diferenciales de eficacia y tolerabilidad de los antipsicóticos de segunda generación en el tratamiento de trastornos psicóticos en niños y adolescentes

Resumen
En los últimos años se ha producido un aumento exponencial en la prescripción de antipsicóticos de segunda generación (ASG) en niños y adolescentes para el tratamiento de trastornos psicóticos y otros trastornos mentales. Sin embargo, hay muy pocos estudios que comparen la tolerabilidad y la eficacia entre los distintos ASG en esta población.

*Corresponding author.
E-mail: david.fraguas@cibersam.es (D. Fraguas).

1888-9891/$ - see front matter

Este artículo revisa los datos actuales sobre las características diferenciales de eficacia y tolerabilidad de los ASG en población infanto-juvenil. Los datos muestran que los ASG no forman un grupo homogéneo, sino que cada fármaco de este grupo tiene un perfil característico, sobre todo con respecto a los efectos secundarios, especialmente las complicaciones metabólicas. En concreto, en las comparativas entre ASG, el tratamiento con olanzapina se relacionó con mayor aumento de peso y de colesterol, y el tratamiento con risperidona se asoció con mayor aumento de prolactina. Por ello, antes de prescribir un ASG resulta imprescindible tener en cuenta el perfil diferencial de estos fármacos.

Introduction

Prescription of second-generation antipsychotics (SGAs) for the treatment of psychotic disorders and other psychiatric disorders in children and adolescents has become a common practice in the psychiatric clinic.[1-3] Studies on the prevalence of the use of these drugs in the paediatric population show that, in recent years and in various countries around the world, there has been a significant increase in SGA prescriptions,[4] which has been accompanied, worldwide, by a progressive decrease in the use of typical or first-generation antipsychotics (FGAs).[5] In the U.S., between 1990 and 2000, SGA prescriptions increased 160%,[6] and in the United Kingdom between 1994 to 2005, SGA use in this age group increased nearly 60-fold (0.01 users per 1,000 patient-years in 1994 versus 0.61 users per 1,000 patient-years in 2005).[5] This increase in SGA use is due to an increase in prescriptions, but also because this drugs are now being used for longer periods of time. In The Netherlands, the length of SGA use in children and adolescents doubled (from 0.8 years in 1998-1999 to 1.6 years in 2001-2001)[7] (Figure 1).

The dramatic increase in the use of SGAs in the last 15-20 years has revealed an important underlying truth: there are few studies comparing the tolerability and efficacy between different SGAs and between SGAs and FGAs for the treatment of children and adolescents with psychotic spectrum disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, bipolar disorder, and depressive episode with psychotic features).

Studies of SGA tolerability in the paediatric population have shown that, although SGAs have fewer extrapyramidal side effects than FGAs,[8] SGA use is associated with increased risk of developing metabolic complications such as obesity, type 2 diabetes mellitus, dyslipidaemia and, in general, abnormalities along the spectrum of cardiovascular morbidity.[8-11]

Furthermore, international agencies governing the use of drugs (the FDA in the United States and the EMA in Europe) have carefully followed the significant increase in SGA prescriptions for children and adolescents. Indeed, FDA and EMA approval of SGAs for use in the paediatric population, in general, has lagged behind clinical use and findings of efficacy and tolerability in phase 4 clinical studies. Recent regulations from the FDA (Paediatric Research Equity Act, 2003) and the EMA (EU Paediatric Regulation, January 2007) that require mandatory and exclusive studies specifically in the paediatric population for drug approval in this age group have promoted the development of SGA efficacy and tolerability studies in children and adolescents, but also have slowed the approval process of these drugs in the paediatric population.

This article provides a general and systematic review of the current state of this issue, paying particular attention to clinical studies that have compared the efficacy and

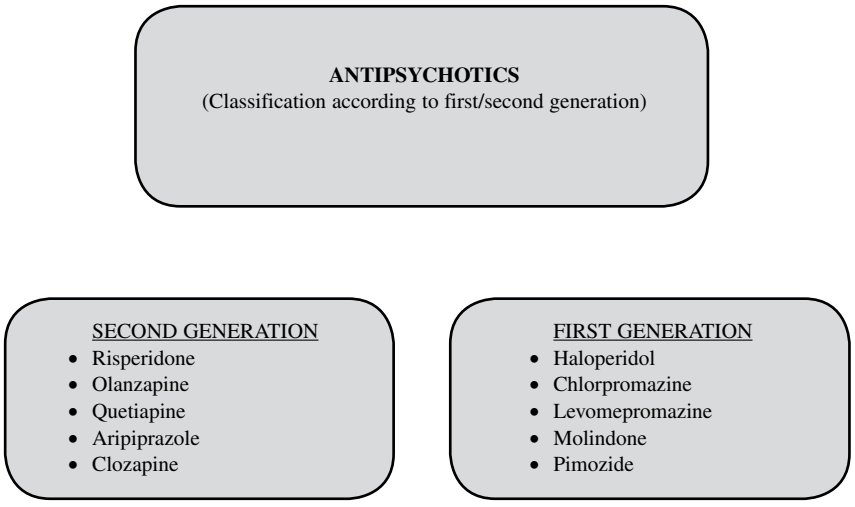


Figure 1 Classification of antipsychotics studied in this review according to first or second generation.

Table 1 Second-generation antipsychotics for clinical use in the treatment of psychotic disorders in children and adolescents

FDA	EMA
Risperidone: • Schizophrenia, age 13-17 years • Mixed episodes or acute mania in bipolar disorder I, age 10-17 years	Aripiprazole: • Schizophrenia, age 15-17 years • Anticipated approval for bipolar disorder, age 13-17 years
Aripiprazole: • Schizophrenia, age 13-17 years. • Mixed episodes or acute mania in bipolar disorder I, age 10-17 years	
Olanzapine: • Schizophrenia, age 13-17 years (second-line drug; not as first choice) • Mixed episodes or acute mania in bipolar disorder I, age 13-17 years (second-line drug; not as first choice)	
Quetiapine: • Schizophrenia, age 13-17 years. • Mixed episodes or acute mania in bipolar disorder I, age 10-17 years, as monotherapy or in combination with lithium or valproic acid	

EMA: European Medicines Agency; FDA: Food and Drug Administration of the United States.

tolerability of different SGAs with each other and with FGAs in the paediatric population with psychotic spectrum disorders (Table 1).

Methods

The authors performed a literature search of studies published in international journals from 1990 to January 2010, available on *Medline/PubMed/Google Scholar* that compared efficacy and/or tolerability between different SGAs, or between an SGA and an FGA, in children and adolescents with a psychotic disorder. For this search we used the following keywords: antipsychotic, olanzapine, risperidone, aripiprazole, clozapine, quetiapine, ziprasidone, psychosis, early onset psychosis, schizophrenia, bipolar disorder, adolescent, child, youth, adverse effects, weight gain, cholesterol, prolactin, metabolic syndrome, parkinsonism, dyskinesia, akathisia, effectiveness. Terms were entered in English in the following manner: "antipsychotic" or "olanzapine" or "risperidone" or "aripiprazole" or "clozapine" or "quetiapine" or "ziprasidone"; "psychosis" or "early onset psychosis" or "schizophrenia" or "bipolar disorder"; "adolescent" or "child" or "children" or "youth"; "adverse events" or "weight gain" or "cholesterol" or "prolactin" or "metabolic syndrome" or "parkinsonism" or "dyskinesia" or "akathisia"; "efficacy". The electronic search was complemented by a manual search of articles related to this issue.

Once these searches had been performed, articles were selected that met the following inclusion criteria: 1) studies comparing efficacy and/or tolerability among two or more SGAs; 2) studies comparing efficacy and/or tolerability between an SGA and placebo; 3) studies comparing efficacy and/or tolerability between an SGA and an FGA. Furthermore, we excluded those studies that: a) did not compare drugs to drugs or drugs to placebo, and b) whose sample mixed data from the paediatric population and adult population without differential analysis.

Due to the variability in tolerability measures studied in different trials, this article focuses on those variables that have shown greatest importance in terms of morbidity: BMI (body mass index; as an assessment of weight), prolactin, triglycerides, cholesterol, diastolic blood pressure, waist circumference, metabolic syndrome. parkinsonism, dyskinesia, and akathisia.[8,9,12-14] Furthermore, in order to contextualise the comparative data on efficacy and tolerability, comparative data on efficacy and tolerability between SGAs and placebo in this population were also included.

This review focuses on children and adolescents with a psychotic disorder diagnosis (schizophrenic, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, bipolar disorder, and depressive episode with psychotic features). We decided to use the generic construct of psychotic disorder on the basis of the results of studies on diagnostic stability in cases of first psychotic episode, which show that diagnostic stability is limited at least for the first year.[15]

Results

Efficacy

Table 2 shows the result of studies that compare clinical efficacy between different antipsychotics (Table 2).

As an outline: the results of efficacy studies have been: 1) comparisons between SGAs and placebo (or between SGAs at therapeutic doses to SGAs at subtherapeutic doses) have shown superiority of SGAs;[16-19] 2) for the treatment of patients with refractory schizophrenia, clozapine has been shown to be superior to those drugs to which it has been compared,[20-22] and 3) no other significant differences in efficacy have been found between different SGAs, or between SGAs and FGAs.[8,23-26]

Tolerability: metabolic effects

Table 3 shows the results of studies comparing metabolic side effects (weight gain, increased waist circumference, increased total cholesterol, increased triglycerides, increased diastolic blood pressure, and increased prolactin level) between different antipsychotics (Table 3).

The weight gain data indicate that, in broad terms, SGA treatment is associated with significant weight gain. However, the magnitude of weight gain differs between

Table 2 Results of studies comparing efficacy

Articles	Measure of efficacy	Results of efficacy
Arango, 2009[23] N=50, Age: 16±1.3 years, Length: 6 months. Design: RNB Diagnoses: SCH, OP	PANSS	OLZ=QTP
Bastiaens, 2009[60] N=46, Age: 11.9±2.6 years, Length: 8 weeks. Design: Non randomised open study Diagnoses: SCH, BIP, OP	OAS	ARP=ZPD (1)
Castro-Fornieles, 2008[24] N=110, Age: 9–17 years, Length: 6 months. Design: naturalistic Diagnoses: SCH, BIP, OP	PANSS	OLZ=QTP=RIS (1)
DelBello, 2002[61] N=30, Age: 12–18 years, Length: 6 weeks. Design: RDB (valproic acid + QTP versus valproic acid + PLAC) Diagnosis: BIP	YMRS	QTP>PLAC
DelBello, 2009[62] N=32, Age: 12–18 years, Length: 8 weeks. Design : RDB Diagnosis: BIP	CDRS-R	QTP=PLAC
Findling, 2008[16] N=302, Age: 13–17 years, Length: 6 weeks. Design : RDB Diagnosis: SCH	PANSS	ARP>PLAC
Findling, 2009[63] N=296, Age: 10–17 years, Length: 4 weeks. Design: RDB Diagnosis: BIP	YMRS	ARP>PLAC
Gothelf, 2003[25] N=43, Age: 17±2 years, Length: 8 weeks. Design: naturalistic. Diagnosis: SCH	PANSS	HAL=RIS=OLZ (1)
Haas, 2009a[17] N=257, Age: 13–17 years, Length: 8 weeks. Design: RDB. Diagnosis: SCH	PANSS	RIS (1.5–6.0mg/day)>RIS (0.15–0.6mg/day)
Haas, 2009b[64] N=169, Age: 10–17 years, Length: 3 weeks. Design: RDB. Diagnosis: BIP	YMRS	RIS>PLAC
Hass, 2009c[52] N=160, Age: 13–17 years, Length: 6 weeks. Design: RDB. Diagnosis: SCH	PANSS	RIS(1–3mg/d)>PLAC RIS(4–6mg/d)>PLAC RIS(1–3mg/d)=RIS(4–6mg/d)
Jensen, 2008[65] N=21, Age: 10–18 years, Length: 12 weeks. Design: RNB. Diagnosis: SCH, OP	PANSS	RIS=OLZ=QTP
Kryzhanovskaya, 2009[18] N=107, Age: 13–17 years, Length: 6 weeks. Design: RDB Diagnosis: SCH	PANSS	OLZ>PLAC
Kumra, 1996[66] N=21, Age: 14.0±2.3, Length: 6 weeks. Design: RDB Diagnosis: SCH	SAPS/SANS	CLZ>HAL
Kumra, 2008[20] N=39, Age: 10–18 years, Length: 12 weeks. Design: RDB Diagnosis: SCH	SANS	CLZ>OLZ

Table 2 Results of studies comparing efficacy

Articles	Measure of efficacy	Results of efficacy
Mozes, 2006[67]		
N=20 (completed follow-up), Age: 11.1±1.6 years, Length: 12 weeks. Design: RNB. Diagnosis: SCH	PANSS	RIS=OLZ
Shaw, 2006[22]		
N=25, Age: 7–16 years, Length: 8 weeks. Design: RDB Diagnosis: SCH	SAPS/SANS	CLZ>OLZ
Sikich, 2004[26]		
N=50, Age: 8–19 years, Length: 8 weeks. Design: RDB Diagnosis: SCH, OP	BPRS-C	RIS=OLZ=HAL (1)
Sikich, 2008[8]		
N=116, Age: 8–19 years, Length: 8 weeks. Design: RDB Diagnosis: SCH, OP	PANSS	OLZ=RIS=MOL (1)
Swadi, 2010[68]		
N=26, Age: <19 years old, Length: 6 weeks. Design: RNB Diagnosis: first psychotic episode or affective episode with psychotic features	PANSS	QTP=RIS
Tohen, 2007[19]		
N=161, Age: 13–17 years, Length: 3 weeks. Design: RDB Diagnosis: BIP	YMRS	OLZ>PLAC
Tramontina, 2009[69]		
N=41, Age: 8–17 years, Length: 6 weeks. Design: RDB Diagnosis: BIP+ADHD	YMRS	ARP>PLAC

RDB: randomised double-blind; RNB: randomised, not-blinded; ANS: Schedule for the Assessments of Negative Symptoms; ARP: aripiprazole; BIP: bipolar disorder; BPRS: Brief Psychiatric Rating Scale; BPRS-C: Brief Psychiatric Rating Scale for Children; CDRS-R: Children's Depression Rating Scale-Revised Version; CLZ: clozapine; CPRS: Children's Psychiatric Rating Scale; Length: length of treatment in study; SCH: schizophrenia or schizoaffective disorder; HAL: haloperidol; MOL: molindone; N: number of subjects included in the study; OAS: Overt Aggression Scale; OLZ: olanzapine; OP: Other psychotic disorder, including schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, depression with psychotic features; PANSS: Positive and Negative Syndrome Scale; PLAC: placebo; QTP: quetiapine; RIS: risperidone; SANS: Schedule for the Assessments of Negative Symptoms; SAPS: Schedule for the Assessments of Positive Symptoms; ADHD: attention deficit and hyperactivity disorder; YMRS: Young Mania Rating Scale.
The sign ">" means "there are statistically significant differences ($P<.05$), the mean measure with treatment A is greater than with treatment B (A>B)". The sign "=" means that there were no differences between the compared measures, or that if there were, they were not statistically significant.
NOTES:
1. The study drugs showed general clinical efficacy.

the various SGAs. Olanzapine is the SGA associated with the most weight gain.[8,10,13,24,27,28]

Data on increased cholesterol and prolactin levels are more controversial. In general, and taking a recently conducted clinical trial as a reference point (randomised, double-blind),[8] it can be seen that the increase in cholesterol is greater with olanzapine treatment, while the increase in prolactin levels is greater in subjects treated with risperidone.

Tolerability: movement disorders

Table 4 shows the results of studies comparing movement disorders (parkinsonism, dyskinesia, akathisia) secondary to antipsychotic treatment (Table 4).

Studies of movement disorders associated with antipsychotic treatment in children and adolescents have shown that SGA use is associated with lower incidence of parkinsonism or akathisia than FGA use (using haloperidol and molindone as FGA references).[8,26]

Discussion

Data from this review suggests two general conclusions: 1) studies that have compared the clinical efficacy of various SGAs in the treatment of children and adolescents with psychotic disorders have found no significant differences in efficacy measures, with the exception of

Table 3 Results of studies comparing tolerability (metabolic complications)

Articles	Weight gain - BMI	Prolactin level increase	Total cholesterol increase	Triglycerides level increase	Increase in BP	Increase in waist circumference
Arango, 2009[23]						
N=50, Age: 16±1.3 years, Length: 6 months. Design: RNB Diagnoses: SCH, OP	OLZ>QTP (1)					
Bastiaens, 2009[60]						
N=46, Age: 11.9±2.6 years, Length: 8 weeks. Design: Non randomised open study Diagnosis: SCH, BIP, OP	ARP=ZPD					
Biederman, 2005[70]						
N=31, Age: 4-6 years, Length: 8 weeks. Design: Non randomised open study Diagnosis: BIP	OLZ=RIS	RIS>OLZ (2)	OLZ=RIS	OLZ=RIS	OLZ=RIS	
Castro-Fornieles, 2008[24]						
N=110, Age: 9-17 years, Length: 6 months. Design: naturalistic Diagnosis: SCH, BIP, OP	OLZ>RIS=QTP (1)					OLZ>QTP=RIS
Correll, 2009[13]						
N=272, Age: 4-19 years, Length: 12 weeks. Design: naturalistic	OLZ>QTP=RIS=ARP (1)		OLZ=QTP=RIS=ARP (3)	OLZ=QTP=RIS=ARP (4)		
Diagnosis: SCH, BIP, OP, CT						OLZ=ARP ARP=QTP=RIS (5)
DelBello, 2002[61]						
N=30, Age: 12-18 years, Length: 6 weeks. Design: RDB (valproic acid + QTP versus valproic acid +PLAC) Diagnosis: BIP	QTP=PLAC	QTP=PLAC				
DelBello, 2009[62]						
N=32, Age: 12-18 years, Length: 8 weeks. Design: RDB Diagnosis: BI	QTP=PLAC	QTP=PLAC	QTP=PLAC	QTP=PLAC	QTP=PLAC	
Findling, 2008[16]						
N=302, Age: 13-17 years, Length: 6 weeks. Design: RDB Diagnosis: SCH	ARP(10mg)=PLAC ARP(30mg)>PLAC	ARP<PLAC (9)	ARP=PLAC	ARP=PLAC	ARP=PLAC (DBP)	
Findling, 2009[63]						
N=296, Age: 10-17 years, Length: 4 weeks. Design: RDB Diagnosis: BIP	ARP=PLAC					
Fleischhaker, 2006[71]						
N=49, Age: 9-21 years, Length: 3 weeks. Design: naturalistic Diagnosis: SCH, OP, CT other diagnoses (8)	OLZ>RIS=CLZ (1)					

Table 3 (*continuation*)

Articles	Weight gain - BMI	Prolactin level increase	Total cholesterol increase	Triglycerides level increase	Increase in BP	Increase in waist circumference
Fleischhaker, 2007[27]						
N=45, Age: 9-21 years, Length: 6 weeks. Design: naturalistic	OLZ>RIS=CLZ (1)					
Diagnosis: SCH, OP, CT other diagnoses (8).						
Fleischhaker, 2008[28]						
N=33, Age: 9-21 years, Length: 45 weeks. Design: naturalistic	OLZ>RIS=CLZ (1)					
Diagnosis: SCH, OP, CT other diagnoses (8)						
Fraguas, 2008[10]						
N=66, Age: 15.2±2.9, Length: 6 months. Design: naturalistic. Diagnosis: SCH, BIP, OP, CT other diagnoses (8)	OLZ>RIS=QTP		OLZ=RIS=QTP (7)			
Haas, 2009a[17]						
N=257, Age: 13-17 years, Length: 8 weeks. Design: RDB	RIS (1,5-6,0mg/d) >RIS (0,15-0,6mg/d)	RIS (1,5-6,0mg/d) >RIS (0,15-0,6mg/d)	RIS (1,5-6,0mg/d)=RIS (0,15-0,6mg/d)	RIS (1,5-6,0mg/d)=RIS (0,15-0,6mg/d)	RIS (1,5-6,0mg/d)= RIS (0,15-0,6mg/d) (DBP)	
Diagnosis: SCH						
Haas, 2009b[64]						
N=169, Age: 10-17 years, Length: 3 weeks. Design: RDB Diagnosis: BIP	RIS>PLAC	RIS>PLAC				
Hass, 2009c[52]						
N=160, Age: 13-17 years, Length: 6 weeks. Design: RDB Diagnosis: SCH	RIS (1-3mg/d)>PLAC	RIS (1-3 mg/d)>PLAC				
	RIS (4-6mg/d)>PLAC	RIS (4-6mg/d)>PLAC				
	RIS (4-6mg/d)>RIS (1-3mg/d)	RIS (4-6mg/d)>RIS (1-3mg/d)				
Hrdlicka, 2009[72]						
N=79, Age: 15.8±1.6 years, Length: 6 weeks. Design: naturalistic Diagnosis: SCH, OP	RIS=OLZ=CLZ					
Jensen, 2008[65]						
N=21, Age: 10-18 years, Length: 12 weeks. Design: RNB Diagnosis: SCH, OP	OLZ=QTP=RIS					
Khan, 2009[73]						
N=49, Age (mean): 13 years, Length. (mean): 27 days. Design: naturalistic. Diagnosis: SCH, BIP, OP	RIS=OLZ (1)				RIS=OLZ (DBP)	
Kryzhanovskaya, 2009[18]						
N=107, Age: 13-17 years, Length: 6 weeks. Design: RDB	OLZ>PLAC	OLZ>PLAC	OLZ=PLAC	OLZ>PLAC		

Diagnosis: SCH					OLZ=PLAC (DBP)
Kumra, 1996[66]					
N=21, Age: 14.0±2.3 years, Length: 6 weeks. Design: RDB	CLZ=HAL				CLZ=HAL
Diagnosis: SCH					
Kumra, 2008[20]					
N=39, Age: 10-18, Length: 12 weeks. Design: RDB	CLZ=OLZ (1)		OLZ>CLZ	CLZ=OLZ	
Diagnosis: SCH					
Migliardi, 2009[74]					
N=41, Age: 12.8±2.3 years, Length: 12 months.					
Design: naturalistic		RIS>OLZ(2)			
Diagnosis: BIP, OP, CT, other diagnoses (8)					
Mozes, 2006[67]					
N=25, Age: 11.1±1.6 years, Length: 12 weeks. Design: non randomised open study	OLZ=RIS				OLZ=RIS
Diagnosis: SCH					
Ratzoni, 2002[75]					
N=50, Age: 13-20 years, Length: 12 weeks. Design: non randomised open study	OLZ>HAL				
Diagnosis: SCH, CT	OLZ>RIS HAL=RIS				
Saito, 2004[76]					
N=40, Age: 5-18 years, Length: 4-15 weeks.		RIS>OLZ=QTP			
Design: naturalistic					
Diagnosis: BIP, OP, CT, other diagnoses (8)					
Shaw, 2006[22]					
N=25, Age: 7-16 years, Length: 8 weeks. Design: RDB	CLZ=OLZ(1)	CLZ<OLZ			CLZ>OLZ(DBP)
Diagnosis: SCH					
Sikich, 2004[26]					
N=50, Age: 8-19, Length: 8 weeks.	OLZ=RIS=HAL(1)	OLZ=RIS=HAL		OLZ=RIS=HAL	
Design: RDB					
Diagnosis: SCH, OP					
Sikich, 2008[8]					
N=116, Age: 8-19 years, Length: 8 weeks.	OLZ>RIS>MOL	RIS>MOL=OLZ	OLZ>RIS=MOL	OLZ=RIS=MOL	
Design: RDB					
Diagnosis: SCH, OP					
Stevens, 2005[77]					
N=70, Age: 13.5±2.4 years, Length: 6 weeks. Design: naturalistic. Diagnosis: at least one symptom out of the following groups: psychosis, aggressiveness, impulsivity and/or hypomania		RIS>QTP(2)			

Table 3 (*continuation*)

Articles	Weight gain - BMI	Prolactin level increase	Total cholesterol increase	Triglycerides level increase	Increase in BP	Increase in waist circumference
Swadi, 2010[68]						
N=26, Age: <19 years old, Length: 6 weeks. Design: RNB Diagnosis: first psychotic episode or affective episode with psychotic features	QTP=RIS	RIS>QTP	QTP=RIS			
Tohen, 2007[19]						
N=161, Age: 13-17 years, Length: 3 weeks. Design: RDB Diagnosis: BIP	OLZ>PLAC	OLZ>PLAC	OLZ>PLAC	OLZ>PLAC	OLZ>PLAC(SBP)	
Tramontina, 2009[69]						
N=41, Age: 8-17 years, Length: 6 weeks. Design: RDB Diagnosis: BIP+TDAH	ARP=PLAC					
Wudarsky, 1999[78]						
N=35, Age: 9-19 years, Length: 6 weeks. Design: RNB Diagnosis: SCH, BIP, OP		HAL>OLZ=CLZ				

RDB: randomised double-blind; RNB: randomised, not-blinded; ARP: aripiprazole; BIP: bipolar disorder; CLZ: clozapine; Length: length of treatment in study; SCH: schizophrenia or schizoaffective disorder; HAL: haloperidol; BMI: Body mass index weight (kg)/ height $(m)^2$; MOL: molindone; N: number of subjects included in the study; OLZ: olanzapine; OP: Other psychotic disorders, including schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, depression with psychotic features; PLAC: placebo; QTP: quetiapine; R: age range; RIS: risperidone; BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; CD: conduct disorder, oppositional defiant disorder or eating disorder.

The sign ">" or "<" means "there are statistically significant differences (P<.05)": the parameter measured with treatment A is greater than with treatment B (A>B) or is less than with treatment B (A<B)". The sign "=" means that there were no differences between the compared parameters, or that if there were, they were not statistically significant.

NOTES:

1. The data showed significant weight gain in all medication groups in this study.
2. The data showed significant increase in prolactin levels in all medication groups in this study.
3. In this study (Correll, 2009), inter-group differences were not statistically significant. Intra-group measures (before/after) showed that treatment with OLZ and with QTP was associated with significant increase in total cholesterol levels. Treatment with ARP and RIS was not associated with significant increase in cholesterol levels.
4. In this study (Correll, 2009), intra-group measures (before/after) showed that treatment with OLZ, RIS, and QTP was associated with significant increase in triglycerides. Treatment with ARP was not associated with increased triglycerides.
5. The data showed significant increase in waist circumference in all medication groups in this study.
6. Treatment with ARP was not associated with significant weight gain. The difference with respect to PLAC is due to weight loss that occurred in the PLAC group.
7. Inter-group differences were not statistically significant. Intra-group evaluations (before/after) found significant increase in cholesterol in those subjects who took OLZ and QTP.
8. Other diagnoses include: obsessive compulsive disorder, autism, generalised developmental disorder, tic disorders, attention deficit and hyperactivity disorder, mental retardation, personality disorder, Tourette's syndrome, anxiety disorder, cannabis abuse disorder.
9. Treatment with ARP led to mild decrease in prolactin levels; the decrease in the ARP treatment group was great than in the PLAC group.

Table 4 Results of studies comparing tolerability (movement disorders)

Articles	Increase in parkinsonism	Increase in dyskinesia	Increase in akathisia
Arango, 2009[23]			
N=50, Age 16±1.3 years, Length: 6 months. Design: RNB Diagnoses: SCH, OP	OLZ>QTP (evaluated with SAS)	OLZ=QTP (evaluated with UKU)	OLZ=QTP (evaluated with BARS)
Castro-Fornieles, 2008[24]			
N=110, Age: 9–17 years, Length: 6 months. Design: naturalistic Diagnoses: SCH, BIP, OP	RIS=OLZ=QTP (evaluated with UKU)	RIS>OLZ=QTP (evaluated with UKU)	RIS=OLZ=QTP (evaluated with UKU)
DelBello, 2002[61]			
N=30, Age: 12–18 years, Length: 6 weeks. Design: RDB (valproic acid + QTP versus valproic acid +PLAC) Diagnosis: BIP	QTP=PLAC (evaluated with SAS)	QTP=PLAC (evaluated with AIMS)	QTP=PLAC (evaluated with BARS)
DelBello, 2009[62]			
N=32, Age: 12–18 years, Length: 8 weeks. Design: RDB Diagnosis: BIP	QTP=PLAC (evaluated with SAS)	QTP=PLAC (evaluated with AIMS)	
Findling, 2008[16]			
N=302, Age: 13–17 years, Length: 6 weeks. Design: RDB Diagnoses: SCH	ARP>PLAC (evaluated with SAS)	ARP=PLAC (evaluated with AIMS)	ARP=PLAC (evaluated with BARS)
Gothelf, 2003[25]			
N=43, Age: 17±2 years, Length: 8 weeks. Design: naturalistic Diagnoses: SCH	HAL>RIS=OLZ (evaluated with UKU)		
Haas, 2009a[17]			
N=257, Age: 13–17 years, Length: 8 weeks. Design: RDB Diagnosis: SCH	RIS (1.5–6.0mg/d) >RIS (0.15–0.6mg/d) (evaluated with SAS)	RIS (1.5–6.0mg/d) >RIS (0.15–0.6mg/d) (evaluated with AIMS)	RIS (1.5–6.0mg/d) >RIS (0.15–0.6mg/d) (evaluated with BARS)
Hass, 2009c[52]			
N=160, Age: 13–17 years, Length: 6 weeks. Design: RDB Diagnosis: SCH	RIS (1–3mg/d)= RIS (4–6mg/d)=PLAC (evaluated with SAS)	RIS (1–3mg/d)= RIS (4–6mg/d)=PLAC (evaluated with AIMS)	RIS (1–3mg/d)= RIS (4–6mg/d)=PLAC (evaluated with BARS)
Jensen, 2008[65]			
N=21, Age: 10–18 years, Length: 12 weeks. Design: RNB Diagnoses: SCH, OP	OLZ=QTP=RIS (evaluated with SAS)	OLZ=QTP=RIS (evaluated with AIMS)	
Kryzhanovskaya, 2009[18]			
N=107, Age: 13–17 years, Length: 6 weeks. Design: RDB Diagnoses: SCH	OLZ=PLAC (evaluated with SAS)	OLZ=PLAC (evaluated with AIMS)	OLZ=PLAC (evaluated with BARS)
Mozes, 2006[67]			
N=20 (completed follow-up), Age: 11.1±1.6 years, Length: 12 weeks. Design: RNB Diagnosis: SCH	RIS=OLZ (evaluated with SAS)		RIS=OLZ (evaluated with BARS)
Shaw, 2006[22]			
N=25, Age: 7–16 years, Length: 8 weeks. Design: RDB Diagnoses: SCH	CLZ=OLZ (evaluated with SAS)	CLZ=OLZ (evaluated with AIMS)	
Sikich, 2004[26]			
N=50, Age: 8–19 years, Length: 8 weeks. Design: RDB Diagnoses: SCH, OP	HAL>OLZ=RIS (evaluated with SAS)		HAL=OLZ=RIS (evaluated with AIMS)
Sikich, 2008[8]			
N=116, Age: 8–19 years, Length: 8 weeks. Design: RDB Diagnoses: SCH, OP	OLZ=RIS=MOL (evaluated with SAS)	OLZ=RIS=MOL (evaluated with AIMS)	OLZ=RIS=MOL (1) (evaluated with BARS)
Swadi, 2010[68]			
N=26, Age: <19 years old, Length: 6 weeks. Design: RNB Diagnoses: first psychotic episode or affective episode with psychotic symptoms	QTP=RIS (evaluated with SAS)	QTP=RIS (evaluated with AIMS)	QTP=RIS (evaluated with BARS)

Table 4 (*continuation*)

Articles	Increase in parkinsonism	Increase in dyskinesia	Increase in akathisia
Tohen, 2007[19] N=161, Age: 13-17 years, Length: 3 weeks. Design: RDB Diagnosis: BIP	OLZ=PLAC (evaluated with SAS)	OLZ=PLAC (evaluated with AIMS)	OLZ=PLAC (evaluated with BARS)
Tramontina, 2009[69] N=41, Age: 8-17 years, Length: 6 weeks. Design: RDB Diagnoses: BIP+TDAH	ARP=PLAC (evaluated with a checklist of adverse effects created by the authors)		ARP=PLAC (evaluated with a checklist of adverse effects created by the authors)

RDB: randomised double-blind; AIMS: abnormal involuntary movement scale[79]; RNB: randomised, not blinded; ARP: aripiprazole; BARS: Barnes Akathisia Rating Scale[80]; BIP: bipolar disorder; CLZ: clozapine; Length: length of treatment in the study; SCH: schizophrenia or schizoaffective disorder; HAL: haloperidol; MOL: molindone; N: number of subjects included in the study; OLZ: olanzapine; OP: Other psychotic disorders, including schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, depression with psychotic features; PLAC: placebo; QTP: quetiapine; R: age range; RIS: risperidone; SAS: Simpson Angus Scale[81]; UKU: Udvalg for Kliniske Undersøgelser, drug adverse effects scale.[82]

The sign ">" means "there are statistically significant differences ($P<.05$)"; the parameter measured with treatment A is greater than with treatment B (A>B)". The sign "=" means that there were no differences between the compared parameters, or that if there were, they were not statistically significant.

NOTES:

1. Intra-group analyses (before/after) showed that treatment with MOL was associated with statistically significant increase in akathisia; this was not the case with OLZ or RIS treatment.

the superiority of clozapine in patients with treatment-refractory schizophrenia,[20-22] and 2) the incidence and severity of adverse effects from SGAs depends, to a great extent, on the drug used, such that a global pattern of SGA tolerability in children and adolescents cannot be established. That is, SGAs are not a homogenous group of drugs, but rather include drugs with differing profiles under the same umbrella term. These results highlight the importance of the differential profile of antipsychotics as it relates to side effects, particularly with metabolic complications.

Reviews of side effects of second-generation antipsychotics

The last decade of the twentieth century saw a dramatic increase in the use of SGAs in children and adolescents. This increased was supported by, amongst other things, the high expectations on SGAs, particularly relating to their claims of safety. In a recent publication, Vitiello et al[3] reviewed the main factors that have contributed to increased prescribing of SGAs in the paediatric population. They highlighted three important factors: the boom in the last two decades of the twentieth century in the use of a medical model of disease to explain emotional and behavioural disorders in children and adolescents, the apparent safety of SGAs as compared with the older FGAs, and the general trend towards reducing the length of stay in psychiatric inpatient units, with consequent pressure on clinicians to achieve more rapid stabilisation.[3] However, despite the unquestionable value of SGAs in the treatment of various psychiatric disorders in children and adolescents, the discovery of their adverse effects has called into question their supposed safety. Consequently in this first decade of the twenty-first century, several reviews of the side effects of SGAs in children and adolescents have been published.[1,3,12,29-43] The first reviews stressed the importance of studying the side effects of SGAs in the paediatric population, as the inference that the effects of these drugs in children and adolescents were equivalent to those found in adults was a major limitation. As data later showed, the response of children and adolescents to SGAs is not directly transferable to that of adults: studies in the paediatric population have found that SGA side effects are more pronounced in children and adolescents than in adults.[12,42,44] The weight gain and increased prolactin levels secondary to SGA treatment are, across various studies, consistently greater in children and adolescents than in adults.[29] Furthermore, in relation to weight gain in children and adolescents, other problems such as diabetes mellitus and hyperlipidaemia may occur, which significantly predicts future morbidity.

From the start, the reviews in this area have noted that, with regard to side effects, SGAs are not a homogenous group.[45,46] The effect on weight is a prime example of this heterogeneity: the drugs associated with greater weight gain were clozapine and olanzapine, while risperidone and quetiapine have been associated with moderate weight gain and ziprasidone and aripiprazole with a low

risk of weight gain.[30,31] Furthermore, a recent systematic review (of articles published between 1965 and 2008) on the effect of antipsychotics (FGAs and SGAs) on prolactin levels in children and adolescents showed that among the drugs studied (haloperidol, pimozide, risperidone, olanzapine, clozapine, ziprasidone and quetiapine), all antipsychotics, with the exception of clozapine, ziprasidone and quetiapine, increased prolactin levels, thus limiting that factor as a point of differentiation between FGAs and SGAs.[32]

Our review evaluated a very heterogeneous set of studies, both in methodology, follow-up time, and sample size. Consequently, one must bear in mind these limitations when making comparisons between the results of different studies. The selection of the studies included in this review precludes sophisticated statistical analysis and meta-analysis or NNT (number needed to treat) and NNH (number needed to harm) calculations. In spite of the above, we decided to include all these articles in order to provide a review of all published data to date on results of comparative efficacy and tolerability between different SGAs in the paediatric population.

Children and adolescents are more vulnerable than adults to the side effects of antipsychotic medication

Studies of the SGAs in the paediatric population have proven crucial, since children and adolescents are not only more vulnerable than adults to the side effects of antipsychotic drugs, but are also more sensitive to the negative impact these effects have on body image or self-esteem.[1]

In this regard, the differential profile of antipsychotics takes on unique value in the paediatric population. Children and adolescents are much more vulnerable than adults, from the perspective of personality development as well as physical changes such as associated weight gain.[1,3,29,42] Furthermore, a strong relationship has been shown between childhood obesity and childhood and adult cardiovascular risk, i.e., children with obesity, as adults, will have greater cardiovascular risk than the general population.[47] Subjects treated with antipsychotics have, as we have seen, greater metabolic risk than those not taking antipsychotics. But this increased risk in people with psychotic disorders is not only due to pharmacologic treatment. The presence of a psychotic disorder, in adults and probably also in children and adolescents (specific studies are still lacking in this age group) involves *per se* an increased risk of developing metabolic complications. That is, people with psychosis have greater metabolic risk than the general population, regardless of treatment.[48] This implies that cardiovascular risk monitoring in this paediatric population is "triply" important: for being children or adolescents, for having psychosis, and for taking antipsychotics.

Naturally, in the same way that subjects with psychosis have more cardiovascular risk than the general population, it is expected that among the various pathologies that make up the heterogeneous group of psychotic disorders, not all involve the same degree of metabolic risk. In line with this approach, a recent study found that among children and adolescents treated with SGAs, the incidence of SGA treatment-related metabolic syndrome in antipsychotic-naïve adolescents is significantly greater in patients with bipolar disorder than in subjects with other diagnoses.[49] These data invite us to study the, as yet unknown, pathophysiological mechanisms underlying this association.

Relationship between adverse effects and drug doses

Clinical experience suggests the existence of a relationship between SGA dose and the occurrence of side effects. However, few studies have investigated this association. A recent review of this subject has emphasised that there is a positive correlation between weight gain and plasma concentrations of olanzapine and clozapine, although the relationship between weight gain and dose is more controversial. Data on risperidone are even less conclusive.[50] This review draws attention to the lack of information between weight gain and doses of other SGAs.

With regard to increased prolactin levels secondary to SGA treatment in the paediatric population, a study with subjects from different samples found a significant relationship between plasma concentrations of olanzapine and prolactin levels, while this relationship was not found in those treated with haloperidol and clozapine.[51] Furthermore, a recent study found a positive relationship between the dose of risperidone and increased prolactin levels with 6-month follow-up.[52]

Duration of treatment

Duration of treatment is a key variable in the study of SGA side effects. However, the short duration of follow-up in efficacy and tolerability studies highlights, almost in a systematic fashion, a common limitation of these published studies.[37] Studies on metabolic complications in this review have mean follow-up durations (and therefore treatment durations) of 14.6 weeks, without any follow-up longer than one year. This short duration of follow-up may limit the value of the findings, especially in light of recent results that question the temporal stability of the differences in metabolic side effects among different drugs. A randomised controlled study with Spanish subjects, both adolescents and adults (N = 144, Age: 15-60 years), treated with antipsychotics (olanzapine, risperidone, and haloperidol), showed that at 3 months, weight gain was greater in patients treated with olanzapine than in the rest (olanzapine>risperidone=haloperidol), while at 12 months this difference was no longer significant (olanzapine=risperidone=haloperidol).[53] Furthermore, a recent study also in a Spanish population, compared the side effects of antipsychotics (FGA and SGA) among children and adolescents treated for less than 30 days and subjects treated for more than 12 months. The group of subjects with more than 12

months of exposure to antipsychotics had significantly higher degrees of weight gain, increased cholesterol, parkinsonism and dyskinesia that subjects treated for less than 30 days. No differences were found between the groups in terms of triglyceride level, blood pressure or akathisia.[54]

Is the distinction between first and second-generation antipsychotics valid?

The data on efficacy and tolerability of antipsychotics questions the validity of the conceptual distinction between FGAs and SGAs. A recent meta-analysis comparing the efficacy and tolerability of FGAs and SGAs in the treatment of adults with schizophrenia, highlighted that the drugs classified within the SGA grouping differ in many properties and do not form a homogenous group.[46] In recent years many people have called to attention this lack of homogeneity of the SGAs as a group, both in their use in adults as well as in children and adolescents.[45,46,55,56] In light of these data, and considering that the main differences between SGAs relate to adverse metabolic effects, replacement of the FGA versus SGA classification has been proposed in favour of another classification system that distinguishes antipsychotics based on their metabolic risk. Carmel and Gorman have recently proposed such a classification of antipsychotics based on metabolic risk.[57] In this proposed classification scheme, antipsychotics with low metabolic risk would include: molindone, ziprasidone, fluphenazine, haloperidol, and aripiprazole, while antipsychotics with high metabolic risk would include: clozapine, olanzapine, thioridazine, mesoridazine, sertindole, risperidone, and quetiapine[57] (Figure 2).

Recommendations for clinical monitoring of metabolic complications in children and adolescents treated with antipsychotics

The importance of these findings underscores the need for careful monitoring of SGA-associated adverse effects both in adults and in children and adolescents.[58] However, as noted throughout this review, children and adolescents are particularly vulnerable to the adverse effects of antipsychotics. Consequently, it is important to anticipate the risks of treating the paediatric population with SGAs in order to prevent, wherever possible, those complications arising from the use of these drugs (Table 5). In light of this, we believe that there is fundamental value in routinely checking for side effects from the prescribed SGA as well as involving both patients and their families in assessing the risks and benefits of these medications. Since the appearance of the first warning signs about the metabolic effects of SGAs in adults, various authors and institutions have published recommended guidelines for monitoring adverse effects. Although these guidelines in general have little impact on the daily tasks of clinicians,[59] we want to emphasise their importance. Consequently, Table 5 shows recommended guidelines for monitoring adverse effects of SGAs in children and adolescents, based on work by Correll (2008).[9] In the event of serious side effects, it may be necessary to consider changing to a lower-risk medication.[9]

Funding

This work received editorial support from Adelphi Targis, S.L. and received funding from BMS. The authors assume full responsibility for the information contained in the manuscript.

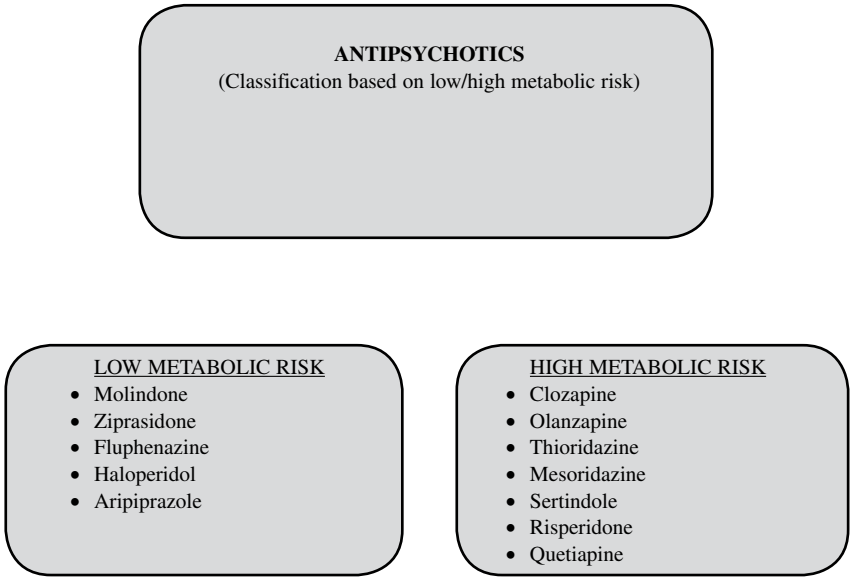


Figure 2 Classification of antipsychotics as a function of their metabolic risk (low/high metabolic risk) (based on Carmel and Gorman, 2009[57]).

Table 5 SGA adverse effects monitoring in children and adolescents (Adapted from Correll, 2008[9])

Evaluation	Frequency
Personal and Family History	• Baseline • Every 12 months
Healthy lifestyles	• Every medical visit (minimum every 3 months)
Weight, height, body mass index	• Every medical visit (minimum every 3 months)
Somnolence / sedation	• Every medical visit (minimum every 3 months)
Sexual function	• Baseline • During dose adjustments • Every 3 months
Blood pressure, heart rate	• Baseline • at 3 months • every 12 months
Glucose, lipid profile	• Baseline • at 3 months • every 6 months
Electrolytes, Complete blood count, renal function, liver function	• Baseline • every 12 months • In the case of clozapine, the weekly blood count monitoring protocol should be followed during the first 18 weeks, and monthly thereafter
Prolactin level	• If indicated by symptoms
Extrapyramidal symptoms, akathisia	• Baseline • During dose adjustments • At 3 months • Every 12 months
Tardive dyskinesia	• At 3 months • Every 12 months
Electrocardiogram:	• Initial (Especially in the case of ziprasidone and clozapine) • In the case of ziprasidone: during dose adjustments

References

1. Arango C, Parellada M, Moreno DM. Clinical effectiveness of new generation antipsychotics in adolescent patients. Eur Neuropsychopharmacol. 2004;14(Suppl 4):S471-9.
2. Findling RL, Steiner H, Weller EB. Use of antipsychotics in children and adolescents. J Clin Psychiatry. 2005;66(Suppl 7):29-40.
3. Vitiello B, Correll C, Van Zwieten-Boot B, Zuddas A, Parellada M, Arango C. Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. Eur Neuropsychopharmacol. 2009;19:629-35.
4. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry. 2006;63:679-85.
5. Rani F, Murray ML, Byrne PJ, Wong IC. Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. Pediatrics. 2008;121: 1002-9.
6. Patel NC, Crismon ML, Hoagwood K, Johnsrud MT, Rascati KL, Wilson JP, et al. Trends in the use of typical and atypical antipsychotics in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2005;44:548-56.
7. Kalverdijk LJ, Tobi H, Van den Berg PB, Buiskool J, Wagenaar L, Minderaa RB, et al. Use of antipsychotic drugs among Dutch youths between 1997 and 2005. Psychiatr Serv. 2008;59:554-60.
8. Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry. 2008;165:1420-31.
9. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. J Am Acad Child Adolesc Psychiatry. 2008;47:9-20.
10. Fraguas D, Merchán-Naranjo J, Laita P, Parellada M, Moreno D, Ruiz-Sancho A, et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. J Clin Psychiatry. 2008;69:1166-75.
11. Tyrer P, Kendall T. The spurious advance of antipsychotic drug therapy. Lancet. 2009;373:4-5.
12. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2006;45:771-91.
13. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302:1765-73.
14. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362-74.
15. Fraguas D, de Castro MJ, Medina O, Parellada M, Moreno D, Graell M, et al. Does diagnostic classification of early-onset psychosis change over follow-up?. Child Psychiatry Hum Dev. 2008;39:137-45.
16. Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. Am J Psychiatry. 2008;165:1432-41.
17. Haas M, Eerdekens M, Kushner S, Singer J, Augustyns I, Quiroz J, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. Br J Psychiatry. 2009;194:158-64.
18. Kryzhanovskaya L, Schulz SC, McDougle C, Frazier J, Dittmann R, Robertson-Plouch C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2009;48:60-70.
19. Tohen M, Kryzhanovskaya L, Carlson G, Delbello M, Wozniak J, Kowatch R, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. Am J Psychiatry. 2007;164: 1547-56.
20. Kumra S, Kranzler H, Gerbino-Rosen G, Kester HM, De Thomas C, Kafantaris V, et al. Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. Biol Psychiatry. 2008;63:524-9.
21. Kumra S, Oberstar JV, Sikich L, Findling RL, McClellan JM, Vinogradov S, et al. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. Schizophr Bull. 2008;34:60-71.
22. Shaw P, Sporn A, Gogtay N, Overman GP, Greenstein D, Gochman P, et al. Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. Arch Gen Psychiatry. 2006;63:721-30.

23. Arango C, Robles O, Parellada M, Fraguas D, Ruiz-Sancho A, Medina O, et al. Olanzapine compared to quetiapine in adolescents with a first psychotic episode. Eur Child Adolesc Psychiatry. 2009;18:418-28.
24. Castro-Fornieles J, Parellada M, Soutullo CA, Baeza I, González-Pinto A, Graell M, et al. Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach. J Child Adolesc Psychopharmacol. 2008;18:327-36.
25. Gothelf D, Apter A, Reidman J, Brand-Gothelf A, Bloch Y, Gal G, et al. Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. J Neural Transm. 2003;110:545-60.
26. Sikich L, Hamer RM, Bashford RA, Sheitman BB, Lieberman JA. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacology. 2004;29:133-45.
27. Fleischhaker C, Heiser P, Hennighausen K, Herpertz-Dahlmann B, Holtkamp K, Mehler-Wex C, et al. Weight gain associated with clozapine, olanzapine and risperidone in children and adolescents. J Neural Transm. 2007;114:273-80.
28. Fleischhaker C, Heiser P, Hennighausen K, Herpertz-Dahlmann B, Holtkamp K, Mehler-Wex C, et al. Weight gain in children and adolescents during 45 weeks treatment with clozapine, olanzapine and risperidone. J Neural Transm. 2008;115:1599-608.
29. Fedorowicz VJ, Fombonne E. Metabolic side effects of atypical antipsychotics in children: a literature review. J Psychopharmacol. 2005;19:533-50.
30. Stigler KA, Potenza MN, McDougle CJ. Tolerability profile of atypical antipsychotics in children and adolescents. Paediatr Drugs. 2001;3:927-42.
31. Vieweg WV, Sood AB, Pandurangi A, Silverman JJ. Newer antipsychotic drugs and obesity in children and adolescents. How should we assess drug-associated weight gain?. Acta Psychiatr Scand. 2005;111:177-84.
32. Roke Y, Van Harten PN, Boot AM, Buitelaar JK. Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects. J Child Adolesc Psychopharmacol. 2009;19:403-14.
33. Pappagallo M, Silva R. The effect of atypical antipsychotic agents on prolactin levels in children and adolescents. J Child Adolesc Psychopharmacol. 2004 Fall;14:359–71.
34. Richardson MA, Haugland G, Craig TJ. Neuroleptic use, parkinsonian symptoms, tardive dyskinesia, and associated factors in child and adolescent psychiatric patients. Am J Psychiatry. 1991;148:1322-8.
35. Cheng-Shannon J, McGough JJ, Pataki C, McCracken JT. Second-generation antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol. Fall. 2004;14: 372-94.
36. Glick ID, Murray SR, Vasudevan P, Marder SR, Hu RJ. Treatment with atypical antipsychotics: new indications and new populations. J Psychiatr Res. 2001;35:187-91.
37. Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. Eur Child Adolesc Psychiatry. 2007;16:104-20.
38. Correll CU, Kane JM. One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review. J Child Adolesc Psychopharmacol. 2007;17:647-56.
39. Toren P, Ratner S, Laor N, Weizman A. Benefit-risk assessment of atypical antipsychotics in the treatment of schizophrenia and comorbid disorders in children and adolescents. Drug Saf. 2004;27:1135-56.
40. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. Arch Pediatr Adolesc Med. 2008;162:929-35.
41. Harrison-Woolrych M, Garcia-Quiroga J, Ashton J, Herbison P. Safety and usage of atypical antipsychotic medicines in children: a nationwide prospective cohort study. Drug Saf. 2007;30:569-79.
42. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. Bipolar Disord. 2010; 12:116-41.
43. Singh MK, Ketter TA, Chang KD. Atypical antipsychotics for acute manic and mixed episodes in children and adolescents with bipolar disorder: efficacy and tolerability. Drugs. 2010; 70:433-42.
44. DelBello MP, Correll CU. Primum non nocere: balancing the risks and benefits of prescribing psychotropic medications for youth with bipolar disorder. Bipolar Disord. 2010;12:113-5.
45. Findling RL, McNamara NK. Atypical antipsychotics in the treatment of children and adolescents: clinical applications. J Clin Psychiatry. 2004;65(Suppl 6):30-44.
46. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31-41.
47. Burke V. Obesity in childhood and cardiovascular risk. Clin Exp Pharmacol Physiol. 2006;33:831-7.
48. Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk?. Acta Psychiatr Scand. 2009;119:171-9.
49. Moreno CM-NJ, Álvarez M, Baeza I, Alda JA, Martínez-Cantarero C, Parellada M, Sánchez B, De la Serna E, Giráldez M, Arango C. Metabolic effects of second-generation antipsychotics in bipolar youth: comparison with other psychotic and non-psychotic diagnoses. Bipolar Disroder. En prensa.
50. Simon V, Van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry. 2009;70:1041-50.
51. Alfaro CL, Wudarsky M, Nicolson R, Gochman P, Sporn A, Lenane M, et al. Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. J Child Adolesc Psychopharmacol. 2002 Summer;12:83–91.
52. Haas M, Unis AS, Armenteros J, Copenhaver MD, Quiroz JA, Kushner SF. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. J Child Adolesc Psychopharmacol. 2009;19:611-21.
53. Pérez-Iglesias R, Crespo-Facorro B, Martínez-García O, Ramírez-Bonilla ML, Álvarez-Jiménez M, Pelayo-Terán JM, et al. Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naive population. Schizophr Res. 2008;99:13-22.
54. Laita P, Cifuentes A, Doll A, Llorente C, Cortes I, Parellada M, et al. Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. J Child Adolesc Psychopharmacol. 2007;17:487-502.
55. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553-64.
56. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry. 2009;166:152-63.
57. Carmel H, Gorman JM. Classifying antipsychotics by likelihood of metabolic side-effects. Psychiatr Serv. 2009;60:1143.
58. Cohn TA, Sernyak MJ. Metabolic monitoring for patients treated with antipsychotic medications. Can J Psychiatry. 2006;51: 492-501.

59. Morrato EH, Druss B, Hartung DM, Valuck RJ, Allen R, Campagna E, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. Arch Gen Psychiatry. 2010;67: 17-24.
60. Bastiaens L. A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. Community Ment Health J. 2009; 45:73-7.
61. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2002;41:1216-23.
62. DelBello MP, Chang K, Welge JA, Adler CM, Rana M, Howe M, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disord. 2009;11:483-93.
63. Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2009;70:1441-51.
64. Haas M, Delbello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2009;11:687-700.
65. Jensen JB, Kumra S, Leitten W, Oberstar J, Anjum A, White T, et al. A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. J Child Adolesc Psychopharmacol. 2008; 18:317-26.
66. Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. Arch Gen Psychiatry. 1996;53:1090-7.
67. Mozes T, Ebert T, Michal SE, Spivak B, Weizman A. An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. J Child Adolesc Psychopharmacol. 2006;16:393-403.
68. Swadi HS, Craig BJ, Pirwani NZ, Black VC, Buchan JC, Bobier CM. A trial of quetiapine compared with risperidone in the treatment of first onset psychosis among 15- to 18-year-old adolescents. Int Clin Psychopharmacol. 2010;25:1-6.
69. Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. J Clin Psychiatry. 2009;70:756-64.
70. Biederman J, Mick E, Hammerness P, Harpold T, Aleardi M, Dougherty M, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. Biol Psychiatry. 2005;58:589-94.
71. Fleischhaker C, Heiser P, Hennighausen K, Herpertz-Dahlmann B, Holtkamp K, Mehler-Wex C, et al. Clinical drug monitoring in child and adolescent psychiatry: side effects of atypical neuroleptics. J Child Adolesc Psychopharmacol. 2006;16: 308-16.
72. Hrdlicka M, Zedkova I, Blatny M, Urbanek T. Weight gain associated with atypical and typical antipsychotics during treatment of adolescent schizophrenic psychoses: A retrospective study. Neuro Endocrinol Lett. 2009;30:256-61.
73. Khan RA, Mican LM, Suehs BT. Effects of olanzapine and risperidone on metabolic factors in children and adolescents: a retrospective evaluation. J Psychiatr Pract. 2009;15:320-8.
74. Migliardi G, Spina E, D'Arrigo C, Gagliano A, Germano E, Siracusano R, et al. Short- and long-term effects on prolactin of risperidone and olanzapine treatments in children and adolescents. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33:1496-501.
75. Ratzoni G, Gothelf D, Brand-Gothelf A, Reidman J, Kikinzon L, Gal G, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. J Am Acad Child Adolesc Psychiatry. 2002;41:337-43.
76. Saito E, Correll CU, Gallelli K, McMenimun M, Parikh UH, Malhotra AK, et al. A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. J Child Adolesc Psychopharmacol. 2004 Fall;14:350-8.
77. Stevens JR, Kymissis PI, Baker AJ. Elevated prolactin levels in male youths treated with risperidone and quetiapine. J Child Adolesc Psychopharmacol. 2005;15:893-900.
78. Wudarsky M, Nicolson R, Hamburger SD, Spechler L, Gochman P, Bedwell J, et al. Elevated prolactin in pediatric patients on typical and atypical antipsychotics. J Child Adolesc Psychopharmacol. 1999;9:239-45.
79. Guy W. ECDEU Assessment Manual for Psychopharmacology, edición revisada. Washington, DC, US Department of Health, Education, and Welfare, 1976.
80. Barnes TR. The Barnes Akathisia Rating Scale--revisited. J Psychopharmacol. 2003;17:365-70.
81. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-9.
82. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl. 1987;334:1-100.