REVIEW

Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: Comprehensive review of prospective head-to-head and placebo-controlled comparisons

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Abstract

Objective: To review data on efficacy and safety of second-generation antipsychotics (SGAs) in children and adolescents with psychotic and bipolar spectrum disorders. *Methods:* Medline/ PubMed/Google Scholar search for studies comparing efficacy and/or tolerability: (i) between two or more SGAs; (ii) between SGAs and placebo; and (iii) between at least one SGA and one first-generation antipsychotic (FGA). The review focused on three major side-effect clusters: 1. body weight, body mass index, and cardiometabolic parameters, 2. prolactin levels, and 3. neuromotor side effects. *Results:* In total, 34 studies with 2719 children and adolescents were included. Studies lasted between 3 weeks and 12 months, with most studies (79.4%) lasting 3 months or less. Nine studies (n=788) were conducted in patients with schizophrenia, 6 (n=719) in subjects with bipolar disorder, and 19 (n=1212) in a mixed population. Data on efficacy showed that, except for clozapine being superior for refractory schizophrenia, there were no significant differences between SGAs. By contrast, safety assessments showed relevant differences between SGAs. Mean weight gain ranged from 3.8 kg to 16.2 kg in patients treated with olanzapine (n=353), from 0.9 kg to 9.5 kg in subjects receiving clozapine (n=97), from 1.9 kg to 7.2 kg in those on risperidone (n=571), from 2.3 kg to 6.1 kg among patients taking

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quetiapine (n = 133), and from 0 kg to 4.4 kg in those treated with aripiprazole (n = 451). Prolactin levels increased the most in subjects on risperidone (mean change ranging from 8.3 ng/mL to 49.6 ng/mL), followed by olanzapine (−1.5 ng/mL to +13.7 ng/mL). Treatment with aripiprazole was associated with decreased prolactin levels, while clozapine and quetiapine were found to be mostly neutral. With respect to neuromotor side effects, SGAs were associated with less parkinsonism and akathisia than FGAs. Most of the studies comparing neuromotor side effects between SGAs found no significant differences. *Conclusions:* SGAs do not behave as a homogeneous group in children and adolescents with psychotic and mood disorders. Except for clozapine, the heterogeneity within the SGA group is mainly due to differences in the rates and severity of adverse events, especially regarding weight gain as a proxy for the risk of cardiometabolic disturbances.

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1. Introduction

Despite clinical studies showing that children and adolescents as well as patients with minimal treatment history are vulnerable to side effects, such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities (American Diabetes Association, 2004; Correll, 2008a; De Hert et al., 2008; Fraguas et al., 2008b; Sikich et al., 2008; Tarricone et al., 2010; Tyrer and Kendall, 2009), the prescription of second-generation antipsychotics (SGAs) in children and adolescents has become a common occurrence in psychiatric practice as first-line treatment for schizophrenia spectrum disorders, bipolar disorder, and non-psychotic mental disorders (Arango et al., 2004; Findling et al., 2005; Olfson et al., 2006; Vitiello et al., 2009).

Furthermore, the number of prescriptions and the duration of treatment with these drugs in paediatric populations have greatly increased in Europe and especially in the USA (Aparasu and Bhatara, 2007; Olfson et al., 2006, 2010; Patel et al., 2005; Rani et al., 2008). Different clinical and socio-demographic factors have been related to the increased use of SGAs in children and adolescents. SGAs were introduced with the belief that they were better tolerated, especially with regard to lower risk of extrapyramidal side effects, and that they were more efficacious than first-generation antipsychotics (FGAs). Additionally, the tendency to diagnose psychiatric conditions earlier in young people and, thus, to start drug treatment at earlier stages, is related to the fact that antipsychotic medications are now used for longer periods of time in paediatric patients. In Holland, the duration of SGA treatment in children and adolescents has doubled in a short time span (from 0.8 years in 1998−1999 to 1.6 years in 2001−2002) (Kalverdijk et al., 2008). Other factors, such as the generalization of a medical model for explaining emotional and behavioural disorders, and recent changes in mental health services with pressure for quick clinical stabilization, have further contributed to the increase in the use of SGAs (Vitiello et al., 2009).

However, the increased use of SGAs in developing children and adolescents has caused considerable concern because multiple studies have shown that these medications are associated with adverse effects on prolactin (Roke et al. 2009) and, especially, with cardiometabolic side effects, such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities (American Diabetes Association, 2004; Correll, 2008a; Correll et al., 2009; De Hert et al., 2008; Fraguas et al., 2008b; Sikich et al., 2008; Tarricone et al., 2010; Tyrer and Kendall, 2009). Cardiometabolic side effects are particularly relevant in children and adolescents, because young people are especially vulnerable to SGA-induced metabolic side effects, and because the onset of these abnormalities during development predicts adult obesity, metabolic syndrome, and cardiovascular morbidity (Baker et al., 2007; Bhargava et al., 2004; Correll, 2008b; Sinaiko et al., 1999). However, despite the importance of these data, there are very few studies that have compared the tolerability and efficacy of different SGAs and FGAs in children and adolescents.

Rules recently implemented by the Food and Drug Administration (FDA) in the United States and European Medicines Agency (EMA) in Europe have prompted efficacy and tolerability studies of SGAs in young people, but have also highlighted the need for a debate on the risks and benefits of prescribing SGAs in the paediatric population.

While antipsychotic effects have been compared extensively in adults with schizophrenia (Davis et al., 2003; Jones et al. 2006; Leucht et al., 2009a,b,c; Lieberman et al. 2005) and in adults with bipolar disorder (Perlis et al. 2006; Scherk et al. 2007; Smith et al. 2007), much less is known about the comparative effectiveness of antipsychotics in young people with schizophrenia and bipolar spectrum disorders.

Therefore, we conducted a comprehensive review of the data from controlled and uncontrolled prospective studies in children and adolescents with psychotic and bipolar disorder spectrum disorders that compared the efficacy and/or tolerability of SGAs, either head-to-head, against an FGA, or against placebo. Although schizophrenia and bipolar disorder are currently considered separate disorders and not all patients with bipolar disorder experience psychosis, we considered it reasonable to examine the effects of SGAs in patients with psychosis and with bipolar disorder, as current results suggest a relative lack of diagnostic stability in psychotic and mood disorders diagnosed in young people (Correll et al. 2005; Fraguas et al., 2008a; Hollis, 2000; Olfson et al. 2009; Salvatore et al., 2009).

2. Methods

We conducted a systematic Medline/PubMed/Google Scholar search of studies published in English between 1990 and April 2010 (i.e. after the introduction of SGAs) comparing the efficacy and/or tolerability of antipsychotics against each other or against placebo in patients younger than 18 years of age. We restricted the studies to those that included children and adolescents with a psychotic

disorder (including schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and psychosis not otherwise specified) or mood disorder that may be associated with psychosis (bipolar disorder and depressive disorder with psychotic symptoms). We also included studies that reported on mixed populations, as long as at least 50% of patients had one of the diagnoses listed above. We decided to restrict the sample to patients with psychotic or bipolar spectrum disorders in order to get a more homogeneous composition of participants and to enhance the clinical interpretation of our results.

For the electronic Medline/PubMed/Google Scholar search, the following key words were used: "antipsychotic"; AND/OR "psychosis"; AND/OR "adolescent"; AND/OR "adverse events"; AND/OR "efficacy". We also repeated the search replacing "antipsychotic" with "olanzapine", "risperidone", "aripiprazole", "clozapine", "quetiapine", "ziprasidone", "paliperidone", or "amisulpride"; replacing "psychosis" with "early onset psychosis", "schizophrenia", "bipolar disorder"; replacing "adolescent" with "child", "children", or "youth"; and replacing "adverse events" with "weight gain", "metabolic", "prolactin", "parkinsonism", "dyskinesia", or "akathisia". Furthermore, manuscript bibliographies of identified trials and of related reviews were searched for additional studies.

We identified 72 studies analyzing efficacy and/or tolerability of SGAs in young people (<18 years old) with psychotic or bipolar spectrum disorders. Out of these 72 studies, 34 articles fulfilling the following inclusion criteria were selected: (i) studies comparing efficacy and/or tolerability between two or more SGAs (23 studies fulfilled this criterion); (ii) studies comparing efficacy and/or tolerability between antipsychotics and placebo (9 studies); and (iii) studies comparing efficacy and/or tolerability between at least one SGA and one FGA (2 studies fulfilled this criterion).

On the other hand, 38 studies were excluded for the following reasons: 1. not presenting comparisons between antipsychotics or between antipsychotics and placebo (22 studies); 2. data in child and adolescent populations mixed with adult populations without separate analyses (12 studies); and 3. mixed population with less than 50% of patients with psychotic or bipolar disorder (4 studies). Fig. 1 shows a flow chart of included and excluded studies.

Due to the variability of the efficacy and tolerability assessments in different studies, the current review focused on three major side-effect clusters of particular importance: 1. body weight, body mass index (BMI), and cardiometabolic parameters (glucose, cholesterol, triglycerides, and blood pressure), 2. prolactin levels, and 3. neuromotor side effects (dystonia, parkinsonism, rigidity, tremor, hypokinesia/akinesia, and akathisia).

Data analysis: This is a descriptive review. Therefore, descriptive statistics are used and inferential statistics are reported as provided by each study. Because of the methodological variability of the included studies, no other statistical analyses were performed.

3. Results

In total, 34 studies with 2719 children and adolescents were included. Seventeen studies were randomized controlled trials (n=1682), either blinded (14 studies, n=1595), or open (3 studies, n=87), while one study reported on both open non-randomized and randomized controlled samples (n=47). Five studies were open, non-randomized studies (n=192); 9 were naturalistic (n=670), and 2 were retrospective chart reviews (n=128). Studies lasted between 3 weeks and 12 months, with
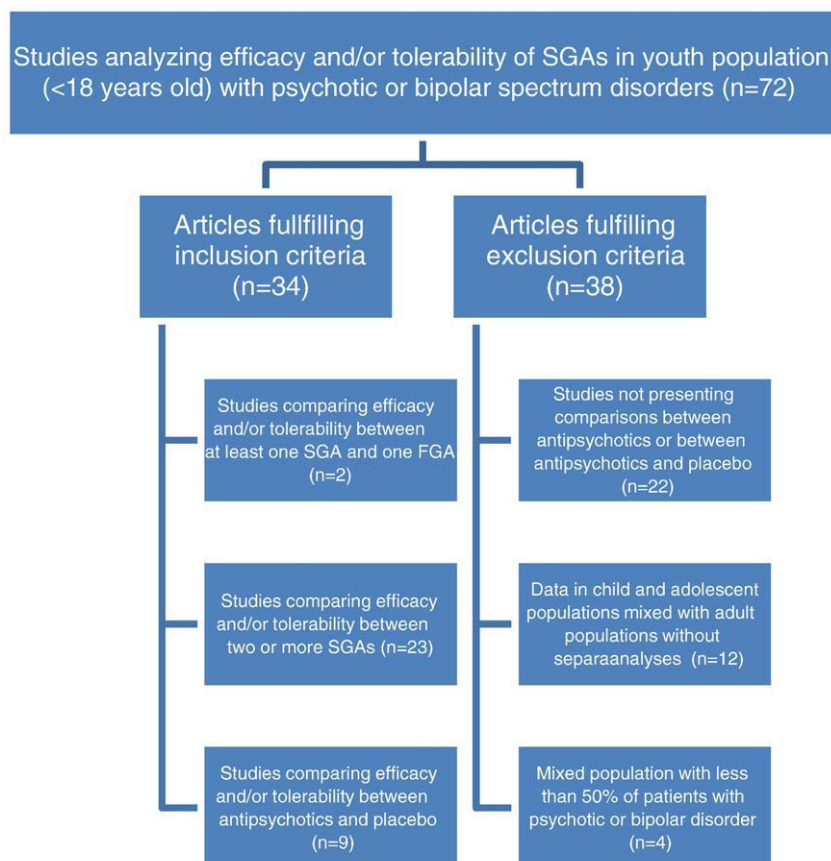

Figure 1   Flow-chart of included and excluded studies.

Table 1 Study, patient and treatment characteristics.

Study	Design	Setting (inpatient/ outpatient)	Duration	N	Drug	Daily mean dose (mg/day)	Diagnosis	Age (mean±SD or range) years	Sex (% male)
Randomized, double-blind controlled trials									
Kumra et al. (1996)	DBCT	Inpatient	6 weeks	21	CLZ (N=10) HAL (N=11)	CLZ: 176±149 HAL: 16±8	SCHIZ	14.0±2.3 years	52.4%
Shaw et al. (2006)	DBCT	Outpatient	8 weeks	25	CLZ (N=12) OLZ (N=13)	CLZ: 327±113 OLZ: 18.1±4.3	SCHIZ	7–16 years	60.0%
Findling et al. (2008)	DBCT	Outpatient/ inpatient	6 weeks	294	ARP 10 mg (N=99) ARP 30 mg (N=97) PBO (N=98)	ARP: 10 ARP: 30	SCHIZ	13–17 years	56.6%
Kumra et al. (2008b)	DBCT	Inpatient	12 weeks	39	CLZ (N=18) OLZ (N=21)	CLZ: 403.1±201.8 OLZ: 26.2±6.5	SCHIZ	10–18 years	53.5%
Kryzhanovskaya et al. (2009)	DBCT	Inpatient/ outpatient	6 weeks	64	OLZ (N=49) PBO (N=15)	OLZ: 11.1	SCHIZ	13–17 years	70.1%
Haas et al. (2009a)	DBCT	Inpatient/ outpatient	8 weeks	257	RIS 1.5–6.0 mg (N=90) RIS 0.15–0.6 mg (N=82)	RIS: 1.5–6.0 RIS: 0.15–0.6	SCHIZ	13–17 years	56.4%
Sikich et al. (2008)	DBCT	Inpatient	8 weeks	116	MOL (N=40) OLZ (N=35) RIS (N=41)	MOL: 59.9±33.5 OLZ: 12.3±3.5 RIS: 2.8±1.4	SCHIZ, OPSY	8–19 years	60.0%
Sikich et al. (2004)	DBCT	Inpatient/ outpatient	8 weeks	50	HAL (N=15) OLZ (N=16) RIS (N=19)	HAL: 5.0±2.0 OLZ: 12.3±3.5 RIS: 4.0±1.2	SCHIZ, OPSY	8–19 years	60.0%
DelBello et al. (2002)	DBCT (divalproex+ QTP vs. divalproex+ PBO)	Inpatient	6 weeks	30	QTP (N=15) PBO (N=15)	QTP: 432	BD	12–18 years	53.3%
Tohen et al. (2007)	DBCT	Inpatient/ outpatient	3 weeks	161	OLZ (N=107) PBO (N=54)	OLZ: 10.7±4.5	BD	13–17 years	52.8%
DelBello et al. (2009)	DBCT	Outpatient	8 weeks	32	QTP (N=16) PBO (N=16)	QTP: 300–600	BD	12–18 years	31.3%
Haas et al. (2009b)	DBCT	Inpatient/ outpatient	3 weeks	169	RIS 0.5–2.5 mg (N=50) RIS 3–6 mg (N=61) PBO (N=58)	RIS: 0.5–2.5 RIS: 3–6 mg/day	BD	10–17 years	49%
Findling et al. (2009)	DBCT	Inpatient/ outpatient	4 weeks	296	ARP 10 mg/day (N=98) ARP 30 mg/day (N=99) PBO (N=99)	ARP: 10 ARP: 30	BD	10–17 years	53.7%

Tramontina et al. (2009)	DBCT	Outpatient	6 weeks	41	ARP (N=17) PBO (N=24)	ARP: 13.6±5.4	BD+ADHD	8–17 years	46.5%
Wudarsky et al. (1999)	DBCT and OLNRT samples	Outpatient	6 weeks	47	CLZ (N=22) HAL (N=15) OLZ (N=10)	CLZ: 325.4±211 HAL: 15.3±8.23 OLZ: 17.0±3.5	SCHIZ, BD, OPSY	9–19 years	62.9%
Randomized, open label trials									
Arango et al. (2009)	OLRT	Inpatient/ outpatient	6 months	32	OLZ (N=16) QTP (N=16)	OLZ: 9.7±6.5 QTP: 532.8±459.6	SCHIZ, BD, OPSY	16±1.3 years	79.2%
Jensen et al. (2008)	OLRT	Inpatient/ outpatient	12 weeks	29	OLZ (N=10) QTP (N=9) RIS (N=10)	OLZ : 14.0±4.6 QTP: 611±253.4 RIS: 3.4±1.5	SCHIZ, OPSY	10–18 years	40.0%
Swadi et al. (2010)	OLRT (with blind midpoint and endpoint assessments)	Inpatient	6 weeks	26	QTP (N=11) RIS (N=11)	QTP: 607 RIS: 2.9	First onset psychotic disorder or mood disorder with psychotic features	<19 years	59.1%
Open label, non-randomized trials									
Bastiaens (2009)	OLNRT	Outpatient	8 weeks	46	ARP (N=20) ZPD (N=14)	ARP: 4.5±2.3 ZPD: 42.9±18.0	SCHIZ, BD, OPSY, OTHER, BEHAV	11.9±2.6 years	78.3%
Biederman et al. (2005)	OLNRT	Outpatient	8 weeks	31	OLZ (N=15) RIS (n=16)	OLZ: 6.3±2.3 RIS: 1.4±0.5	BD	4–6 years	80.0%
Ratzoni et al. (2002)	OLNRT	Inpatient/ outpatient	12 weeks	50	HAL (N=8) OLZ (N=21) RIS (N=21)	HAL: OLZ: RIS:	SCHIZ, BEHAV	13–20 years	62.0%
Schulz et al. (1996)	OLNRT	Inpatient	36 weeks	40	CLZ (N=20) FGAs (N=20)	CLZ: 324 FGAs: 465 (2)	SCHIZ	14–22 years	55.0%
Mozes et al. (2006)	OLNRT	Inpatient	12 weeks	25	OLZ (N=12) RIS (N=13)	OLZ: 8.2±4.4 RIS: 1.6±1.0	SCHIZ	11.1±1.6 years	40.0%
Naturalistic studies									
Gothelf et al. (2003)	Naturalistic	Inpatient	8 weeks	43	HAL (N=7) OLZ (N=19) RIS (N=17)	HAL: 8.3±3.8 OLZ: 19.9±3.1 RIS: 3.3±1.1	SCHIZ	17±2 years	62.8%
Saito et al. (2004)	Naturalistic	Inpatient/ outpatient	4–15 weeks	40	OLZ (N=13) QTP (N=6) RIS (N=21)	OLZ: 7.8±4.2 QTP: 283.3±222.9 RIS: 2.2±2.0	SCHIZ, BD, OPSY, BEHAV, OTHER	5–18 years	55.0%
Stevens et al. (2005)	Naturalistic	Inpatient	6 weeks	70	QTP (N=20) RIS (N=50)	QTP: 317.5 RIS: 2.4	(1)	13.5±2.4 years	100%
Fleischhaker et al. (2007)	Naturalistic	Inpatient	6 weeks	45	CLZ (N=15) OLZ (N=15) RIS (N=15)	CLZ: 294.9±133.9 OLZ: 16.1±6.9 RIS: 2.9±1.5	SCHIZ, OPSY, BEHAV, OTHER	9–21 years	68.9%

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Table 1 (continued)

Study	Design	Setting (inpatient/ outpatient)	Duration	N	Drug	Daily mean dose (mg/day)	Diagnosis	Age (mean±SD or range) years	Sex (% male)
Naturalistic studies									
Fleischhaker et al. (2008)	Naturalistic	Inpatient	45 weeks	33	CLZ (N=15) OLZ (N=8) RIS (N=10)	CLZ: 311.7±137.5 OLZ: 10.2±3.5 RIS: 2.6±1.7	SCHIZ, OPSY, BEHAV, OTHER	9–21 years	72.7%
Castro-Fornieles et al. (2008)	Naturalistic	Inpatient/ outpatient	6 months	60	OLZ (N=14) QTP (N=15) RIS, (N=31)	OLZ: 11.7±7.0 QTP: 626.8±526.1 RIS: 2.8±1.2	SCHIZ, BD, OPSY	9–17 years	68.3%
Fraguas et al. (2008b)	Naturalistic	Inpatient/ outpatient	6 months	66	OLZ (N=20) RIS (N=22) QTP (N=24)	OLZ: 9.8±5.6 RIS: 3.5±3.1 QTP: 390.8±321.2	SCHIZ, OPSY, BEHAV, OTHER	15.2±2.9 years	66.7%
Correll et al. (2009)	Naturalistic	Inpatient/ outpatient	12 weeks	272	ARP (N=41) OLZ (N=45) QTP (N=36) RIS (N=135) Untreated (N=15)	ARP: 19 OLZ: 10 QTP: 275 RIS: 1.5	SCHIZ, BD, OP, BEHAV	4–19 years	57.0%
Migliardi et al. (2009)	Naturalistic	Outpatient	12 months	41	OLZ (N=13) RIS (N=28)	OLZ: 8.3±3.0 females; 9.3±5.9 males RIS: 2.0±1.0 females; 1.7±1.2 males	SCHIZ, BD, OPSY, BEHAV, OTHER	12.8±2.3 years	70.7%
Retrospective chart review studies									
Hrdlicka et al. (2009)	RCR	Inpatient/ outpatient	6 weeks	79	CLZ (N=7) OLZ (N=20) RIS (N=52)	CLZ: 247.5 OLZ: 15.0 RIS: 2.7	SCHIZ, OPSY	15.8±1.6 years	47.7%
Khan et al. (2009)	RCR	Inpatient/ outpatient	27± 12 days	49	OLZ (N=25) RIS (N=24)	OLZ: 12.5±5.25 RIS: 2.6±1.7	SCHIZ, BD, OPSY	13.0±3.5	73.5%

Abbreviations: ADHD (Attention-Deficit Hyperactivity Disorder), BD (bipolar disorder), BEHAV (behavioural disorder), CLZ (clozapine), DBCT (double-blind controlled trial), FGAs (first-generation antipsychotics), HAL (haloperidol), MOL (molindone), OLRT (open label randomized trial), OLNRT (open label non-randomized trial), OLZ (olanzapine), OPSY (other psychoses, including schizphreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified), OTHER (including pervasive developmental disorders, cannabis related disorder, hyperkinetic conduct disorder, obssesive–compulsive disorder, or anxiety disorders), PBO (placebo), QTP (quetiapine), RCR (retrospective chart review), RIS (risperidone), SBCT (single-blinded control trial), SCHIZ (schizophrenia or schizoaffective disorder), and ZPD (ziprasidone).

Notes:

1. At least one symptom of the following groups: psychosis, aggressive behaviour, impulsivity, and hippomania.
2. Dosage of FGA group is given in chlorpromazine-equivalents.

Table 2 Efficacy results.

Study	N	Diagnosis	Main measurement of efficacy	Baseline and endpoint values	Comparisons between drugs (1)	Comparisons within groups (1)
Randomized, double-blind controlled trials						
Kumra et al. (1996)	21	SCHIZ	BPRS	CLZ: 63±14–52.5±12.8 HAL: 84.7±17.6–64.7±16.1	CLZ>HAL: p<0.05 (5)	CLZ: p<0.05 HAL: p<0.05
Shaw et al. (2006)	25	SCHIZ	SANS	CLZ: 52±23 (change: −25) OLZ: 52±19 (change: −14)	CLZ>OLZ: p<0.05 (6)	CLZ: p<0.05 OLZ: p<0.05
Findling et al. (2008)	294	SCHIZ	PANSS	ARP (10): 93.7±15.7 (change: −26.7±1.9) ARP (30): 94.9±15.5 (change: −28.6±0.9) PBO: 95.0±15.5 (change: −21.2±1.9)	ARP (10)−ARP (30): NS ARP (10)>PBO: p=0.05 (3) ARP (30)>PBO: p<0.05	Not available
Kumra et al. (2008b)	39	SCHIZ	SANS	CLZ: 10.3±3.6–6.6±4.4 OLZ: 9.4±2.7–7.6±3.8	CLZ>OLZ: p<0.05 (6)	Not available
Kryzhanovskaya et al. (2009)	64	SCHIZ	BPRS-C	OLZ: 50.3±10.0 (change: −19.4) PBO: 50.1±8.6 (change: −9.3)	OLZ−PBO: p<0.05	OLZ: p<0.05 PBO: Not available
Haas et al. (2009a)	257	SCHIZ	PANSS	RIS (1.5–6): 96.4±15.4–72.8±22.5 RIS (0.15–0.6): 93.3±14.1–80.8±24.3	RIS (1.5–6)>RIS (0.15–0.6): p<0.05	RIS (1.5–6): p<0.05 RIS (0.15–0.6): p<0.05
Sikich et al. (2008)	116	SCHIZ, OPSY	PANSS	MOL: 99.7±20.3 (change: −27.0±17.7) OLZ: 100.3±17.4 (change: −26.6±17.8) RIS: 103.3±21.6 (change: −23.7±25.5)	MOL−RIS: NS MOL−OLZ: NS RIS−OLZ: NS	MOL: p<0.05 OLZ: p<0.05 RIS: p<0.05
Sikich et al. (2004)	50	SCHIZ, OPSY	BPRS-C	HAL: 49.0±14.0–33.0±19 OLZ: 50.0±10–22.0±12 RIS: 54.0±1.3–27.0±20	HAL−RIS: NS AL−OLZ: NS RIS−OL: NS	HAL: p<0.05 OLZ: p<0.05 RIS: p<0.05
DelBello et al. (2002)	30	BD	YMRS	QTP: Not available PBO: Not available	QTP>PBO: p<0.05 (2)	QTP: p<0.05 PBO: p<0.05
Tohen et al. (2007)	161	BD	YMRS	OLZ: 33.1±6.6 (change: −17.7) PBO: 32.0±6.2 (change: −10.0)	OLZ>PBO: p<0.05	Not available
DelBello et al. (2009)	32	BD	CDRS-R	QTP: 53.5±7.8–34.7±15.1 PBO: 53.9±7.9–34.4±14.8	QTP−PBO: NS	QTP: p<0.05 PBO: p<0.05
Haas et al. (2009b)	169	BD	YMRS	(Change values): RIS (0.5–2.5): −18±9.7 RIS (3–6): −16.5±10.3 PBO: −9.1±11	RIS (0.5–2.5)−RIS (3–6): NS RIS (0.5–2.5)>PBO: p<0.05 RIS (3–6)>PBO: p<0.05	RIS (0.5–2.5): p<0.05 RIS (3–6): p<0.05 PBO: Not available

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Table 2 (*continued*)

Study	N	Diagnosis	Main measurement of efficacy	Baseline and endpoint values	Comparisons between drugs (1)	Comparisons within groups (1)
Randomized, double-blind controlled trials						
Findling et al. (2009)	296	BD	YMRS	ARP (10): 29.8±6.5 (change: −14.2) ARP (30): 29.5±6.3 (change: −16.5) PBO: 30.7±6.8 (change: −8.2)	ARP (10)−ARP (30): NS ARP (10)>PBO: $p<0.05$ ARP (30)>PBO: $p<0.05$	Not available
Tramontina et al. (2009)	41	BD+ADHD	YMRS	ARP: 35.9±8.6 (change: −27.2) PBO: 40.6±9.0 (change: −19.2)	ARP>PBO: $p<0.05$	Not available
Randomized, open label trials						
Arango et al. (2009)	32	SCHIZ, BD, OPSY	PANSS	OLZ: 105.7±20.0−71.6±17.3 QTP: 91.1±21.4−67.3±17.9	OLZ−QTP: NS	OLZ: $p<0.05$ QTP: $p<0.05$
Jensen et al. (2008)	29	SCHIZ, OPSY	PANSS	Not available	OLZ−QTP: NS RIS−OLZ: NS RIS>QTP: $p<0.05$ (4)	Not available
Swadi et al. (2010)	26	First onset psychotic disorder or mood disorder with psychotic features	PANSS	QTP: 89.0±16.9 (change: −23%) RIS: 87.1±16.6 (change: −29%)	QTP−RIS: NS	Not available
Open label, non-randomized trials						
Bastiaens (2009)	46	SCHIZ, BD, OPSY, OTHER, BEHAV	OAS	Outcome measures: ARP: 6.8±1.8 ZPD: 7.4±2.1	ARP−ZPD: NS	ARP: $p<0.05$ ZPD: $p<0.05$
Biederman et al. (2005)	31	BD	YMRS	OLZ: 34.2±6.4−22.1±8.3 RIS: 35.2±8.2−16.4±12.0	OLZ−RIS: NS	OLZ: $p<0.05$ RIS: $p<0.05$
Jensen et al. (2008)	29	SCHIZ, OPSY	PANSS	Not available	OLZ−QTP: NS RIS−OLZ: NS RIS>QTP: $p<0.05$ (4)	Not available
Mozes et al. (2006)	25	SCHIZ	PANSS	OLZ: 92.8±26.9−50.5±13.3 RIS: 93.9±27.14−63.46±21.72	OLZ−RIS: NS	OLZ: $p<0.05$ RIS: $p<0.05$
Naturalistic studies						
Gothelf et al. (2003)	43	SCHIZ	PANSS	HAL: 86.1±24.4−66.3±21.8 OLZ: 71.6±23.8−61.6±28.4 RIS: 90.2±26.4−73.9±19.1	HAL−OLZ: NS HAL−RIS: NS RIS−OLZ:NS	HAL: $p<0.05$ OLZ: $p<0.05$ RIS: $p<0.05$
Castro-Fornieles et al. (2008)	60	SCHIZ, BD, OPSY	PANSS	OLZ: 100.2±20.7−63.7±10.2 QTP: 91.9 ±16.7−59.1±14.4 RIS: 81.8 ±18−56.4±19.8	OLZ−QTP: NS OLZ−RIS: NS RIS−QTP: NS	OLZ: $p<0.05$ QTP: $p<0.05$ RIS: $p<0.05$

most studies (27/34 = 79.4%) lasting three months or less. Nine (n = 788) studies were conducted in patients with schizophrenia, 6 studies (n = 719) in subjects with bipolar disorder, and 19 studies in a mixed population (n = 1212). Twenty-three studies compared two or more SGAs (n = 1314). Of these 23 studies, 5 included comparisons between at least one SGA and an FGA. Two studies compared one SGA with one or more FGAs (n = 61). In addition, 9 studies compared an SGA against placebo (n = 1087) or an SGA at therapeutic doses against the same SGA at subtherapeutic doses (n = 257) (Table 1).

3.1. Efficacy

Table 2 shows the comparative clinical efficacy results between different antipsychotics. To summarise, efficacy results indicate that: 1. SGAs are superior to placebo (in the studies comparing SGA and placebo or comparing SGA at therapeutic doses with the same SGA at subtherapeutic doses) (DelBello et al., 2002; Findling et al., 2008, 2009; Kryzhanovskaya et al., 2009; Haas et al., 2009a,b; Tohen et al., 2007; Tramontina et al., 2009); 2. Clozapine is superior to haloperidol (Kumra et al. 1996) or olanzapine (Kumra et al., 2008a,b; Shaw et al., 2006) in treatment-refractory schizophrenia; and 3. There were no significant differences in efficacy between different SGAs, nor between SGAs and FGAs (Arango et al., 2009; Biederman et al., 2005; Castro-Fornieles et al., 2008; Gothelf et al., 2003; Sikich et al., 2004, 2008), although the number of trials comparing different antipsychotics and number of enrolled patients were modest.

3.2. Tolerability

3.2.1. Weight gain

Table 3 shows the comparative results for weight gain and changes in metabolic and cardiovascular parameters with different antipsychotics. Across the reviewed studies, mean weight gain ranged from 3.8 kg to 16.2 kg in patients treated with olanzapine (OLZ) (n = 353), from 0.9 kg to 9.5 kg in subjects receiving clozapine (CLZ) (n = 97), from 1.9 kg to 7.2 kg in those on risperidone (RIS) (n = 610), from 2.3 kg to 6.1 kg among patients on quetiapine (QTP) (n = 142), and from 0 kg to 4.4 kg in those treated with aripiprazole (ARP) (n = 451). Among subjects receiving placebo (n = 321), the mean weight change ranged from 0.8 kg weight loss to 2.5 kg weight gain. Head-to-head studies of SGAs compared weight gain between

olanzapine and risperidone in 13 studies (7 findings that olanzapine caused significantly more weight gain than risperidone (OLZ > RIS), while 6 found no significant differences (OLZ = RIS)), 5 studies compared olanzapine with quetiapine (4 OLZ > QTP and 1 OLZ = QTP), 5 studies compared risperidone and quetiapine (5 RIS = QTP), 4 studies compared clozapine and olanzapine (2 OLZ > CLZ and 2 OLZ = CLZ), and 3 studies compared risperidone and clozapine (3 RIS = CLZ). Other comparisons included 1 study OLZ > ARP, 1 study RIS = ARP, and 1 study QTP = ARP.

Thus, the data summarised above show that, in general, treatment with SGAs is associated with significant weight gain, but that the magnitude of that weight gain differs by SGA. Olanzapine is the SGA that causes the most significant weight gain (Arango et al. 2009; Castro-Fornieles et al., 2008; Correll et al., 2009; Fleischhaker et al., 2007, 2008; Fraguas et al., 2008b; Ratzoni et al., 2002; Sikich et al., 2008). Moreover, FGAs generally cause less weight gain than SGAs (Ratzoni et al., 2002; Sikich et al., 2004, 2008), but studies directly comparing SGAs that cause less weight gain, such as aripiprazole and ziprasidone, with FGAs are lacking in young people. The dose effect has also not been well studied, as only one paediatric study has investigated this question, finding that antipsychotic dose correlated with weight gain in patients on risperidone, the antipsychotic with the largest sample and power to show an effect (Correll et al., 2009).

3.2.2. Prolactin changes

Table 4 shows the comparative results for SGA-induced prolactin changes. Data on elevated prolactin levels are more heterogeneous. In general, taking a recent randomized double-blind trial (Sikich et al., 2008) as a reference, it can be seen that the increase in prolactin levels is highest in subjects treated with risperidone (with mean increases ranging from 8.3 ng/mL to 49.6 ng/mL), followed by olanzapine (with mean changes ranging from −1.5 ng/dL to +13.7 ng/dL). On the other hand, treatment with aripiprazole was associated with decreased prolactin levels, while clozapine, quetiapine, and ziprasidone were found to be mostly neutral. In only one paediatric study did antipsychotic dose correlate with prolactin elevation (Alfaro et al., 2002). Regarding head-to-head comparisons of the effects of SGAs on prolactin increases, we found 3 studies with RIS > OLZ (risperidone causing significantly greater prolactin increases than olanzapine), 3 studies with RIS > QTP, 2 studies with RIS = OLZ, 1 study with OLZ = CLZ, and 1 study with QTP = OLZ.

Notes to Table 2
Abbreviations: ADHD (Attention-Deficit Hyperactivity Disorder), BD (bipolar disorder), BEHAV (behavioural disorder), CLZ (clozapine), DBCT (double-blind controlled trial), FGAs (first-generation antipsychotics), HAL (haloperidol), MOL (molindone), NS (not significant), OAS (Overt Aggression Scale), OLRT (open label randomized trial), OLNRT (open label non-randomized trial), OLZ (olanzapine), OPSY (other psychoses, including schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified), OTHER (including pervasive developmental disorders, cannabis related disorder, hyperkinetic conduct disorder, obsessive−compulsive disorder, or anxiety disorders), PBO (placebo), QTP (quetiapine), RCR (retrospective chart review), RIS (risperidone), SBCT (single-blinded control trial), SCHIZ (schizophrenia or schizoaffective disorder), and ZPD (ziprasidone).
Notes:

1. Comparisons on baseline-to-endpoint efficacy measures changes.
2. QTP was associated with a greater improvement than PBO.
3. Significance (p = 0.05) for last observation carried forward. Significance for observed cases p < 0.05.
4. Observed reduction in PANSS total scores was greater for risperidone in comparison to quetiapine.
5. CLZ was related to a greater improvement than HAL.
6. CLZ was related to a greater improvement than OLZ.

Table 3 Weight gain, metabolic and cardiovascular parameters.

Study	N	Diagnosis	Weight increase (mean)	Baseline–endpoint BMI (mean)	Weight–BMI comparisons between drugs (1)	Weight–BMI comparisons within drugs (1)	Mean glucose increase (mg/dL)	Mean cholesterol increase (mg/dL)	Mean triglyceride increase (mg/dL)	Mean diastolic blood pressure increase (mm Hg)
Randomized, double-blind controlled trials										
Kumra et al. (1996)	21	SCHIZ	CLZ: 0.9 kg HAL: 0.9 kg	Not available	CLZ–HAL: NS	Not available	Not available	Not available	Not available	CLZ: −4.4 HAL: −7.0 CLZ–HAL: NS
Shaw et al. (2006)	25	SCHIZ	CLZ: 3.8 kg OLZ: 3.6 kg	BMI increase CLZ: 1.6 OLZ: 1.4	CLZ–OLZ: NS	Not available	Not available	Not available	Not available	% patients with hypertension (2) CLZ: 63.6% OLZ: 9.1% CLZ–OLZ: p<0.05
Findling et al. (2008)	294	SCHIZ	ARP (10): 0 kg ARP (30): 0.2 kg PBO: −0.8 kg	ARP (10): 23.5–23.5 ARP (30): 23.0–23.0 PBO: 22.9–22.6	ARP (10)–ARP (30): NS ARP (10)–PBO: NS ARP (30)–PBO: NS	ARP (10): NS ARP (30): NS PBO: NS	ARP (10): +2.1 ARP (30): −1.0 PBO: −3.2 Comparisons between groups: NS	High-density lipoprotein (HDL) cholesterol ARP (10): +0.1 ARP (30): +0.1 PBO: −6.1 Comparisons between groups: NS	ARP (10): −4.5 ARP (30): −0.7 PBO: −6.5 Comparisons between groups: NS	Comparisons between groups: NS
Kumra et al. (2008b)	39	SCHIZ	Not available	CLZ: 28.0–28.7 OLZ: 28.5–29.2	CLZ–OLZ: NS	Not available	CLZ: +4.5 OLZ: +3.6 CLZ–OLZ: NS	Total cholesterol CLZ: −3.5 OLZ: +17.2 CLZ–OLZ: NS	CLZ: +16.8 OLZ: +11.4 CLZ–OLZ: NS	Not available
Kryzhanovskaya et al. (2009)	64	SCHIZ	OLZ: 4.3 kg PBO: 0.1 kg	OLZ: 23.5–24.9 PBO: 24.0–23.9	OLZ>PBO: p<0.05	OLZ: p<0.05 PBO: NS	OLZ: +2.9 PBO: −1.6 OLZ–PBO: NS	HDL cholesterol OLZ: −3.1 PBO: +0.8 OLZ–PBO: NS	OLZ: +41.6 PBO: +4.4 OLZ–PBO: p<0.05	Not available
Haas et al. (2009a)	257	SCHIZ	RIS (1.5–6.0): 3.2 kg RIS (0.15–0.6): 1.7 kg		Comparisons between groups: p<0.05		Comparisons between groups: NS	HDL cholesterol Comparisons between groups: NS	Comparisons between groups: NS	Not available

Study	N	Dx	Weight							
Sikich et al. (2008)	116	SCHIZ, OPSY	MOL: 0.3 kg	MOL: 24.0–24.2	OLZ>MOL: p<0.05	MOL: NS	Percent change of Insulin:	Percent change of low-density lipoprotein (LDL):	Percent change:	Not available
			OLZ: 6.1 kg	OLZ: 23.5–25.7	RIS>MOL: p<0.05	OLZ: p<0.05	MOL: about +10%	MOL: about 0%	MOL: about −5%	
			RIS: 3.6 kg	RIS: 23.2–24.5	OLZ>RIS: p<0.05	RIS: p<0.05	OLZ: about +95%	OLZ: about +18%	OLZ: about +20%	
							RIS: about −15%	RIS: about −10% Comparisons between groups: OLZ>RIS=MOL	RIS: about +10%	
Sikich et al. (2004)	50	SCHIZ, OPSY	HAL: 3.5 kg	HAL: 26.4–27.6	OLZ>HAL: p<0.05	HAL: p<0.05	HAL: −0.3	HDL cholesterol	HAL: +22.0	Not available
			OLZ: 7.1 kg	OLZ: 23.5–25.9	OLZ–RIS: NS	OLZ: p<0.05	OLZ: +10.0	HAL: −1.7	OLZ: +26.0	
			RIS: 4.9 kg	RIS: 22.9–24.5	RIS>HAL: p<0.05	RIS: p<0.05	RIS: −7.9	OLZ: −7.5	RIS: −2.0	
							Comparisons between groups: OLZ>HAL=RIS	RIS: +0.7 Comparisons between groups: NS	Comparisons between groups: NS	
DelBello et al. (2002)	30	BD	QTP: 4.2 kg PBO: 2.5 kg	Not available	QTP–PBO: NS	Not available	Not available	Not available	Not available	Not available
Tohen et al. (2007)	161	BD	OLZ: 3.7 kg	OLZ: 24.1–25.3	OLZ>PBO: p<0.05	OLZ: p<0.05	Normal to high levels (3):	HDL normal to low levels (4):	Normal to borderline or high levels (5):	Not available
			PBO: 0.3 kg	PBO: 24.0–24.0		PBO: NS	OLZ: 1.2% PBO: 0% OLZ–PBO: NS	OLZ: 11.8% PBO: 15.6% OLZ–PBO: NS	OLZ: 23.1% PBO: 0% OLZ–PBO: p<0.05	
DelBello et al. (2009)	32	BD	QTP: 2.3 kg	BMI changes: QTP: +0.9	QTP–PBO: NS	Not available	Normal to high levels (3): QTP: 0% PBO: 0%	HDL normal to low levels (4): QTP: 18% PBO: 13%	Normal to high levels QTP: 24% PBO: 0%	QTP–PBO: NS
			PBO: 0.9 kg	PBO: +0.3				QTP–PBO: NS	QTP–PBO: NS	
Haas et al. (2009b)	169	BD	RIS (0.5–2.5): 1.9 kg	BMI changes:	RIS (0.5–2.5)–RIS (3–6): NS	RIS (0.5–2.5): Not available	RIS (0.5–2.5): +5.4	Total Cholesterol	RIS (0.5–2.5): +26.7	Not available
			RIS (3–6): 1.4 kg	RIS (0.5–2.5): +0.7	RIS (0.5–2.5)>PBO:	RIS (3–6): Not available	RIS (3–6): +3.6	RIS (0.5–2.5): +3.9	RIS (3–6): −8.9	

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Table 3 (continued)

Study	N	Diagnosis	Weight increase (mean)	Baseline–endpoint BMI (mean)	Weight–BMI comparisons between drugs (1)	Weight–BMI comparisons within drugs (1)	Mean glucose increase (mg/dL)	Mean cholesterol increase (mg/dL)	Mean triglyceride increase (mg/dL)	Mean diastolic blood pressure increase (mm Hg)
			PBO: 0.7 kg	±0.8 RIS (3–6): +0.5 ±0.9 PBO: +0.1 ±0.9	p<0.05 RIS (3–6)> PBO: p<0.05	PBO: NS	PBO: −1.8	RIS (3–6): 0 PBO: −7.8	PBO: −8.9	
Findling et al. (2009)	296	BD	ARP (10): 0.8 kg ARP (30): 1.1 kg	ARP (10): 24.2–24.4 ARP (30): 23.7–24.0	ARP (10)–ARP (30): NS ARP (10)–PBO: NS	ARP (10): NS ARP (30): NS	Comparisons between groups: NS	HDL cholesterol Comparisons between groups: NS	Comparisons between groups: NS	Not available
			PBO: 0.6 kg	PBO: 23.7–23.8	ARP (30)–PBA: NS	PBO: NS				
Tramontina et al. (2009)	41	BD+ADHD	ARP: 1.2 kg PBO: 0.7 kg	Not available	ARP–PBO: NS	Not available	Not available	Not available	Not available	Not available
Randomized, open label trials										
Arango et al. (2009)	32	SCHIZ, BD, OPSY	OLZ: 15.5 kg	OLZ: 21.7–27.1	OLZ>QTP: p<0.05	OLZ: p<0.05	OLZ–QTP: NS	An increased was observed in HDL in QTP group: QTP–OLZ: p<0.05	Not available	OLZ–QTP: NS
			QTP: 5.4 kg	QTP: 21.5–23.3		QTP: p<0.05				
Jensen et al. (2008)	29	SCHIZ, OPSY	Percentage of patients who gained≥7% OLZ: 60% QTP: 55.6% RIS: 80%	Not available	Comparisons between groups: NS	Not available	Not available	Not available	Not available	Not available
Swadi et al. (2010)	26	First onset psychotic disorder or mood disorder with psychotic features	Percentage with increase>5% weight gain QTP: 72.7% RIS: 63.6% Percentage with increase>10% weight gain QTP: 27.3% RIS: 9.1%	Not available	QTP–RIS: NS	Not available	QTP–RIS: NS	HDL cholesterol QTP–RIS: NS	Not available	Not available

Open label, non-randomized trials										
Bastiaens (2009)	46	SCHIZ, BD, OPSY, OTHER, BEHAV	Not available	Not available	ARP–ZPD: NS	Not available	Not available	Not available	Not available	Not available
Biederman et al. (2005)	31	BD	OLZ: 3.2 kg RIS: 2.2 kg	Not available	OLZ–RIS: NS	OLZ: p<0.05 RIS: p<0.05	OLZ: +2.8 RIS: +7.5 OLZ–RIS: NS	HDL cholesterol OLZ: −2.5 RIS: +6.9 OLZ–RIS: NS	OLZ: +24.9 RIS: −33.1 OLZ–RIS: NS	OLZ: −1.3 RIS: −0.1 OLZ–RIS: NS
Ratzoni et al. (2002)	50	SCHIZ, BEHAV	HAL: 1.1 kg OLZ: 7.2 kg RIS: 3.9 kg	HAL: 22.0–22.3 OLZ: 23.6–26 RIS: 23.4–24.7	OLZ>HAL: p<0.05 OLZ>RIS: p<0.05	HAL: NS OLZ: p<0.05 RIS: p<0.05	Not available	Not available	Not available	Not available
Mozes et al. (2006)	25	SCHIZ	OLZ: 5.8 kg RIS: 4.5 kg	Not available	OLZ–RIS: NS	OLZ: p<0.05 RIS: p<0.05	Not available	Not available	Not available	OLZ–RIS: NS
Naturalistic studies										
Fleischhaker et al. (2007)	45	SCHIZ, OPSY, BEHAV, OTHER	CLZ: 2.5 kg OLZ: 4.6 kg RIS: 2.8 kg	CLZ: 21.9–22.7 OLZ: 20.8–22.4 RIS: 21.6–22.6	OLZ>CLZ: p<0.05 OLZ>RIS: p<0.05 RIS–CLZ: NS	CLZ: p<0.05 OLZ: p<0.05 RIS: p<0.05	Not available	Not available	Not available	Not available
Fleischhaker et al. (2008)	33	SCHIZ, OPSY, BEHAV, OTHER	CLZ: 9.5 kg OLZ: 16.2 kg RIS: 7.2 kg	CLZ: 22.0–25.0 OLZ: 19.4–24.6 RIS: 22.1–24.0	OLZ>CLZ: p<0.05 OLZ>RIS: p<0.05 RIS–CLZ: NS	CLZ: p<0.05 OLZ: p<0.05 RIS: p<0.05	Not available	Not available	Not available	Not available
Castro-Fornieles et al. (2008)	60	SCHIZ, BD, OPSY	OLZ: 11.7 kg RIS: 6.1 kg QTP: 6.0 kg	RIS: 21.3–22.9 OLZ: 22.5–26.4 QTP: 20.1–20.5	OLZ>QTP: p<0.05 OLZ>RIS: p<0.05 RIS–QTP: NS	Not available	Not available	Not available	Not available	Not available
Fraguas et al. (2008b)	66	SCHIZ, OPSY, BEHAV, OTHER	OLZ: 11.1 kg QTP: 2.5 kg RIS: 5.0 kg	OLZ: 22.7–26.4 QTP: 21.5–22.4 RIS: 21.8–23.2	OLZ>QTP: p<0.05 OLZ>RIS: p<0.05 RIS–QTP: NS	OLZ: p<0.05 QTP: NS RIS: p<0.05	OLZ: +3.1 QTP: +1.2 RIS: +0.6	HDL cholesterol OLZ: +2.6 QTP: +4.3	OLZ: +17.3 QTP: +10.5 RIS: +10.7	OLZ: +2.0 QTP: +0.4 RIS: +5.5

Table 3 (continued)

Study	N	Diagnosis	Weight increase (mean)	Baseline–endpoint BMI (mean)	Weight–BMI comparisons between drugs (1)	Weight–BMI comparisons within drugs (1)	Mean glucose increase (mg/dL)	Mean cholesterol increase (mg/dL)	Mean triglyceride increase (mg/dL)	Mean diastolic blood pressure increase (mm Hg)
							Comparisons between groups: NS	RIS: −2.9 Comparisons between groups: NS	Comparisons between groups: NS	Comparisons between groups: NS
Correll et al. (2009)	272	SCHIZ, BD, OP, BEHAV	ARP: 4.4 kg	ARP: 22.4–24.1	OLZ>QTP: p<0.05	ARP: p<0.05	ARP: +0.5	HDL cholesterol	ARP: −2.4	Not available
			OLZ: 8.3 kg	OLZ: 20.4–23.4	OLZ>RIS: p<0.05	OLZ: p<0.05	OLZ: +3.1	ARP: +0.3	OLZ: +24.3	
			QTP: 6.1 kg	QTP: 23.3–25.4	OLZ>ARP: p<0.05	QTP: p<0.05	QTP: +2.6	OLZ: −1.3	QTP: +37.0	
			RIS: 5.3 kg	RIS: 20.6–22.5	RIS–QTP: NS	RIS: p<0.05	RIS: +1.1	QTP: −1.5	RIS: +9.7	
			Untreated: 0.2 kg	Untreated: 22.1–22.1	RIS–ARP: NS	Untreated: NS	Untreated: +0.7	RIS: +0.3	Untreated: −11.8	
					QTP–ARP: NS		Comparisons between groups: NS	Untreated: +1.5	Comparisons between groups: NS	
								Comparisons between groups: NS		
Retrospective chart review studies										
Hrdlicka et al. (2009)	79	SCHIZ, OPSY	CLZ: 2.1 kg OLZ: 4.4 kg RIS: 3.6 kg	Not available	CLZ–OLZ: NS OLZ–RIS: NS RIS–CLZ: NS	Not available	Not available	Not available	Not available	Not available
Khan et al. (2009)	49	SCHIZ, BD, OPSY	OLZ: 4.1 kg	OLZ: 20–22	OLZ–RIS: NS	OLZ: p<0.05	New cases of impaired fasting glucose	Not available	Subjects with high levels (≥110 mg/dL)	OLZ: +5.4
			RIS: 3.4 kg	RIS: 21–23		RIS: p<0.05	OLZ: 0% RIS: 0%		OLZ: 22.2% RIS: 5.6%	RIS: −3.2 OLZ–RIS: p<0.05

3.2.3. Neuromotor adverse effects

Table 5 shows comparative results for neuromotor side effects caused by antipsychotic treatment. Studies on neuromotor side effects related to antipsychotic treatment in child and adolescent populations have shown that SGAs are associated with less parkinsonism and akathisia than FGAs (taking haloperidol and molindone as the reference FGAs) (Gothelf et al., 2003; Sikich et al., 2004, 2008). Head-to-head comparisons between SGAs resulted in only one study with a significant finding, showing that risperidone caused more rigidity than olanzapine (Mozes et al., 2006). None of the remaining antipsychotic comparisons in this area reached significance.

4. Discussion

This review confirms that, as in adults, SGAs are not a homogeneous group in children and adolescents with psychotic and mood disorders. However, also as in adults, except for superior efficacy with clozapine, the heterogeneity within the SGA group is mainly limited to differences in the rates and severity of adverse events. These data point to the importance of taking into consideration the differential adverse event profiles of antipsychotics, especially regarding weight gain as a proxy of the risk for cardiometabolic disorders.

Despite the utility of SGAs in the treatment of psychotic and severe mood disorders in children and adolescents based on consistent results from a number of placebo-controlled studies, findings of relevant adverse effects have called their short-term and, particularly, their long-term safety into question. This has fueled the debate about the risk/benefit ratio of SGAs in young people (Arango et al., 2004; Correll and Carlson, 2006; Correll et al., 2010; DelBello and Correll, 2010; De Hert et al., 2008; Tarricone et al., 2010; Vitiello et al., 2009). The importance of studying adverse effects of SGAs in the child and adolescent population has been emphasised, primarily because the response to SGAs in children and adolescents cannot be directly inferred from the observed response in adults (Correll and Carlson, 2006; Correll et al., 2010). Children and adolescents are not only more vulnerable to side effects, but also more sensitive to their negative impact on body image and self-esteem than adults (Arango et al., 2004). On the other hand, the presence of a psychotic or major mood disorder likely constitutes a risk *per se* for having metabolic complications. That is to say, people with psychosis and bipolar disorder have higher metabolic risk than the general population, which might be independent of treatment to some degree (Bobes et al., 2008; Goodwin et al., 2009; Regenold et al., 2002; Stahl et al., 2009). This implies that cardiovascular risk monitoring in children and adolescents is very important, as the risk is enhanced by being a child or adolescent, by having a psychotic or major mood disorder, and by taking antipsychotic drugs. In view of this fact, recent data are even more disconcerting, showing that young people exposed to antipsychotics are less likely to undergo fasting blood glucose and lipid monitoring than adults treated with antipsychotics, and that they are no more likely to undergo such monitoring than a paediatric control group without a mental disorder treated with albuterol (Morrato et al., 2010b).

4.1. Lack of differences in efficacy between different SGAs and between SGAs and FGAs

A comparison of the efficacy results showed no significant differences between different SGAs and between SGAs and FGAs in children and adolescents with psychotic disorders and bipolar disorder, with the exception of an advantage of clozapine compared to haloperidol (Kumra et al., 1996) or olanzapine (Kumra et al., 2008a,b; Shaw et al., 2006) in patients treated for refractory schizophrenia. This lack of difference in clinical efficacy was independent of the diagnosis of the patients enrolled in the studies, suggesting that the clinical efficacy of SGAs could not be distinguished, at least as measured by the clinical scales used and in mostly relatively small samples. However, these results, which are based on group means, do not imply that SGAs or FGAs have identical efficacy in individuals. Clearly, more research is needed to identify response predictors in individuals.

4.2. Specific profile of SGAs is based on tolerability differences

4.2.1. Weight gain
As has been pointed out, the heterogeneity of SGAs is due to their differential adverse event profile. Significant weight gain is one of the most relevant side effects of SGAs (Correll, 2008b; Correll and Carlson, 2006; Correll et al., 2006; Jensen et al., 2007; McIntyre and Jerrell, 2008; Tarricone et al., 2010; Vieweg et al., 2005; Vitiello et al., 2009; Wetterling and Mussigbrodt, 1999). Obesity is associated with a

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Notes to Table 3

Abbreviations: ADHD (Attention-Deficit Hyperactivity Disorder), BD (bipolar disorder), BEHAV (behavioural disorder), CLZ (clozapine), DBCT (double-blind controlled trial), FGAs (first-generation antipsychotics), HAL (haloperidol), MOL (molindone), NS (not significant), OLRT (open label randomized trial), OLNRT (open label non-randomized trial), OLZ (olanzapine), OPSY (other psychoses, including schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified), OTHER (including pervasive developmental disorders, cannabis related disorder, hyperkinetic conduct disorder, obsessive–compulsive disorder, or anxiety disorders), PBO (placebo), QTP (quetiapine), RCR (retrospective chart review), RIS (risperidone), SBCT (single-blinded control trial), SCHIZ (schizophrenia or schizoaffective disorder), and ZPD (ziprasidone).

Notes:
1. Comparisons on BMI (or weight, if BMI is not available) baseline-to-endpoint increases.
2. Hypertension was defined as >95% percentile for systolic or diastolic blood pressure controlled for age and height group.
3. Glucose normal (<126 mg/dL) to high levels (≥126 mg/dL).
4. HDL normal (≥40 mg/dL) to low (<40 mg/dL) levels.
5. Triglycerides normal (<150 mg/dL) to borderline or high levels (≥150 mg/dL).
6. Triglycerides normal (<110 mg/dL) to high levels (≥110 mg/dL).
7. Glucose normal (<110 mg/dL) to high levels (≥110 mg/dL).

Table 4   Prolactin levels.

Study	N	Diagnosis	Mean change of prolactin levels (ng/mL)	Comparisons between groups	Comparisons within groups
Randomized, double-blind controlled trials					
Findling et al. (2008)	294	SCHIZ	ARP (10 mg/day): −11.9 ARP (30 mg/day): −15.4 PBO: −8.5	ARP (10)−ARP (30): NS ARP (10)<PBO: p<0.05 ARP (30)<PBO: p<0.05	Not available
Kryzhanovskaya et al. (2009)	64	SCHIZ	OLZ: +8.8 PBO: −3.3	OLZ−PBO: p<0.05	OLZ: NS PBO: NS
Haas et al. (2009a)	257	SCHIZ	Percentage of patients with elevations in prolactin levels beyond the upper limit of normal RIS (1.5–6.0): 97% RIS (0.15–0.6): 64%	RIS (1.5–6.0)>RIS (0.15–0.6): p<0.05	Not available
Sikich et al. (2008)	116	SCHIZ, OPSY	MOL: −8.8 OLZ: −1.5 RIS: +19.5	RIS>OLZ: p<0.05 RIS>MOL: p<0.05 OLZ−MOL: NS	MOL: NS OLZ: NS RIS: p<0.05
Sikich et al. (2004)	50	SCHIZ, OPSY	HAL: +3.4 OLZ: −1.5 RIS: +3.1	HAL−OLZ: NS HAL−RIS: NS RIS−OLZ: NS	HAL: NS OLZ: NS RIS: NS
DelBello et al. (2002)	30	BD	QTP: −1.6 PBO: −5.7	QTP−PBO: NS	QTP: NS PBO: NS
Tohen et al. (2007)	161	BD	OLZ: +15.4 (females), +11.5 (males) PBO: +2.7 (females), +0.7 (males)	OLZ−PBO: p<0.05	OLZ: p<0.05 PBO: NS
DelBello et al. (2009)	32	BD	QTP: +2.5 PBO: +0.1	QTP−PBO: NS	Not available
Haas et al. (2009b)	169	BD	RIS (0.5–2.5): +50 (females), +32 (males) RIS (3–6): +48.3 (females), +49.6 (males) PBO: +1.6 (females), +0.6 (males)	RIS (0.5–2.5)−RIS (3–6): NS RIS (0.5–2.5)>PBO: p<0.05 RIS (3–6)>PBO: p<0.05	RIS (0.5–2.5): p<0.05 RIS (3–6): p<0.05 PBO: NS
Findling et al. (2009)	296	BD	ARP (10): −5.7 (females), −3.4 (males) ARP (30): −1.6 (females), −4.2 (males) PBO: −2.7 (females), −0.1 (males)	Not available	Not available
Randomized, double-blind controlled and open label non-randomized trials					
Wudarsky et al. (1999)	47	SCHIZ, BD, OPSY	HAL: +38.6 CLZ: +2.2 OLZ: +13.7	HAL>CLZ: p<0.05 HAL>OLZ: p<0.05 OLZ−CLZ: NS	HAL: p<0.05 CLZ: p<0.05 (1) OLZ: p<0.05
Randomized, open label trials					
Swadi et al. (2010)	26	First onset psychotic disorder or mood disorder with psychotic features	Percentage of patients with elevated prolactin (definition of 'elevated prolactin' not available): QTP: 9.1% RIS: 90.9% RIS>QTP: p<0.05		
Biederman et al. (2005)	31	BD	OLZ: +11.9 RIS: +35.7	RIS>OLZ: p<0.05	OLZ: p<0.05 RIS: p<0.05

Table 4 (*continued*)

Study	N	Diagnosis	Mean change of prolactin levels (ng/mL)	Comparisons between groups	Comparisons within groups
Randomized, open label trials					
Schulz et al. (1996)	40	SCHIZ	Endpoint values : CLZ: 11.2 FGAs: 26.7	FGAs>CLZ: $p<0.05$	CLZ : NS FGAs : $p<0.05$
Saito et al. (2004)	40	SCHIZ, BD, OPSY, BEHAV, OTHER	RIS: +21.5 OLZ: −0.1 QTP: +1.1	RIS>OLZ: $p<0.05$ RIS>QTP: $p<0.05$ QTO−OLZ: NS	RIS: $p<0.05$ OLZ: NS QTP: NS
Stevens et al. (2005)	70	At least one symptom of the following groups: psychosis, aggressive behaviour, impulsivity, and hippomania	Cross-sectional study (only endpoint values are provided) QTP: 8.5 RIS: 20.3	Endpoint value comparison: RIS>QTP: $p<0.05$	Not available
Migliardi et al. (2009)	41	SCHIZ, BD, OPSY, BEHAV, OTHER	RIS: +15.0 (females), +8.3 (males) OLZ: +9.2 (females), +3.5 (males)	RIS>OLZ: $p<0.05$	Not available

Abbreviations: ADHD (Attention-Deficit Hyperactivity Disorder), BD (bipolar disorder), BEHAV (behavioural disorder), CLZ (clozapine), DBCT (double-blind controlled trial), FGAs (first-generation antipsychotics), HAL (haloperidol), MOL (molindone), OLRT (open label randomized trial), OLNRT (open label non-randomized trial), OLZ (olanzapine), OPSY (other psychoses, including schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified), OTHER (including pervasive developmental disorders, cannabis related disorder, hyperkinetic conduct disorder, obsessive−compulsive disorder, or anxiety disorders), PBO (placebo), QTP (quetiapine), RCR (retrospective chart review), RIS (risperidone), SBCT (single-blinded control trial), SCHIZ (schizophrenia or schizoaffective disorder), and ZPD (ziprasidone).
Notes:
1. Although statistically significantly elevated, mean prolactin on clozapine stayed within the normal range for all male and female subjects.

constellation of problematic metabolic disturbances (dyslipidemia, hypertension, and impaired glucose tolerance) subsumed under the concept of metabolic syndrome (Boney et al., 2005; Franks et al., 2010; Weiss et al., 2004). Childhood obesity represents a serious medical concern, which is increasing worldwide and which is associated with childhood and adult cardiovascular morbidity and accelerated mortality. Obesity, glucose intolerance, and hypertension in childhood are strongly associated with increased rates of premature death (Franks et al., 2010). Moreover, there is evidence for a direct relationship between childhood obesity and increased cardiovascular risk in adulthood compared with the general population (Burke, 2006). Among the SGAs, olanzapine has the most concerning weight gain profile. Treatment with olanzapine in children and adolescents is related to significant weight gain, i.e. 6.1 kg after 8 weeks in a doubled-blind controlled trial (Sikich et al., 2008), 8.3 kg after 12 weeks (Correll et al., 2009), 11.1 kg after 24 weeks (Fraguas et al., 2008b) in naturalistic follow-up studies, and 15.5 kg after 6 months in a randomized open label study (Arango et al., 2009). But olanzapine is not the only SGA that causes weight gain. In children and adolescents who frequently have limited past antipsychotic exposure and related weight gain history, all SGAs are potentially associated with significant weight gain (Correll et al., 2009). Due to the heterogeneity of the studies included in this review and a relative lack of controlled head-to-head comparisons, it is impossible to establish a valid ranking of SGA-induced weight gain in the paediatric population. However, an approximation based on the available data suggests the following ranking: olanzapine≥clozapine>risperidone≥quetiapine>aripiprazole=ziprasidone. However, since clozapine is used in patients with a history of treatment with multiple antipsychotics and associated weight gain, its relative weight gain potential in young people is unclear from the reviewed data. Moreover, although haloperidol and molindone were associated with significantly less weight gain than olanzapine and risperidone, the weight gain potential relative to aripiprazole and ziprasidone in young people has not been investigated. Although one small naturalistic study did not find any differences in weight gain in young people with psychotic vs. non-psychotic bipolar disorder (Moreno et al., 2010), further studies are needed to assess whether or not diagnosis affects the cardiovascular impact of antipsychotics in young people, independent of differences in antipsychotics doses, age, and developmental stage of the patients.

4.2.2. Prolactin increase
Prolactin increase in children and adolescents is considered to have relevant clinical implications, as hyperprolactinemia is related to osteoporosis and sexual and neuroendocrine complications (Correll and Carlson 2006; Mancini et al., 2008). Changes in prolactin levels are a known antipsychotic side effect (Roke et al., 2009). Although, the increase of prolactin levels is greater in young people treated with risperidone than in those treated with other SGAs, it can occur also with olanzapine and even with quetiapine, although at much lower levels and less frequently. By contrast, due to its partial dopamine D2 agonism, aripiprazole tends to decrease prolactin levels in young people, even below baseline when used as a single agent.

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Table 5 Neuromotor side effects.

Study	N	Diagnosis	Dystonia (% of patients with symptoms)	Rigidity (% of patients with symptoms)	Tremor (% of patients with symptoms)	Hypokinesia/akinesia (% of patients with symptoms)	Akathisia (% of patients with symptoms)
Randomized, double-blind controlled trials							
Shaw et al. (2006)	25	SCHIZ	CLZ–OLZ: NS	CLZ–OLZ: NS	CLZ–OLZ: NS	CLZ–OLZ: NS	Not available
Findling et al. (2008)	294	SCHIZ	ARP (10): 4% ARP (30): 2% PBO: 0% Comparisons between groups: NS	ARP (10): 15% ARP (30): 30% PBO: 7% ARP (10)>PBO: p<0.05 ARP (30)>PBO: p=0.05	ARP (10): 2% ARP (30): 12% PBO: 2% Comparisons between groups: NS	ARP (10): 7% ARP (30): 4% PBO: 3% Comparisons between groups: NS	ARP (10): 6% ARP (30): 12% PBO: 6% Comparisons between groups: NS
Kryzhanovskaya et al. (2009)	64	SCHIZ		OLZ–PBO: NS	OLZ–PBO: NS	OLZ–PBO: NS	OLZ–PBO: NS
Haas et al. (2009a)	257	SCHIZ	RIS (1.5–6.0): 18.4% RIS (0.15–0.6): 6.1%	RIS (1.5–6.0): 4% RIS (0.15–0.6): 0%	RIS (1.5–6.0): 10.4% RIS (0.15–0.6): 3%	RIS (1.5–6.0): 5.6% RIS (0.15–0.6): 1.5%	RIS (1.5–6.0): 8.8% RIS (0.15–0.6): 1.5%
Sikich et al. (2008)	116	SCHIZ, OPSY	Comparisons between groups: NS	Comparisons between groups: NS	Comparisons between groups: NS	Comparisons between groups: NS	MOL: p<0.05 RIS: NS OLZ: NS
Sikich et al. (2004)	50	SCHIZ, OPSY	Extrapyramidal symptoms: HAL>RIS : p<0.05 HAL>OLZ: p<0.05				Not available
DelBello et al. (2002)	30	BD	Extrapyramidal symptoms: QTP–PBO: NS				QTP–PBO: NS
Tohen et al. (2007)	161	BD	Extrapyramidal symptoms: OLZ–PBO: NS				OLZ–PBO: NS
DelBello et al. (2009)	32	BD	Extrapyramidal symptoms: QTP–PBO: NS				Not available
Haas et al. (2009b)	169	BD	Percent of patients with at least 1 extrapyramidal symptom: RIS (0.5–2.5): 8% RIS (3–6): 25% PBO: 5%				Not available
Findling et al. (2009)	296	BD	Percent of patients with dystonic events ARP (10): 0% ARP (30): 7% PBO: 2%	Percent of patients with any parkinsonian event ARP (10): 14.2% ARP (30): 29.2% PBO: 4.1%			Percent of patients with akathisia event ARP (10): 8.1% ARP (30): 12.1% PBO: 2%
Tramontina et al. (2009)	41	BD+ADHD	Not available	ARP: about 25% PBO: about 20% ARP–PBO: NS	ARP: about 40% PBO: about 30% ARP–PBO: NS	Not available	ARP: about 15% PBO: about 15% ARP–PBO: NS

Randomized, open label trials							
Arango et al. (2009)	32	SCHIZ, BD, OPSY	Not available	Not available	OLZ: 23% (at endpoint) QTP: 25% (at endpoint) OLZ–QTP (endpoint): NS	OLZ: 23% (at endpoint) QTP: 12% (at endpoint) OLZ–QTP (endpoint): NS	OLZ: 18% (at endpoint) QTP: 0% (at endpoint) OLZ–QTP (endpoint): NS
Jensen et al. (2008)	29	SCHIZ, OPSY	Extrapyramidal symptoms: Comparisons between groups: NS				
Swadi et al. (2010)	26	First onset psychotic disorder or mood disorder with psychotic features	Extrapyramidal symptoms: QTP: 27.3% RIS: 54.5% Comparisons between groups: NS				QTP: 45.5% RIS: 45.5% Comparisons between groups: NS
Open label, non-randomized trials							
Mozes et al. (2006)	25	SCHIZ	Not available	OLZ: 0% RIS: 30.8% RIS>OLZ: p<0.05	OLZ: 50.0% RIS: 69.2% OLZ–RIS: NS	Not available	OLZ: 16.7% RIS: 7.7% OLZ–RIS: NS
Naturalistic studies							
Gothelf et al. (2003)	43	SCHIZ	HAL: 28.6% OLZ: 0% RIS: 5.9% HAL–OLZ–RISP: p<0.05	HAL: 42.9% OLZ: 5.3% RIS: 0% RIS>HAL: p<0.05 RIS>OLZ: p<0.05	HAL: .14.3% OLZ: 10.5% RIS: 11.8% Comparisons between groups: NS	HAL: 28.6% OLZ: 5.3% RIS: 11.8% Comparisons between groups: NS	HAL: 42.9% OLZ: 0% RIS: 5.9% HAL–OLZ–RISP: p<0.05
Castro-Fornieles et al. (2008)	60	SCHIZ, BD, OPSY	OLZ: 0% QTP: 0% RIS: 6.5% Comparisons between groups: NS	OLZ: 0% QTP: 0% RIS: 19.4% Comparisons between groups: NS	OLZ: 15.4% QTP: 26.7% RIS: 16.1% Comparisons between groups: NS	OLZ: 15.4% QTP: 13.3% RIS: 50.0% Comparisons between groups: RIS>OLZ=QTP	OLZ: 0% QTP: 0% RIS: 16.1% Comparisons between groups: NS

Abbreviations: ADHD (Attention-Deficit Hyperactivity Disorder), BD (bipolar disorder), BEHAV (behavioural disorder), CLZ (clozapine), DBCT (double-blind controlled trial), FGAs (first-generation antipsychotics), HAL (haloperidol), MOL (molindone), OLRT (open label randomized trial), OLNRT (open label non-randomized trial), OLZ (olanzapine), OPSY (other psychoses, including schizphreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified), OTHER (including pervasive developmental disorders, cannabis related disorder, hyperkinetic conduct disorder, obsessive–compulsive disorder, or anxiety disorders), PBO (placebo), QTP (quetiapine), RCR (retrospective chart review), RIS (risperidone), SBCT (single-blinded controlled trial), SCHIZ (schizophrenia or schizoaffective disorder), and ZPD (ziprasidone).

Notes:

1. Although statistically significantly elevated, mean prolactin levels with clozapine stayed within the normal range for all male and female subjects.

The question of the stability of the prolactin increase has been assessed in several studies. Some suggest that the antipsychotic-related prolactin increase may not be stable over time, rising towards a peak, probably between the 1st and 3rd month of treatment (Migliardi et al., 2009), and then progressively decreasing. Thus, it is possible that the increased prolactin levels observed in the first months are transient, so that differences would be lower or even no longer exist after one or more years (Findling and McNamara, 2004). However, this downward trend has not been found in all studies, and particularly not in those that used higher antipsychotic doses and included postpubertal individuals (Saito et al., 2004). Thus, the likelihood of a sustained elevation in prolactin levels may depend on the antipsychotic maintenance dose and the degree of prolactin elevation (i.e. extremely high prolactin levels may not normalise, unless the most sensitive patients drop out of the study due to prolactin-related side effects) (Crawford et al., 1997; Saito et al., 2004). This is supported by recent data suggesting that prolactin elevation may persist for periods up to 1 or 2 years in subjects treated with risperidone (Laita et al., 2007; Roke et al., 2009). Further longitudinal studies are needed to determine if and in which patients the initial elevation in prolactin levels persists through follow-up and what the potential long-term consequences are on pubertal development and bone density.

4.2.3. Neuromotor side effects

Because of their advantageous neuromotor side-effect profile compared with FGAs, SGAs were termed "atypical". However, SGAs are not free from neuromotor side effects either. Treatment with risperidone has been associated with higher tremor and dystonia rates than other SGAs. However, the methodological discrepancies with regard to patient population, heterogeneous assessment instruments, follow-up periods, titration schedules, and maximum doses between the studies included in this review prevent us from drawing an unambiguous conclusion.

A review of chronic neurological side effects of SGAs in paediatric patients has shown relatively low one-year tardive dyskinesia rates of 0.4% (Correll and Kane, 2007). However, these results were limited by the small sample size of studies with SGAs other than risperidone and by the use of relatively low doses, which may have obscured a potentially greater risk for tardive dyskinesia in children and adolescents treated with higher total SGA doses and for longer durations (Correll and Kane, 2007). Thus, here again, more and larger long-term studies are needed in young people.

4.3. Association between adverse events and medication dose

Although clinical experience suggests an association between antipsychotic doses and adverse effects, very few studies have examined this association. A recent review of this topic in adults reported a positive correlation between weight gain and serum concentrations of olanzapine and clozapine, but inconclusive results for risperidone (Simon et al., 2009). The present review points out the absence of information regarding weight gain and SGA doses, except for one study. In the only paediatric study investigating this question, there was no dose dependency with aripiprazole or

quetiapine, yet olanzapine doses higher than 10 mg/day were associated with metabolic abnormalities but not with weight gain, while risperidone doses higher than 1.5 mg/day were associated with both greater lipid abnormalities and greater weight gain (Correll et al., 2009). Nevertheless, the relationship between weight gain and medication doses is still unclear and should be investigated, also examining the relationship with antipsychotic serum levels.

4.4. Treatment duration

Duration of treatment constitutes a key variable for the study of adverse effects associated with SGAs. The generally brief duration of follow-up is a relevant limitation of the reviewed prospective studies. A study comparing the side effects of antipsychotics (both FGAs and SGAs) in young people treated for fewer than 30 days with subjects treated for more than 12 months found that the group treated for more than 12 months showed significantly higher body weights and total cholesterol levels, as well as rates of parkinsonism and dyskinesia, compared with subjects treated for fewer than 30 days. No differences were found between the two groups in triglyceride levels, blood pressure, or akathisia rates (Laita et al., 2007). Studies focusing on metabolic changes included in this review had a mean follow-up duration of only 14.6 weeks. None of these studies followed the patients for more than 12 months. This short duration of follow-up seriously limits the value of their findings, especially in light of recent findings that question the temporal stability of differences in metabolic side effects for different medications (Perez-Iglesias et al., 2008). In a 3-month, naturalistic cohort study of 272 antipsychotic-naïve children and adolescents started on SGAs, only 1.6% of young people newly developed metabolic syndrome, despite rapid and massive weight gain in all antipsychotic groups (Correll et al., 2009). However, it is unclear to what degree and when rates of metabolic syndrome would increase in paediatric samples experiencing massive weight gain. Since the biggest concern focuses on the long-term implications of antipsychotic-related cardiometabolic effects, the absence of comparative studies lasting longer than 12 months in the reviewed paediatric database is highly problematic. Clearly, irrespective of issues of funding and retention, studies are needed that follow antipsychotic-exposed young people over longer periods of time to determine rates, risk factors, and mechanisms of the development of metabolic syndrome and related cardiovascular morbidity.

4.5. Can we consider the class distinction between first-generation and second-generation antipsychotics valid?

As in adults, data on efficacy and tolerability with antipsychotics in children and adolescents call into question the conceptual validity of a clinically meaningful class distinction between FGAs and SGAs. SGA-induced weight gain is a paradigmatic example of the heterogeneity of the SGA group. Moreover, a systematic review of antipsychotic effects on prolactin and related sexual and reproductive system functioning in children and adolescents (including articles published between 1965 and 2008) showed that among the studied antipsychotics, which included haloperidol, pimozide,

risperidone, olanzapine, clozapine, ziprasidone, and quetiapine, all increased prolactin levels, except for clozapine, ziprasidone, and quetiapine. However, the degree of prolactin increase varied. Yet, since risperidone and the two FGAs pimozide and haloperidol were among the antipsychotics that elevated prolactin levels the most, prolactin levels are not useful to discriminate between FGAs and SGAs (Roke et al., 2009). Similarly, a recent meta-analysis that compared the efficacy and tolerability of FGAs and SGAs in adults with schizophrenia also showed that SGAs differed in their properties and are not a homogeneous group (Leucht et al., 2009a). A number of authors have remarked the lack of homogeneity of the SGA group in recent years (Davis et al., 2003; De Hert et al., 2008; Findling and McNamara, 2004; Leucht et al., 2009b). Taking this into account and considering that the main differences among SGAs relate to adverse metabolic effects, a proposal has been made to substitute the current FGA/SGA classification with a distinction based on metabolic risk (Carmel and Gorman, 2009). In this proposed classification, antipsychotics with a lower metabolic risk would include molindone, ziprasidone, fluphenazine, haloperidol, and aripiprazole; while antipsychotics with a higher metabolic risk would include clozapine, olanzapine, thioridazine, mesoridazine, sertindole, risperidone, and quetiapine (Carmel and Gorman, 2009). Furthermore, the 'typical'/'atypical' dichotomy based on extrapyramidal symptoms has also been challenged (Fischer-Barnicol et al., 2008) and might need to be abandoned.

4.6. Tolerability of SGAs by psychotic subtype

Whether differences in adverse events related to SGAs are influenced by the underlying psychiatric condition is still a matter of controversy. Studies carried out in adult clinical samples have not found a clearly distinct pattern of SGA-related adverse events based on psychiatric diagnosis, with different groups finding contradictory results (Birkenaes et al., 2007; van Winkel et al., 2008). Recently, Moreno et al. (2010) published a study that is, to our knowledge, the only one to address this topic in young people. It compared weight changes and metabolic adverse events in children and adolescents diagnosed with bipolar disorder (n = 31), other psychotic disorders (n = 29), and other non-psychotic disorders (n = 30), with no (35.6%) or very little (6.6 ± 9.0 days) previous exposure to antipsychotics. Already 3 months after starting treatment with SGAs, 71.1% of the sample had gained significant weight, at a comparable rate across diagnoses, and significant worsening of lipid indices was found in patients with bipolar and psychotic disorders.

4.6.1. Clinical monitoring recommendations for metabolic complications in children and adolescents treated with antipsychotics

These important findings highlight the need for careful monitoring of adverse effects of SGAs in adults, as well as in children and adolescents (Cohn and Sernyak, 2006; Correll and Carlson, 2006; Correll et al., 2010; DelBello and Correll, 2010). As pointed out by this review of the available studies, children and adolescents are especially vulnerable to adverse side effects of antipsychotics. Therefore, it is important to anticipate the risks associated with the use of SGAs in this population in order to prevent or at least attenuate them. It is essential to routinely assess adverse effects in paediatric patients treated with SGAs. It is important to incorporate patients and families in the evaluation of the risks and benefits of these medications.

Since available professional association-supported health monitoring guidelines (American Diabetes Association, 2004; De Hert et al., 2009) only peripherally touch upon paediatric patients, no specifically endorsed monitoring guidelines exist for antipsychotic-treated young people. Current clinical recommendations include assessments of family medical history, healthy lifestyle behaviours, body weight, height, BMI percentile, z score, and blood pressure, as well as of fasting glucose and lipids at baseline; weight, height, BMI percentile and z score at each clinical visit; and of blood pressure and fasting glucose and lipids at three months, and biannually thereafter (Correll and Carlson, 2006; Correll, 2008a).

Because recommendations and guidelines for the monitoring of adverse metabolic effects of antipsychotics have had a low impact in daily clinical practice (Morrato et al., 2010a), the field needs to test different strategies to increase the awareness of cardiovascular risks associated with severe mental disorders and their treatments and to optimise monitoring behaviours in mental health personnel, patients, and their families. Furthermore, to optimise psychiatric as well as health outcomes, studies are needed that assess the differential efficacy of adjunctive treatments (Maayan et al., 2010) and switching strategies to lower-risk antipsychotics in order to minimise the cardiovascular impact of antipsychotic medications (Correll, 2008a).

4.7. Limitations of this review

This is a comprehensive and descriptive review, but we did not conduct a systematic or meta-analysis study, according to international guidelines. Accordingly, descriptive statistics were used and only inferential statistics were reported as provided by each study. We decided not to conduct further statistical analysis because of the methodological variability of the selected studies, which often were small and relatively short-term, which are further limitations of this review.

4.8. Summary and conclusions

SGAs are being used in increasing quantities in children and adolescents for a variety of psychiatric disorders. Except for clozapine, antipsychotic efficacy did not differ significantly in young people with psychotic and bipolar spectrum disorders. Conversely, adverse effect differences were relatively large, especially regarding weight gain and prolactin elevation. With the exception of greater neuromotor adverse effects on FGAs, this is true to a lesser degree regarding extrapyramidal side effects. The clinically relevant adverse effect differences cut across the traditional FGA/SGA classification, calling this simplified differentiation into question. Rather, a more finely grained evaluation of the heterogeneous side effect properties of available antipsychotics should be considered when choosing among these agents, particularly in young people who are particularly sensitive to adverse effects. In order to improve psychopathology, subjective well-being, and functioning, while preserving physical health as much as possible, the lower-risk antipsychotics should be used earlier in the treatment

algorithm and should only be replaced by higher risk agents in case of insufficient response or intolerability of the former.

More research is needed to evaluate mechanisms and predictors of antipsychotic efficacy and tolerability outcomes before prospective individualised treatment selection and sequencing become a reality.

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Contributors

Work list:

1. Design of the review.
2. Search and selection of the articles.
3. Extraction and interpretation of data.
4. Redaction of the first draft of the paper.
5. Redaction of the discussion.
6. Final approval of the manuscript.

Dr. Fraguas participated in: 1, 2, 3, 4, 5 and 6.
Dr. Correll participated in: 1, 2, 5 and 6.
Dr. Merchán-Naranjo participated in: 2, 3 and 6.
Dr. Rapado-Castro participated in: 2, 3 and 6.
Dr. Parellada participated in: 5 and 6.
Dr. Moreno participated in: 5 and 6.
Dr. Arango participated in: 1, 2, 5 and 6.

All the authors declare that they are responsible for all the information contained in this manuscript.

Conflict of interest

Dr. Fraguas has been a consultant and/or advisor to or has received honoraria from Otsuka, Bristol-Myers, and Janssen Cilag.
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