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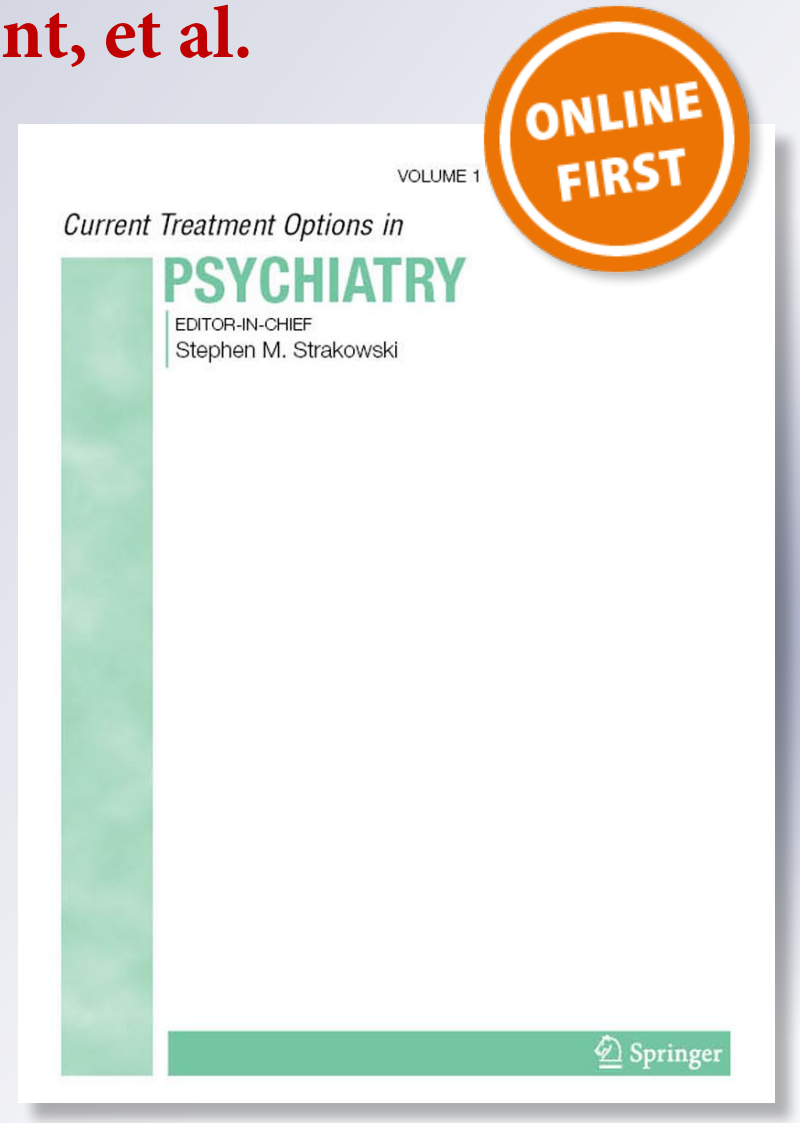

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Child and Adolescent Psychiatry (M DelBello, Section Editor)

Management of Adverse Effects of Second-generation Antipsychotics in Youth

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Opinion statement

Second-generation antipsychotics (SGAs) have been proven effective in treating several psychiatric conditions in children and adolescents. These atypical antipsychotic medications are being used with increasing frequency in Europe, the U.S., and Canada. We aim to expose short-term and long-term adverse effects (AEs) of SGAs in youth populations and to provide management recommendations for major adverse effects. These proposals are based on (1) an in-depth literature review of both short- and long-term studies on the use of SGAs in youth; (2) our own clinical experience in managing such treatment in this population; and (3) the work of the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA). AEs are frequent in youth treated with SGAs, and include primarily weight gain, metabolic and hormonal changes, somnolence, extrapyramidal syndrome, and QT modifica-

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tions. However, frequency and type of AE vary according to compound, and each compound's AE profile is specific. Acknowledgment of these distinct profiles should aid clinicians in making treatment decisions. After an SGA is prescribed, routine monitoring of AEs is recommended, and should an AE occur, clinical management recommendations should be followed. To date, there are no clinically validated monitoring recommendations.

Introduction

Atypical or second-generation antipsychotic medications (SGAs) have been proven effective for treating several conditions in children and adolescents. As of March 2010, aripiprazole, olanzapine, quetiapine, and risperidone have been approved by the FDA as medications for bipolar mania in children and adolescents (age 10–17 years; except olanzapine, age 13–17 years) and for adolescent schizophrenia (age 13–17 years). In addition, aripiprazole and risperidone are approved for behavioral disturbances (irritability and aggression) associated with autism and/or intellectual disabilities in children and adolescents (age 6–17 years). SGAs were developed to lower the risk of extrapyramidal syndrome (EPS) [1]. Six SGAs are now commonly prescribed to children and adolescents in both the U.S. [2] and Europe [3]. The risk of adverse effects (weight gain, somnolence, and EPS) with olanzapine, however, has been reported to be significantly higher in young patients compared to adults [4•]. Emerging findings indicate that children and adolescents are more vulnerable to weight gain, cardiometabolic effects (increased glucose, triglyceride, and cholesterol levels), and hyperprolactinemia [5, 6]. This raises concerns about the use of SGAs in children [7]. In the U.S., the number of children treated with SGAs increased 22 % from 2004 to 2008, with an average of 250,000 prescriptions per year for children under 6 years of age and numerous prescriptions for non-psychotic disorders and off-label indications [8]. In the 50 U.S. states and the District of Columbia, antipsychotic use increased 62 % from 2002 to 2007, reaching a total of 354,000 child and adolescent psychiatric patients by 2007, most of them presenting bipolar disorders, schizophrenia, and autism, comorbid with ADHD in 50 % of the cases [9]. Similarly, in France, SGAs are prescribed primarily for bipolar disorders, schizophrenia, and autism. In a population of 652 young patients receiving psychotropic medication, 154 were treated with a SGA as monotherapy and 237 as a co-prescription [10]. In light of the controversy regarding the use of selective serotonin reuptake inhibitors (SSRIs) in children [11], the 2003 and 2007 Pediatric Research Equity Acts (PREA) and the 2002 Best Pharmaceuticals for Children Act (BPCA) provided incentives for increased numbers of large double-blind placebo-controlled studies on SGAs and other medications in children.

The present review aims to clarify the frequency, type, and management of adverse effects (AEs) of SGAs in youth. First, we will discuss the major AEs found in both short- and long-term studies on the use of SGAs in youth. This is based on an in-depth literature review of a Bayesian meta-analysis based on short-term studies [12•]; a review of long-term studies in SGAs [13–28]; and our own clinical experience in managing such treatment in youth. Second, we will present the major AEs by compound. Third, we will summarize the practical recommendations for the prescription and monitoring of SGAs as put forth by the CAMESA guideline group, as well as discuss settings when switching from one compound to another is indicated. Details of these recommendations are available online at www.camesaguideline.org. [29•, 30•]. Finally, we will discuss clinical and research implications and discuss the design of an ongoing prospective pharmacovigilance study aimed at systematically assessing the secondary effects of SGAs among children and adolescents [31].

Adverse effects of second-generation antipsychotics in youth

For the purpose of a Bayesian meta-analysis on adverse effects in SGAs [12•], we conducted an in-depth review of the literature. Short-term studies, which

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are summarized in Table 1, comprise 41 case-control studies, 3–12 weeks in length, involving SGA use in children and adolescents with schizophrenia, bipolar disorder, behavioral impairments associated with autism or intellectual disability, Tourette syndrome, and conduct disorder. Most of these studies were supported by industry funding. Long-term AE studies are summarized in Table 2. They include 14 studies with durations ranging from 16 to 64 weeks. Ten of the 14 studies assessed risperidone, and 9 studies were supported by industry funding. Of note, in our review of the Treatment of Early-Onset Schizophrenia Study (TEOSS) assessing long-term safety and effectiveness of olanzapine, risperidone, or molindone among 54 children and adolescents with early-onset schizophrenia, we considered only the olanzapine and risperidone arms, as molindone is not an SGA. [26, 32]. We did not find sufficient data on asenapine and will not discuss any results with this compound. In total, our review comprises the results of 55 studies.

Weight gain

With regard to results from the short-term studies, all compounds but ziprasidone were significantly associated with weight gain compared with placebo/untreated patients. Olanzapine and clozapine demonstrated the highest percentage of patients who experienced meaningful weight gain, a greater increase in body mass index (BMI) and weight as expressed in kg. Aripiprazole and ziprasidone appeared to have less effect on weight gain, although additional studies are needed on ziprasidone, as the number of patients for this compound was low. Risperidone and quetiapine appear to have an intermediate profile [12•].

Long-term studies confirm the occurrence of weight gain. All 10 studies assessing risperidone reported weight gain in the exposed group (n=358). When comparing different SGAs, weight gain was significantly higher for olanzapine compared to risperidone, clozapine, or quetiapine [14, 21, 22]. One study on quetiapine (n=10) reported no significant weight gain or increase in BMI after 64 weeks of treatment [24], while another study reported only moderate weight gain (n=24, duration 25 weeks) [14].

Such short-term differences are nuanced by the results of the TEOSS study assessing long-term safety and effectiveness of olanzapine, risperidone, or molindone among 54 children and adolescents with early-onset schizophrenia. In the first part of the study, weight gain was significantly higher in patients treated with olanzapine, but in the extension trial, no significant differences in weight gain emerged among the various compounds during maintenance treatment [26, 32].

Metabolic changes

Risperidone and olanzapine significantly increased glucose levels compared to placebo. Such differences were not statistically significant for aripiprazole, quetiapine, and ziprasidone. Quetiapine and olanzapine significantly increased cholesterol rates compared to placebo, while the mean increase for aripiprazole, risperidone, and ziprasidone was not significant. Olanzapine and quetiapine significantly increased triglyceride (mg/dl) levels compared to placebo, but the effect was not significant with risperidone, aripiprazole, and ziprasidone.

Table 1. Shortterm studies with atypical antipsychotics in children and adolescents: main characteristics and adverse events

Author year	Arm	Subjects (N)	Dose (mg)	Mean age	Disorder	Duration (weeks)	Main adverse events reported	Industry funded
Pavuluri 2010	Risperidone	32	1.44	10.47	BIP	6	Increased appetite, somnolence, sedation/fatigue, gastrointestinal upset	No
Wozniak 2009	Olanzapine	17	8.6	10.2	BIP	8	Weight gain	No
Tramontina 2009	Aripiprazole	18	13.61	11.72	BIP+ADHD	6	Somnolence	Yes
	Placebo	25		12.6				
Owen 2009	Aripiprazole	47	2/15	9.7	BEH PDD	8	Weight gain	Yes
	Placebo	51		8.8				
Correll 2009	Aripiprazole	41		13.4	MIX	12	Weight gain	No
	Olanzapine	45		14.7			↑TG, ↑HDL, ↑total cholesterol, TG/HDL	
	Quetiapine	36		14			Weight gain, ↑TG, ↑HDL, total cholesterol, TG/HDL	
	Risperidone	35		13.6			Weight gain, ↑TG	
	Untreated	15		15.5				
Hass 2009	Risperidone	55	2	15.7	SCZ	6	Somnolence, agitation, headache	Yes
	Risperidone	51	5	15.7			gastrointestinal upset, EPS	
	Placebo	54		15.4				
Marcus 2009	Aripiprazole	53	5	9	BEH PDD	8	Sedation/fatigue	Yes
	Aripiprazole	59	10	10			Sedation/fatigue	
	Aripiprazole	54	15	9.5			Sedation/fatigue	
	Placebo	52		10.2				
Findling 2008	Placebo	100		15.4	SCZ	6		Yes
	Aripiprazole	100	10	15.6			Somnolence, EPS	
	Aripiprazole	102	30	15.4			Somnolence, EPS	
Findling 2009	Aripiprazole	98	10	13.7	BIP	4	Somnolence, EPS	Yes
	Aripiprazole	99	30	13.3			Somnolence, EPS	
	Placebo	99		13.3				
Hass 2009	Risperidone	125	4	15.6	SCZ	8	Weight gain, ↑PRL, EPS	Yes
	Risperidone	132	0.4	15.6			Weight gain, ↑PRL, EPS	
Sikich 2008	Olanzapine	35	11.4	13.7	SCZ	8	Weight gain, increased appetite, Sedation/fatigue	No
	Risperidone	41	2.8	14.2			Sedation/fatigue	

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Tohen 2007	Olanzapine	107	10.7	15.1	BIP	3	Weight gain, ↑PRL, ↑glucose, ↑Hep enzyme, ↑total cholesterol, ↑uric acid	Yes
	Placebo	54		15.4				
Biederman 2005	Risperidone	16	1.4	5.3	BIP	8	Weight gain, increased appetite, sedation/fatigue, ↑PRL	No
	Olanzapine	15	6.3	5			Weight gain, increased appetite, sedation/fatigue, ↑PRL	
Ratzoni 2002	Olanzapine	21	12.7	17	SCZ	12	Weight gain	No
	Risperidone	21	3.2	17			Weight gain	
Findling 2013	Ziprasidone	193	40–160	15.3	SCZ	6	Somnolence, EPS ↑QTcF intervals	No
	Placebo	90		15.4				
Findling, 2013	Ziprasidone	149	118.2	13.6	BIP	4	Sedation, dizziness, somnolence ↑QTcF intervals	Yes
	Placebo	88		13.7				
Kryzhanovskaya 2009	Olanzapine	72	11.1	16.1	SCZ	6	Weight gain, ↑TG, ↑PRL	Yes
	Placebo	35		16.3				
DelBello 2006	Quetiapine	25	4	15	BIP	4	Sedation/fatigue, gastrointestinal upset	Yes
DelBello 2009	Quetiapine	17	403	16	Other	8	Sedation/fatigue, gastrointestinal upset	Yes
	Placebo	15		15				
Pathak, 2013	Quetiapine	93	400	13.1	BIP	3	Increased appetite, somnolence, Sedation/fatigue, gastrointestinal upset, ↑PRL, ↑glucose, ↑TG, headache	Yes
	Quetiapine	95	600	13.2			↑PRL, ↑glucose, ↑TG	
	Placebo	89		13.3				
Findling, 2012	Quetiapine	73	400	15.45	SCZ	6	Increased appetite, somnolence, sedation/fatigue, gastrointestinal upset, ↑PRL, ↑glucose, ↑TG, headache	Yes
	Quetiapine	74	800	15.45			↑PRL, ↑glucose, ↑TG	
	Placebo	73		15.34				
Hass 2009	Placebo	58		13	BIP	3		Yes
	Risperidone	50	0.5/2.5	13			Somnolence, sedation/fatigue, headache	
	Risperidone	61	0.5/6	13			Somnolence, sedation/fatigue, headache	

Table 1. (Continued)

Author year	Arm	Subjects (N)	Dose (mg)	Mean age	Disorder	Duration (weeks)	Main adverse events reported	Industry funded
RUPPAN 2002	Risperidone	49	1.8	8.8	BEH PDD	8	Weight gain, increased appetite, Sedation/fatigue, gastrointestinal upset	No
	Placebo	52		8.8				
Shea 2004	Risperidone	40	1.17	7.6	BEH PDD	8	Weight gain, somnolence, gastrointestinal upset	Yes
	Placebo	39		7.3				
Aman 2002	Placebo	63		8.1	BEH PDD	6		Yes
	Risperidone	55	1.16	8.7			Weight gain, somnolence, headache	
Kumra 2008	Clozapine	18	403	15.8	SCZ	12	Weight gain, ↑TG	No
	Olanzapine	21	26.2	15.5			Weight gain, ↑PRL	
Sporn 2005	Clozapine	24	304.9	14.3	SCZ	6	Weight gain	No
	Healthy	21		13.4				
Salle 2000	Placebo	12		11.8	TIC	8		Yes
	Ziprasidone	16	28.2	11.3			Somnolence	
Snyder 2002	Placebo	57		8.8	BEH PDD	6		Yes
	Risperidone	53	0.98	8.6			Weight gain, increased appetite, headache	
Kumra 1996	Clozapine	10	176	14.4	SCZ	6	Sedation/fatigue	No
Saito 2004	Risperidone	21	2.2	13,4	MIX	11	↑PRL	No
	Olanzapine	13	7.8	13,4			↑PRL	
	Quetiapine	6	283.3	13,4			↑PRL	
Findling 2000	Placebo	10		9.2	BEH PDD	10		Yes
	Risperidone	10	4.1	9.2			Weight gain, increased appetite, sedation/fatigue	
Delbello 2008	Ziprasidone	23	80	13.6	MIX	3	Somnolence, sedation/fatigue, gastrointestinal upset	Yes
	Ziprasidone	40	160	14.2			Somnolence, sedation/fatigue, gastrointestinal upset	
Gaffney 2002	Risperidone	9	1.5	10.4	TIC	8	Sedation/fatigue	Yes
Barzman 2006	Quetiapine	17	17	15.1	BIP	4	Sedation/fatigue, gastrointestinal upset, headache	Yes
Buitelaar 2001	Risperidone	19	2.9	14	BEH PDD	6	Sedation/fatigue	Yes
	Placebo	19		13.7				

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Shaw 2006	Clozapine	12	327	11.7	SCZ	8	Weight gain	Yes
	Olanzapine	13	19.1	12.8			Weight gain	
Jensen 2008	Risperidone	10	3.4	15.6	SCZ	12	Increased appetite, sedation/ fatigue, agitation	Yes
	Quetiapine	10	611	14.8			Increased appetite, sedation/ fatigue, agitation	
	Olanzapine	10	14	15.3			Increased appetite, sedation/ fatigue, agitation	
Sikich 2004	Risperidone	19	3.3	14.6	MIX	8	Weight gain, sedation/fatigue, EPS	Yes
	Olanzapine	16	12.3	14.6			Weight gain, sedation/fatigue, EPS	
Mozes 2006	Risperidone	12	8.18	11.5	SCZ	12	Weight gain	No
	Olanzapine	13	1.62	10.71			Weight gain	
Fleischhaker 2007	Clozapine	15	294.9	17.4	MIX	6	Weight gain	Yes
	Olanzapine	15	16.1	15.7			Weight gain	
	Risperidone	15	2.9	15.2			Weight gain	

MIX Mixed diagnoses; *SCZ* Schizophrenia; *BEH PDD* Behavioral disturbances in pervasive developmental disorder and/or intellectual disability; *BIP* Bipolar disorder; *ADHD* Attention Deficit Hyperactivity Disorder; *TIC* Tic and Tourette syndrome; RUPPAN = Research units on pediatric psychopharmacology autism network

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Table 2. Long-term studies with atypical antipsychotics in children and adolescents: main characteristics and adverse events

Author year	Arm	Subjects (n)	Mean age	Disorder	Duration (weeks)	Main adverse events reported
Zuddas 2000	Risperidone	11	12.3	BEH PDD	24	Weight gain, sedation/fatigue
DelBello 2008	Ziprasidone	56	13.8	MIX	27	Somnolence, sedation/fatigue, headache
Findling 2013	Aripiprazole	84	13.7	BIP	30	Somnolence, EPS, headache
	Aripiprazole	77	13.3			Somnolence, EPS, headache
	Placebo	76	13.3			
Findling 2010	Olanzapine	13		SCZ	52	Weight gain, ↑LDL, ↑Total cholesterol, ↑hep enzyme, ↑insulin
	Risperidone	21				weight gain, ↑PRL
Findling 2012	Aripiprazole	30	7.1	BIP	90	Increased appetite, stomach pain, headache, (high rates of withdrawal)
	Placebo	30	6.7			
McConville 2003	Quetiapine	10	13.1	SCZ	64	Somnolence, headache
Findling 2013	Quetiapine	381	10-17	MIX	26	Weight gain, ↑HDL, ↑TG, somnolence, headache, sedation, vomiting
Arango 2009	Quetiapine	24	16.3	MIX	25	Weight gain
	Olanzapine	26	15.7			Weight gain
Luby 2006	Risperidone	11	4.1	BEH PDD	24	Weight gain
	Placebo	12	4			
RUPPAN 2005	Risperidone	63	8.6	BEH PDD	16	Sedation/fatigue
Troost 2005	Risperidone	26	9.4	BEH PDD	24	Weight gain, increased appetite, sedation/fatigue
Findling 2004	Risperidone	107	9	BEH PDD	48	Weight gain, somnolence, headache
Turgay 2002	Risperidone	77	8.7	BEH PDD	48	Weight gain, Somnolence, headache
Malone 2002	Risperidone	22	7.1	BEH PDD	30	Weight gain, increased appetite
Castro-Fornieles 2008	Risperidone	31	15.1	MIX	24	Weight gain
	Quetiapine	15	16.4			
	Olanzapine	14	15.7			Weight gain
Fleischhaker 2008	Clozapine	15	17.2	MIX	45	Weight gain
	Olanzapine	8	15.7			Weight gain
	Risperidone	10	14.3			Weight gain

MIX = Mixed diagnoses; SCZ = Schizophrenia; BEH PDD = Behavioral disturbances in pervasive developmental disorder and/or intellectual disability; BIP = Bipolar disorder; RUPPAN = Research units on pediatric psychopharmacology autism network

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Very few long-term studies reported metabolic changes. One study confirmed the effects of quetiapine and olanzapine on lipid profiles. These two compounds increased total cholesterol rate, and quetiapine also increased HDL cholesterol [14]. With regard to weight change, as mentioned above, no significant differences emerged among the compounds in most of these parameters during maintenance treatment of the TEOSS study [26]. Of note, data are insufficient to conclude any metabolic effect of clozapine. Bobo et al. recently demonstrated that young users of antipsychotics had are at threefold increased risk for type II diabetes. The risk increased significantly with increasing cumulative dose and for use restricted to SGAs or to risperidone [33].

Prolactin (PRL) changes

Variations in prolactin levels were poorly reported across studies, with the exception of aripiprazole, for which four studies reported a decrease in prolactin. Risperidone, olanzapine, and ziprasidone significantly increased prolactin levels compared to placebo, while the difference reported for quetiapine was not significant. Data on clozapine are insufficient to reach a conclusion (see Table 1).

One long-term study confirmed that aripiprazole decreases PRL ($n=161$, duration 30 weeks) [18]. Three studies assessed PRL changes with risperidone, reporting largely a transitory PRL increase with no clinical impact. [13, 16, 19]. The TEOSS study reported statistical differences in PRL levels among olanzapine, risperidone, and molindone, although this study reported an average decrease rather than increase from baseline for risperidone. Despite this decrease, however, patients receiving risperidone maintained higher PRL levels than patients in other treatment groups. Interpretation of this study is complicated by the fact that patients were not naïve at inclusion [26, 32].

Effects on other hormones have been poorly investigated. Quetiapine appeared to decrease levels of thyroid hormone T4 in one study [14]. Another study on quetiapine also reported a small and intermittent decrease in free thyroxine levels but no change in mean thyroid-stimulating hormone levels [24].

Somnolence/sedation

As was the case for long-term studies, most short-terms studies reported a significantly increased risk for somnolence/sedation for all compounds compared to placebo [12•, 13, 17–20, 23–25].

Extrapyramidal syndrome (EPS)

With the exception of quetiapine and clozapine, all SGAs significantly increased the risk of EPS compared to placebo in the short-term studies. Although there was no report of EPS (including akathisia) in clozapine studies, it was unclear whether incidence of EPS was systematically assessed. Notably, the odds ratios (OR) of EPS for ziprasidone reached the level of haloperidol, challenging the view that it belongs in the group of SGAs to treat youth [12•].

With regard to the results of long-terms studies, rigidity was more frequent in patients with olanzapine than quetiapine [14], and hypokinesia was more frequent with risperidone than olanzapine and clozapine. In a 6-month naturalistic study, risperidone increased the risk of EPS compared to olanzapine [21]. Regarding acute dyskinesia, five dystonia were reported in

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patients treated with risperidone, two of which were withdrawal dyskinesia [18, 20, 25].

Among the long-term studies, no tardive dyskinesia was described, but longer monitored studies are needed to assess tardive dyskinesia/dystonia. Data from the single cases that have been reported [34], seem to indicate that (1) tardive dyskinesia/dystonia is a rare AE of SGAs; (2) body dystonia are more frequent than extremities/oral dyskinesia in children and adolescents; and (3) tardive dyskinesia/dystonia may be more frequent in young people compared to adults (this was demonstrated for olanzapine in a pharmacovigilance study [4•]).

Lengthening of the QT interval

A number of medications commonly used in pediatric psychopharmacology can prolong the QT interval on the electrocardiogram, which in turn can predispose to torsades de pointes, a sometimes deadly arrhythmia [35]. While most reports of prolonged QT interval have involved adult patients, this adverse effect can also occur in children. Reporting on this AE is limited. Some studies did not assess ECG modifications [36–41], and so a meta-analytic approach was not possible [12•]. In short-term studies, no effect on ECG was reported in 13 studies with risperidone [32, 42–53]. One study reported prolonged QT interval in one patient with risperidone [54]. Four studies reported no changes in ECG among groups with olanzapine [48, 49, 51, 55, 56]. One study reported that the rate-corrected QT (QTc) intervals measured by ECG increased significantly (11.2 ms) in the olanzapine group [32]. Five studies reported no changes in ECG parameters with aripiprazole [57–61]. Few studies assessed cardiac effects of ziprasidone among young patients. Of those that did, two studies found no clinical cardiac effects ($n=12$) and no ECG modifications ($n=28$), whereas one study ($n=13$) found a 19-ms prolongation in the one child for whom both baseline and follow-up ECG data were available [35]. Of note, the large A1281132 study investigating the efficacy of ziprasidone in adolescent bipolar disorder reported a significant increase in QT intervals (Table 1). Finally, regarding quetiapine, no ECG modifications were observed in five studies with quetiapine [27, 48, 62, 63], and no data were available for clozapine.

ECG was not systematically reported as a monitoring parameter in the long-term studies. One study reported that among 10 patients with quetiapine, two asymptomatic patients had mildly prolonged QTc intervals [24]. Five studies on risperidone (total 228 patients) reported no clinically relevant mean change in ECG measures [18–20, 25]. Among 56 patients with ziprasidone, the authors reported one case of prolonged QTc interval (QTc> 450 ms) during a 24-week period [23]. One study on olanzapine ($n=26$) and quetiapine ($n=24$) reported no changes in ECG during a 25-week period.

Summary of AEs by compound

A significant frequency of AE was found for all six compounds investigated here (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), but the profile of each compound was quite unique. Table 3 summarizes semi-quantitatively the frequency of AE per compound. We

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Table 3. Summary of SGA secondary effects reported in controlled short-term studies

	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
↗ Weight	+	++++	++++	+++	++	+/−
↗ Glucose	+/−	?	+	+/−	++	0
↗ Cholesterol	0	?	+++	++++	0	0
↗ Triglycerides	0	+++	++++	++++	+/−	0
Hyperprolactinemia	0	?	+++	+/−	++++	++
Sedation	++	++++	++	+	++	++
Extrapyramidal syndrome	+	0?	++	+/−	+	++++
Change in ECG parameters	+/−	+	+/−	++?	+	+++

From Cohen et al., 2012 [12•]; Blair et al., 2004 [4•]

briefly review them in alphabetical order, adding comments regarding switching from one compound to another when needed.

Aripiprazole

Aripiprazole has the most advantageous profile regarding weight gain and metabolic parameters in adults. In children and adolescents, however, there is significant moderate weight gain. The clinical significance of the decrease in PRL is unknown. The long half-life (3 days) of aripiprazole and its partial agonist profile warrant careful monitoring if a switch is made to this compound due to the high rebound-effect risk (see below), and therefore a "plateau" switch is required [64•]. This profile explains the particular high frequency of dopaminergic rebound if the first SGA is stopped quickly when aripiprazole is introduced. Dopaminergic rebound is characterized by psychotic symptoms, aggressiveness, agitation, manic symptoms, and akathisia [65]. Regarding ECG parameters, clinically significant QTc interval prolongation was not noted in any of several studies of adults [35], and short-term studies conducted in youths also reported no ECG changes (Table 1). However, further studies are needed to evaluate possible rare or long-term ECG effects [35].

Clozapine

The most significant and specific AE of clozapine is the risk of agranulocytosis. Although the incidence of agranulocytosis is rare, clinicians should carefully monitor white blood cell count, at first weekly as treatment is initiated and then monthly. Additional data are needed in order to determine the metabolic, PRL level, and neurological secondary effect profiles of clozapine. Similarly to olanzapine, weight gain with clozapine can be particularly significant in young patients, although one long-term study found less significant weight gain with clozapine compared to olanzapine [22]. Sedation is also an issue in younger patients. When a patient requires a switch from a high-affinity D2 receptor (e.g., risperidone) to clozapine (which presents a lower D2 receptor affinity value), a dopaminergic rebound can

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occur with supersensitivity to psychosis, akathisia, agitation, or aggressiveness. These symptoms must be interpreted carefully, as they may not reflect lack of efficacy of clozapine [65]. Tachycardia has been reported in child and adolescents, [66] but more studies are needed to evaluate ECG effects [35].

Olanzapine

Olanzapine is associated with the most significant rate of weight gain. This compound was shown to significantly increase glucose, cholesterol and triglyceride, and prolactin levels. Olanzapine also increases the risk of somnolence/sedation and EPS. It appears to be the only compound that significantly increased all of the parameters in our meta-analysis. Two long-term studies compared olanzapine to risperidone, quetiapine, and clozapine, in whicholanzapine was associated with significantly more weight gain than other treatments [14, 21, 22]. The TEOSS study, however, reported no significant differences in weight gain during maintenance treatment [26]. With regard to the effect on QTc intervals, an in-depth review by Blair et al. reported that evidence for QTc interval prolongation in olanzapine was equivocal, at best, and that olanzapine was safer than other antipsychotics in this regard, at least at relatively low doses [35]. In the U.S., a large pharmacovigilance study analyzed more than 4 million olanzapine prescriptions, including 24,000 children, 234,000 adolescents. and 4,073,000 adults. Sedation, weight gain, liver function, and tardive dyskinesia were overrepresented AEs among children and adolescents vs. adults. Complaints of increased appetite were 24 times higher in children than in adults and 6 times higher in adolescents than in adults. Complaints of weight gain were 4.3 times higher for children and 3.2 times higher for adolescents than for adults. Sedation complaints were 4.5 times higher in children and 1.9 times higher in adolescents than in adults. Complaints of tardive dyskinesia were 4.1 times higher in children than in adults, and complaints in adolescents were similar to those in adults. This result must be interpreted with caution, as this adverse effect is rare and requires longer periods of treatment to emerge. Liver function test abnormalities were 3.4 times higher in children than in adults, 1.9 times higher in adolescents than in adults, and 1.8 times higher in children than in adolescents. One explanation for this may be that pediatric clinicians monitored liver function test results more frequently than clinicians treating adults [4•].

Quetiapine

Quetiapine appears to have an interesting EPS profile in that it is the only compound that does not increase the risk of EPS compared to placebo. With regard to metabolic complications, quetiapine has intermediate profiles, with moderate weight gain, increases in triglyceride and cholesterol blood levels, and no significant differences in glucose and PRL blood levels [67, 68] . Three long-term studies assessing quetiapine confirmed the moderate effect on weight gain [14, 21, 24]. Two long-term studies reported a decrease in thyroid hormone T4 [14, 24]. We still do not have sufficient data to come to a conclusion on the cardiologic effects of quetiapine, as only one long-term study reported an intermittent, asymptomatic, mild prolongation of QTc interval [24]. In terms of switching, the same dopaminergic rebound de-

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scribed with the introduction of clozapine can be observed with quetiapine [64•, 65].

Risperidone

Risperidone has an intermediate profile with regard to weight gain, with moderate weight gain experienced. It increases blood glucose levels and PRL, but short-term elevation of triglyceride and cholesterol levels is not statistically significant. AE is similar to the other compounds with regard to sedation and EPS. Regarding its cardiac AE profile, QTc interval prolongation is a possibility in risperidone-treated patients of all ages, although it appears to be a rare event [35]. Long-term studies have confirmed results of short-term studies on weight gain and somnolence. According to some authors, the fact that the increase in PRL with risperidone appears to be more frequent in girls than boys may be of significant concern, as an increase in PRL during adolescence affects the number of osteoblasts and could be associated with increased risk of osteoporosis later in life [69].

Ziprasidone

Ziprasidone has the most significant rate of EPS, with an OR of 20 compared to placebo. Given the low frequency of weight and metabolic AEs, this particular profile seems closer to typical antipsychotics than to SGAs in young patients [12•, 70]. Regarding ECG parameters, ziprasidone is an SGA that has been under close scrutiny before and since its approval in 2001 due to its propensity to prolong the QTc interval in adults beyond that of all other SGAs prescribed to young patients. Preliminary studies conducted by the manufacturer found that ziprasidone prolonged the QTc interval 9–14 ms longer than four other drugs (risperidone, olanzapine, haloperidol, and quetiapine) and that few cases of sudden death had occurred in patients taking therapeutic doses [35]. Given the limited data on ECG changes in children and adolescents with ziprasidone, more studies are needed to clarify this risk. However, preliminary findings by Blair et al. [71] and from the two large randomized controlled industry studies, (Table 1) suggest that close electrocardiographic monitoring is warranted when prescribing ziprasidone to children [70, 72].

Monitoring adverse effects of second-generation antipsychotics

Screening schedule and recommendation

We previously concluded that AEs are common among youth treated by SGAs. As AEs are not systematically reported in studies, monitoring of side effects would improve long-term health outcomes. We will focus only on the most common AEs. The CAMESA guideline group proposed a screening schedule to systematically assess adverse effects of SGAs [30•].

At baseline, months 1, 2, 3, 6, 9, and annually thereafter, clinicians should measure each patient's weight, height, BMI, waist circumference, and blood pressure, and proceed to a neurological examination. Regarding laboratory evaluations, fasting plasma glucose, fasting insulin, and fasting

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lipid profile should be measured at baseline, 3 and 6 months, and annually thereafter. Thyroid-stimulating hormone (only for quetiapine) and liver function should be measured at baseline, 6 months, and annually, and prolactin should be measured at baseline, 3 months, and annually thereafter. Electrocardiogram (ECG) should be performed at baseline and repeated at 6 months and annually. In addition, ECG should be repeated in the event of dose change, addition of new drug, or attainment of steady state [35]. If the measure is normal, the authors recommend repeating measurement at next scheduled screen.

How to manage adverse effects when they occur

The CAMESA guideline group proposed strategies in the event of occurrence of each adverse effect. We briefly summarize these strategies and comment on possible alternatives.

Weight gain and/or other weight parameters

To minimize weight gain, patient should first receive counselling (nutrition, lifestyle, and exercise). After this, four options must be considered: discontinuation of medication, reduction of dose, switch to other SGA, and/or modified additional treatment (stopped, changed, and reduced). In this case, the consideration of metformin is an option to be discussed with an expert. This last proposal should be taken with caution, given the other psychotropic effects of such compound.

Blood pressure and electrocardiogram (ECG) changes

In the case of prehypertension, recheck blood pressure (BP) in 6 months, and consider specialist consultation if BP is still elevated at that time. In the case of stage 1 hypertension, recheck BP in 1–2 weeks, or sooner in the case of clinical symptoms. If BP is persistently elevated on two subsequent occasions, consider specialist consultation within 1 month. In the case of stage 2 hypertension, consult a specialist within 1 week, or immediately if symptomatic. In the case of severe hypertension, proceed to an immediate assessment by a specialist for investigation and management. Patients with malignant hypertension should be referred to the nearest emergency room. For definitions of hypertension stages, please refer to "Management recommendations for metabolic complications associated with second-generation antipsychotic use in children and youth" [29•]. When changes in ECG parameters occur, refer to a pediatric cardiologist and consider alternate therapy if resting heart rate remains higher than 130 beats/min, PR remains longer than 200 ms, QRS remains longer than 120 ms (or 25 % change from baseline value), or QTc remains longer than 450 ms [30•].

Fasting plasma glucose and insulin

For individuals with FPG value of 5.6–6 mmol/l, consideration should be given to performing an oral glucose tolerance test (OGTT). If fasting insulin level is above the upper limit of normal for the assay being used, consider oral glucose tolerance test and specialist consultation. We also recommend

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considering switching SGA medication. If FPG is impaired (FPG 6.1–6.9 mmol/l), consider oral glucose tolerance test and specialist consultation, with consideration of metformin. In the case of diabetes (FPG≥7 mmol/l), consult with specialist for the management of diabetes.

Fasting lipid profile

In the case of abnormal low-density lipoprotein (LDL) (≥3.35 mmol/l), non-high-density lipoprotein (HDL) cholesterol (total cholesterol minus HDL) ≥3.7 % mmol/l, or abnormal HDL (<1.05 mmol/l) or triglyceride (TG) (≥1.5 mmol/l), recommendations are (1) to re-evaluate the use of the antipsychotic medication in order to minimize weight gain, and (2) to consider cognitive/behavioural lifestyle intervention aimed at weight loss. In the case of elevated LDL (≥4.15 mmol/l) despite aggressive lifestyle, diet, and exercise modification, as described above, for 3–6 months, consultation with a specialist for possible medical therapy is recommended. In the case of TG≥5 mmol/l, consider consultation with a specialist for possible medical therapy.

Liver function

In the case of abnormal ASAT/ALT levels, consider specialist consultation for further investigation and management to assess drug implication of such increase. In the case of drug-induced ASAT/ALT increase, consider switching SGA.

Thyroid-stimulating hormone (TSH)

TSH is required only for quetiapine. In the case of abnormal TSH level, consider assessment of free thyroxine levels and consider specialist consultation for further investigation and management.

Prolactin elevation and related side effects

In the case of elevated prolactin levels, re-evaluate the use of the antipsychotic medication. Here, a few strategies could be considered: (1) reducing the dose of SGA, as there is some evidence to support that PRL elevation and PRL-related side effects are dose-dependent for risperidone and olanzapine [73, 74]; (2) switching to a prolactin-sparing agent (clozapine, quetiapine, or aripiprazole); and (3) if SGA switch cannot be made, considering specialist consultation for further investigation and management. In the case of clinical concern and PRL-related side effects, consider specialist consultation for further investigation regarding other causes of hyperprolactinemia and/or amenorrhea.

Extrapyramidal syndrome (EPS)

In the case of EPS, and when discontinuing medication is not possible, the first option is dose reduction, and the second is to switch to another SGA and/or modify the prescription using additional treatment such as antiparkinson drugs (e.g., tropatepine). With regard to long-term neurological adverse effects, it is important to distinguish between tardive dyskinesia and tardive dystonia (Table 4). Tardive dystonia are a serious issue among

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Table 4. Distinctions between tardive dystonia and tardive dyskinesia

Tardive dystonia	Tardive dyskinesia
Young subjects	Elderly
During treatment	During and after treatment
Male > Female	Female > Male
Significant pain	Unusual pain
Severe disability	Mild disability
Rare remission	Frequent remission
Improved by anticholinergics	Worsened by anticholinergics
Response to clozapine	No response to clozapine

From Charfi et al., 2004 [34]

young patients, occurring preferentially in the trunk, characterized by involuntary muscle contractions [34]. When tardive dystonia is generalized, either L-dopa or high doses of anticholinergics may be considered, with benzodiazepine and baclofen potentially added as adjuvant treatment. In case of focal dystonia, botulinum toxin A is the first-line treatment. When an antipsychotic treatment is still required for the patient's condition, switching to another atypical antipsychotic may be helpful for both tardive dystonia and the underlying condition. Clozapine appears to be the first-line therapeutic option when a patient needs antipsychotics. Finally, in the context of behavioural manifestations associated with autism, we want to emphasize that severe akathisia is sometimes difficult to distinguish from tardive dyskinesia, and discontinuation of medication with careful observation is required to reconsider SGA needs.

Clinical and research implications

Comments on current knowledge

Most of the studies reviewed here are not comprehensive, and most were focused on efficacy rather than adverse effects. Fortunately, the dearth of knowledge with regard to AEs has improved over recent years following the Pediatric Act. With regard to the studies on short-term adverse effects, several limitations should be acknowledged: the variable reporting of secondary effects, the lack of data on clozapine and ziprasidone, the absence of data on asenapine, the limited number of studies independent of industry funding, the limited number of studies comparing active compounds, the absence of randomization in most observational studies, and the lack of data on concomitant medications that appears to be the rule in everyday practice [10]. Although it is the nature of clinical care not to treat patients for extended periods of time if they cannot tolerate a treatment, the major limitation of long-term studies is that most are follow-up studies from industry-funded acute-phase randomized placebo-controlled trials, and thus patients with the most serious adverse effects are excluded before the longer open phase, which causes the secondary-effect profiles to be biased. In addition, large comparative multisite studies such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [75], the Cost Utility

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of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) [76], and the European First Episode Schizophrenia Trial (EUFEST) [77], that have been conducted in adult patients still need to be performed in young patients.

Switching from one SGA to another

As stated above, in the case of persistent AE, switching antipsychotics must be considered. Receptor affinity profile and half-life of each SGA should be considered before the switch. A dopaminergic rebound effect can be observed when the introduced antipsychotic has a lower affinity for the dopamine D2 receptor than the initial antipsychotic or if it is a partial agonist with a particularly long life, such as aripiprazole. Dopaminergic hyperactivity rebound includes manifestations of dyskinesia, akathisia, and/or exacerbation of psychotic symptoms (or supersensitivity psychosis). A cholinergic or histaminergic rebound can be expected if the new antipsychotic has lesser affinity for these two receptors. Clinically, this manifests as nausea, vomiting, insomnia, diarrhea, agitation, headache, and sweating.

At this point, it is then recommended to proceed to an overlapping or "plateau" switch, which is to progressively introduce the new compound up to therapeutic doses, to maintain the first treatment during this introduction, and then to slowly decrease the treatment being discontinued [65]. The "plateau" switch, which is the best alternative to limit rebound effects, is particularly interesting in four cases: (1) when the first compound has a high histaminergic or cholinergic affinity and the new compound has a low affinity for these two receptors (e.g., changing from risperidone to quetiapine or clozapine); (2) when the switch comes from a short-half-life compound to a long-half-life compound (e.g., changing from quetiapine or risperidone to aripiprazole); (3) when the initial compound has a high dopamine affinity and the new compound has a low affinity for the DA receptor (e.g., changing from risperidone to quetiapine); and (4) when the initial compound has a high dopamine affinity and the new compound is a partial agonist (e.g., changing from risperidone to aripiprazole) [64•].

When a "plateau" switch is not possible (e.g., in the case of agranulocytosis with clozapine), certain adjuvant treatments may be used to limit the rebound effect. Anticholinergics may help to control the cholinergic rebound, and benzodiazepines or sedative treatment may be useful when a high-histaminergic-affinity treatment is discontinued. A short hospitalization may also be useful. In the case of supersensitivity psychosis, benzodiazepines and anticholinergics may be helpful. The aim of all of these strategies is to maintain a sufficient relevant receptor blockade during the switch.

Adverse effects due to a switch are observed at different times: cholinergic rebound and akathisia are observed in the very first days; parkinsonism rebound occurs after one week of discontinuation; dyskinesia due to discontinuation could appear within a month. The reintroduction of the SGAs will ensure that these are rebound symptoms, as they will stop with this reintroduction.

Research implications

As stated above, there is an urgent need for long-term multi-arm comparative studies of SGAs in child and adolescent patients, investigating both efficacy and adverse effects, as has been done in studies of first psychotic episodes in young adults. [12•, 78]. In children and adolescents, the TEOSS study

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(comparing molindone, risperidone, and olanzapine in early-onset schizophrenia) tried to achieve these goals, but only 46 % (54/116) of the subjects entered maintenance treatment after the acute phase (molindone, $n=20$; olanzapine, $n=13$; risperidone, $n=21$) [26]. The lack of statistical power led to cautious interpretation of the data. There is also the need for detailed pharmacovigilance studies based on a large prescription database. The study on olanzapine offered important information regarding AE in young patients [4•], but other compounds have not been investigated in the same way.

The proposals made in the current review, which are based mainly on the monitoring recommendations of the CAMESA guideline group, are in need of empirical validation. This is ongoing within the context of a large prospective naturalistic multicentre study begun in France in 2013 [31]. The ETAPE study (Etude de la Tolérance des AntiPsychotiques chez l'Enfant) aims to monitor SGA AEs among drug-naïve children and adolescents aged 6–18 years over the period of one year. Clinical evaluation and laboratory testing will follow the CAMESA guideline group schedules, adding scales to monitor severity and vitamin D variation, as this will better document the risk of osteoporosis [69].

Conclusion

Adverse effects occur frequently with SGAs, weight gain and metabolic AEs in particular. We still do not know the long-term consequences ascribed to SGAs for child and adolescent patients. Nevertheless, each compound has a specific profile that could assist clinicians in choosing the SGA according to the individual risk factor of each patient. A systematic monitoring schedule could lead to early detection of AE for appropriate targeted intervention, which could help to limit the long-term consequences of AEs.

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Compliance with Ethics Guidelines

Conflict of Interest

Marie Raffin, Marianna Gianitelli, Marie-Line Menard, Florence Askenazy, Claudine Laurent declare that they have no conflict of interest.

During the past two years, David Cohen reported past consultation for or the receipt of honoraria from Bristol-Myers Squibb, Otsuka, Shire, Lundbeck and IntegraGen.

Olivier Bonnot reported past consultation for or the receipt of honoraria from Otsuka and Actelion. Angèle Consoli reported receiving travel support from BMS.

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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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