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Review

Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice

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ABSTRACT

Second-generation antipsychotics (SGA) are being used more often than ever before in children and adolescents with psychotic and a wide range of non-psychotic disorders. Several SGA have received regulatory approval for some paediatric indications in various countries, but off-label use is still frequent. The aim of this paper was to perform a systematic review and critically evaluate the literature on cardiometabolic and endocrine side-effects of SGA in children and adolescents through a Medline/Pubmed/Google Scholar search of randomized, placebo controlled trials of antipsychotics in children and adolescents (<18 years old) until February 2010. In total, 31 randomized, controlled studies including 3595 paediatric patients were identified. A review of these data confirmed that SGA are associated with relevant cardiometabolic and endocrine side-effects, and that children and adolescents have a high liability to experience antipsychotic induced hyperprolactinaemia, weight gain and associated metabolic disturbances. Only weight change data were sufficiently reported to conduct a formal meta-analysis. In 24 trials of 3048 paediatric patients with varying ages and diagnoses, ziprasidone was associated with the lowest weight gain (−0.04 kg, 95% confidence interval [CI]: −0.38 to +0.30), followed by aripiprazole (0.79 kg, 95% CI: 0.54 to 1.04], quetiapine (1.43 kg, 95% CI: 1.17 to 1.69) and risperidone (1.76 kg, 95% CI: 1.27 to 2.25) were intermediate, and olanzapine was associated with weight gain the most (3.45 kg, 95% CI: 2.93 to 3.97). Significant weight gain appeared to be more prevalent in patients with autistic disorder who were also younger and likely less exposed to antipsychotics previously. These data clearly suggest that close screening and monitoring of metabolic side effects is warranted and that the least cardiometabolically problematic agents should be used first whenever possible. A good collaboration between child- and adolescent psychiatrists, general practitioners and paediatricians is essential to maximize overall outcomes and to reduce the likelihood of premature cardiovascular morbidity and mortality.

1. Introduction

Second-generation antipsychotics (SGA) have a long history of being used in adults, and their use in youth is growing rapidly for the treatment of different child and adolescent psychiatric disorders [101,102,105,108,109] (Table 1). In recent years, risperidone use increased in children and adolescents (6–18 years) in Belgium, reaching in 2007 and 2008 the 6th and 10th places, respectively, in expenditure for prescription drugs in boys aged 13–18 years [38]. The increased use of psychotropic medications in adolescents has raised concern and controversy.

SGAs are often prescribed off-label for the treatment of disorders associated with aggressive and disruptive behaviours in pervasive developmental disorders (autistic disorder, Rett's syndrome, childhood disintegrative disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified), disruptive behaviour disorders (e.g. conduct disorder, oppositional-defiant disorder), eating disorders, mental retardation, severe attention deficit hyperactivity disorder, tic disorders like Tourette's disorder, schizophrenia and other psychotic disorders, bipolar spectrum disorders and obsessive-compulsive disorder [17,39,67,70,79].

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Table 1
Atypical antipsychotics.

Atypical antipsychotics	Indication in patients < 18 years
Amisulpiride (Solian®)	None
Aripiprazole (Abilify®)	Schizophrenia (Eur, US), bipolar disorder and irritability in autism (US)
Asenapine (Saphris®)	None
Clozapine (Leponex®)	None
Iloperidone (Fanapt®)	None
Olanzapine (Zyprexa®)	Schizophrenia; bipolar disorder (US)
Paliperidone (Invega®)	None
Quetiapine (Seroquel®)	Schizophrenia; bipolar disorder (US)
Risperidone (Risperdal®)	Severe disruptive disorder (Eur), schizophrenia, bipolar disorder, irritability in autism (US)
Sertindole (Serdolect®)	None
Ziprasidone (Geodon®)	None

Eur: Europe; US: United States.

In the United States, the Food and Drug Administration (FDA; www.fda.gov) approved aripiprazole, olanzapine, quetiapine and risperidone for use in adolescents with schizophrenia (age 13–17 years) and for children and adolescents aged 10–17 years old (except for olanzapine: age 13–17 years old) with bipolar I disorder, manic or mixed episode. In addition, risperidone (age 5–17 years) and aripiprazole (aged 6–17 years) are approved for the treatment of irritability and aggression in youth with autistic disorder [82,85,94,104]. Furthermore, the FDA scientific advisory group voted to approve the use of ziprasidone for the treatment of children and adolescents with bipolar I mania (age 10–17). Across all European Union countries, aripiprazole is currently the only licensed antipsychotic, with an indication for the treatment of schizophrenia in adolescents aged 15–17 years. In isolated European countries, including Belgium, risperidone is approved for the treatment of children and adolescents with severe disruptive disorders [46,63]. Recently, SGA are being used increasingly for the treatment of severe behavioural disturbances in people with pervasive developmental disorders [41,101,102].

However, despite increasing use of SGAs and recent regulatory approval in children and adolescents, data regarding their safety are limited. Based on emerging data consisting of indirect comparisons only, it appears that children and adolescents are at higher risk than adults for antipsychotic-induced hyperprolactinaemia, weight gain and possibly associated metabolic abnormalities [3,7,15,21,24,26,31,37,51,54,74,75,101,102]. Endocrine and metabolic adverse effects are among the most concerning side-effects of commonly used psychotropic medications [17,20]. Growing evidence suggests that children and adolescents who take antipsychotic medications are at a higher risk of weight gain and metabolic effects than adults who use the same drugs [21,25,26,33].

SGA are generally considered to have a favourable neuromotor side-effect profile and comparable efficacy compared to first-generation antipsychotics (FGA), but they are associated with other relevant side-effects (Table 2) [27,78,103]. Current knowledge links therapeutic and adverse effects of antipsychotics to their different effects on dopaminergic, noradrenergic, serotonergic, histaminergic and cholinergic receptors [24,96]. Because SGA have been shown to be associated with fewer extrapyramidal adverse effects, the toxicological potential of these agents may be underestimated [39]. Differences in absorption, distribution and metabolism of antipsychotics mean that higher doses per kilogram weight are required in paediatric populations than in adults to achieve similar efficacy and that more frequent dosing per day may be required in younger children [21]. Young people are more vulnerable to some adverse effects. A slow rate of titration appears to be associated with reduced rates of side effects, particularly extrapyramidal symptoms [26,44].

There are known associations between weight gain and obesity with diabetes, dyslipidemia and hypertension, all of which are leading risk factors for future cardiovascular morbidity (CVD) and mortality [22]. The debate on the use of antipsychotics and other psychotropic agents in children and adolescents is increasingly becoming a discussion about their safety, and less about their efficacy in this population [23,37,51,70].

Given the recent completion of a number of randomized, placebo-controlled trials, this paper reviews the recent literature on side-effects – especially cardiometabolic and endocrine adverse effects – of SGA in children and adolescents. The screening for the management of these adverse effects is given special attention.

2. Method

The background articles cited in this review were found through a Medline/Pubmed/Google Scholar search from 1996 until February 2010 using the following keywords (alone and in different combinations): ‘‘child’’, ‘‘children’’, ‘‘adolescents’’, ‘‘adolescent’’, ‘‘paediatric’’, ‘‘adverse/side effect(s)’’, ‘‘atypical/second-generation antipsychotic(s)’’, ‘‘metabolic syndrome’’, ‘‘weight gain’’, ‘‘diabetes’’. By screening of the references lists of relevant articles, additional studies were obtained. The search strategy of reviewing related articles in Medline and Pubmed was also applied. Authors of identified studies were contacted to obtain

Table 2
Common or potentially dangerous side-effects of atypical antipsychotics [21,38,39,79].

Side-effects of atypical antipsychotics
Metabolic adverse effects: weight gain, hyperglycemia and diabetes, hyperlipidemia
Endocrine adverse effects: hyperprolactinemia, sexual and reproductive system dysfunction, effect on thyroid function, pancreatitis and elevated liver enzymes
Extrapyramidal adverse effects: parkinsonism, acute dystonia, akathisia, tardive dyskinesia
Anticholinergic adverse effects: facial flushing, dry mucous membranes, decreased sweating, constipation, urinary retention, tachycardia, and impaired learning and memory
Cardiac adverse effects: prolonged QT/arrhythmias, hypotension, cardiomyopathy
Agranulocytosis
Sedation, decreased ability to concentrate
Seizures
Malignant neuroleptic syndrome
Priapism

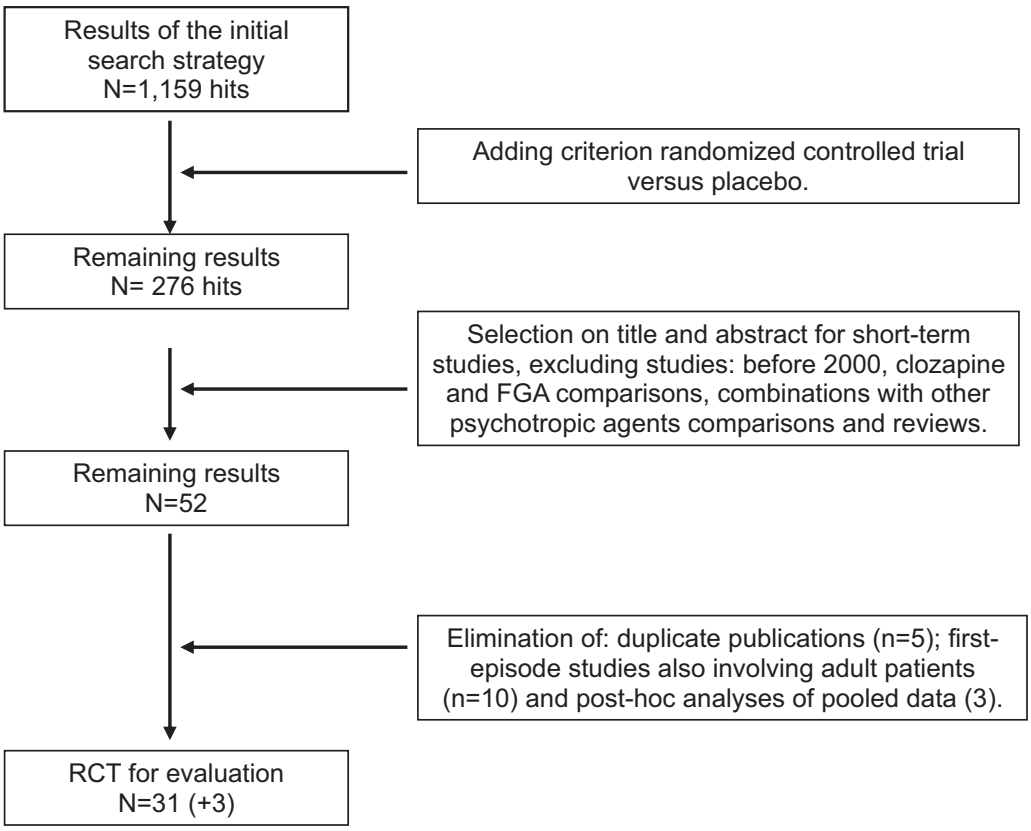

Fig. 1. Results of the systematic literature search (FGA: first generation antipsychotics; (+3): three studies head to head comparison with FGA).

unpublished data. Research papers and clinical trials were excluded if adult patients were the main or only target population. The general review was mainly based on available review papers. The screening process used in the literature search is shown in Fig. 1.

In addition, we systematically reviewed short-term weight gain data in the randomised, placebo-controlled and single-blind trials in children and adolescents of SGA with a paediatric indication (published after 2000). Duplicate papers on the same study or post-hoc analysis of pooled data were excluded. Descriptive statistics were performed with Statistical Analysis Software (SAS, Carey NC). In studies where 7% or more weight gain were reported, we calculated numbers needed to harm (NNH) with 95% confidence intervals (CI). For studies with data on both mean weight gain and standard deviation, a formal meta-analysis was performed using RevMan Analyses (RevMan 5, a meta-analytic standard software used by the Cochrane collaboration [The Cochrane Collaboration, 2003]). Continuous data were reported as presented in the original studies, i.e., last observation carried forward, without any assumptions about those lost to follow-up. In cases were more than one active treatment arm existed per study, the placebo arm was entered twice ($n = 538$). Since all studies reported change in kilogram, we calculated weighted mean differences. Due to the heterogeneity of the included studies, we used the more conservative random effects model. All analyses were two-tailed, with alpha set at 0.05.

3. Results

Results that are presented are derived from a synopsis of the published literature, including a compilation of primary, published data (see tables) and of summaries and conclusions from relevant prior review articles.

In total, we identified 31 studies, with 3595 patients, which reported randomized clinical trial data meeting our inclusion criteria (Table 3) (two schizophrenia trials that compared SGA to FGA were added to the table, but not included in the following analyses of the placebo-controlled trials) [4,5,7,14,34–36,43,46,47,49,50,56–58,63,64,73,81,82,85,86,104,111,112,114,116–118,123,126].

We identified four papers, which presented clinical practice guidelines specifically targeting children and adolescents [21,24,38,103]. A recent systematic evaluation of 18 clinical practice guidelines for screening of metabolic risk in adult patients with schizophrenia [33] identified four additional publications, which also mentioned patients <18 years [4,15,32,55].

3.1. Weight gain

Thirty-one controlled studies with SGA in the defined target population were found including youth with different diagnoses, 29 double-blind trials [4,5,7,14,34,36,43,46,47,49,50,56,58,63,64,73,81,82,85,86,104,111,112,114,118,123,126] and two studies without a placebo arm [35,57].

The mean weight changes and NNHs (data available in 16 trials, $n = 2695$) are presented in Table 3. The mean weight change per SGA in individual short-term studies varied from −0.2 (ziprasidone) to 4.3 kg (olanzapine), while in a pooled analysis, the mean weight change varied significantly between drugs from 0.5 (ziprasidone) to 3.8 kg (olanzapine). Except for ziprasidone, all the weight changes were significant compared to placebo in the majority of studies (Table 3). In a similar way, as the analysis by Allison et al. in adults, Fig. 2 shows the mean weight changes for each individual SGA [2].

The differences between SGA are reflected in the significant NNH ranging from 3 (olanzapine, CI 2.1–3.1), 6 (risperidone, CI 4.2–6.3), 9 (quetiapine, no data on autism, CI 6.4–13.5) to 12

Table 3
Weight changes in randomised controlled trials of second-generation antipsychotics in patients < 18 years.

Drug/study	Indication	Age range	Duration (weeks)	Dose	*n*	ΔWeight gain (kg (sd))	>7% weight gain
Aripiprazole						1.0 (0.6)	
Findling et al. (2008) [46]	Schizophrenia	13 to 17	6	Pla	100	−0.8 (2.6)[a]	1
				10	100	0 (2.1)	4
				30	100	0.2 (2.3)	5
Findling et al. (2009) [47]	Bipolar, mania mixed	10 to 17	4	Pla	99	0.56 (2.14)	4.6
				10	98	0.82 (1.69)	4
				30	99	1.08 (2.27)	12.3
Marcus et al. (2009) [82]	Autism	6 to 17	8	Pla	51	0.3 (0.3)	8.2
				5	53	1.3 (0.3)[a]	32.7
				10	59	1.3 (0.3)[a]	15.3
				15	54	1.5 (0.3)[a]	30.2
Owen et al. (2009) [104]	Autism	5 to 15	8	Pla	51	0.8 (0.39)	6.1
				5–15	47	2 (0.3)[a]	28.9
Tramontina et al. (2009) [124]	Bipolar and ADHD	8 to 18	6	Pla	18	0.7 (1.2)	No data
				2 to 20	25	1.2 (1.5)	No data
				Total NNH pooled versus placebo			12 (95% CI 8.3–16.8)
				NNH only schizophrenia and bipolar			39 (95 % CI −0.2–5.4)
Olanzapine						3.8 (0.5)	
Hollander et al. (2006) [64]	Pervasive developmental disorder	6 to 14	8	Pla	5	0.7 (0.7)	20
				10	6	3.4 (2.2)[a]	66.7
Tohen et al. (2007) [123]	Bipolar, mania	13 to 17	3	Pla	54	0.3 (1.67)	1.9
				2.5–20	107	3.7 (2.2)[a]	41.9
Kryzhanovskaya et al. (2009) [73]	Schizophrenia	13 to 17	6	Pla	35	0.1 (2.8)	14.7
				2.5–20	72	4.3 (3.3)[a]	45.8
				Total NNH pooled versus placebo			3 (95% CI 2.1-3.1)
				NNH only schizophrenia and bipolar			3 (95 % CI 2.1–3.1)
Quetiapine						2.2 (0.9)	
DelBello et al. (2007) [34]	Bipolar, mood	Mean 14.7	12	300 to 600	20	3.8 (16.2)	No data
DelBello et al. (2009) [35]	Bipolar, depressed	12 to 18	8	Pla	15	0.9 (0.6)	No data
				300 to 600	17	2.3 (0.6)[a]	No data
FDA (2010) [53]	Bipolar, mania S149	10 to 17	3	Pla	89	0.4 (1.7)[a]	0
				400	93	1.7 (2.0)	14.5
				600	95	1.7 (2.3)	9.9
FDA (2010) [53]	Schizophrenia, S112	13 to 17	6	Pla	73	−0.1 (2.8)[a]	6.8
				400	73	1.9 (2.5)	23.2
				800	74	1.5 (2.6)	18.2
				Total NNH pooled versus placebo			9 (95% CI 6.4– 13.5)
				NNH only schizophrenia and bipolar			−9 (95% CI 6.4– 13.5)
Risperidone						2.4 (0.9)	
Findling et al. (2000) [43]	Conduct disorder	5 to 15	10	Pla	10	0.74 (0.9)	No data
				0.75 to 1.50	10	4.2 (0.7)[a]	No data
Buitelaar et al. (2001) [14]	Behavioural, aggression	11 to 15	6	Pla	19	0.6	No data
				Mean 2.9	19	2.3[a]	No data
Hellings et al. (2001) [63]	Autism	8 to 16	16	Pla	11	0.1 (1.3)	No data
				Mean 1	11	4.0 (2.5)[a]	No data
Van Bellinghen et al. (2001) [126]	Behavioural	6 to 14	4	Pla	7	0.6	0
				Mean 1.2	6	1.8	33.3
Aman et al. (2002) [4]	Conduct, behavioural	5 to 17	8	Pla	63	0.9 (1.5)	No data
				Mean 1.16	55	2.2 (1.8)[a]	No data
Scahill et al. (2003) [112]	Tourette	6 –62 (young mean 11.1)	8	Pla	14	0	No data
				Mean 2.5	12	2.8[a]	No data

Table 3 (*Continued*)

Drug/study	Indication	Age range	Duration (weeks)	Dose	*n*	ΔWeight gain (kg (sd))	>7% weight gain
Snyder et al. (2002) [118]	Conduct, behavioural	5 to 12	6	Pla	57	0.2 (0.23)	5.4
				Mean 0.98	53	2.0 (0.18)[a]	51.0
Shea et al. (2004) [114]	Autism	5 to 12	8	Pla	39	1 (1.6)	No data
				Mean 1.48	40	2.7 (2.0)[a]	No data
Aman et al (2005) [5,7,85,86]	Autism	5 to 17	8	Pla	52	0.8 (2.2)	No data
				0.5-3.5	49	2.7 (2.9)[a]	No data
Luby et al. (2006) [81]	Autism	2.5 to 6	24	Pla	12	0.61 (1.1)	No data
				Mean 1.14	11	2.96 (2.53)[a]	No data
Nagaraj et al. (2006) [94]	Autism	2 to 9	24	Pla	20	1.71 (1.3)	No data
				Mean 1.0	19	2.81 (2.04)	No data
Armenteros et al. (2007) [8]	ADHD, aggression	7 to 12	4	Pla	13	−0.6	No data
				Mean 1.08	12	0.9	No data
Haas et al. (2009) [56]	Bipolar, mania	10 to 17	3	Pla	58	0.7 (1.9)[a]	5,3
				0.5–2.5	50	1.9 (1.7)	14,3
				3–6	61	1.4 (2.4)	10
Haas et al. (2009) [58]	Schizophrenia	13 to 17	6	Pla	54	0,12 (2.04)[a]	1.8
				1–3	55	1,3 (2.73)	14.5
				4–6	51	1,5 (1.95)	15.7
Haas et al. (2009) [57]	Schizophrenia	13 to 17	8	1.5–6	125	3.2 (3.5)	39.2
				0.15–0.6/kg	132	1.7 (3.2)[a]	15.9
				Total NNH pooled versus placebo			6 (95% CI 4.2–6.3)
				NNH only schizophrenia and bipolar			6 (95 % CI 4.7–7.5)
Ziprasidone						0.5 (0.5)	
Sallee et al. (2000) [111]	Tourette	7 to 17	8	Pla	12	0.8 (2.3)	No data
				Mean 28.2 (5 to 40)	16	0.7 (1.5)	No data
DelBello et al. (2008) [35]	Mixed psychotic sample	10 to 19	3	60 to 160	63	1.0 (1.0)	7.75
FDA [51]	Bipolar mania	10 to 17	4	Pla	88	0.6 (2.3)	3.4
				80–160	149	0.5 (2.2)	6.7
Findling et al. (2010) [50]	Schizophrenia	13 to 17	6	Pla	90	−0.2 (1.6)	No data
				80–160	193	−0.2 (2.0)	No data
				Total NNH pooled versus placebo			36 (95% CI −0.9–6.5 ns)
				NNH only schizophrenia and bipolar			36 (95% CI −0.9–6.5 ns)
Non placebo controlled RCT SGA							
Sikich et al. (2004) [116]	Schizophrenia	8 to 19	8	Hal 5	15	3,5 (3.7)	No data
				Ola 12.3	16	7,1 (4.1)[a]	No data
				Ris 4	19	4,9 (3.6)	No data
Sikich et al. (2008) [117]	Schizophrenia	8 to 19	8	Mol 59.9	40	0,3 (2.9)	No data
				Ola 11.4	35	6,1 (3.6)[a]	No data
				Ris 2.8	41	3,6 (4.0)	No data

Pla: placebo; CI: confidence interval; Hal: haloperidol; Mol: molindone; Ris: risperidone; Ola: olanzapine; NNH: numbers needed to harm.

[a] Significant compared to placebo or significant difference over groups.

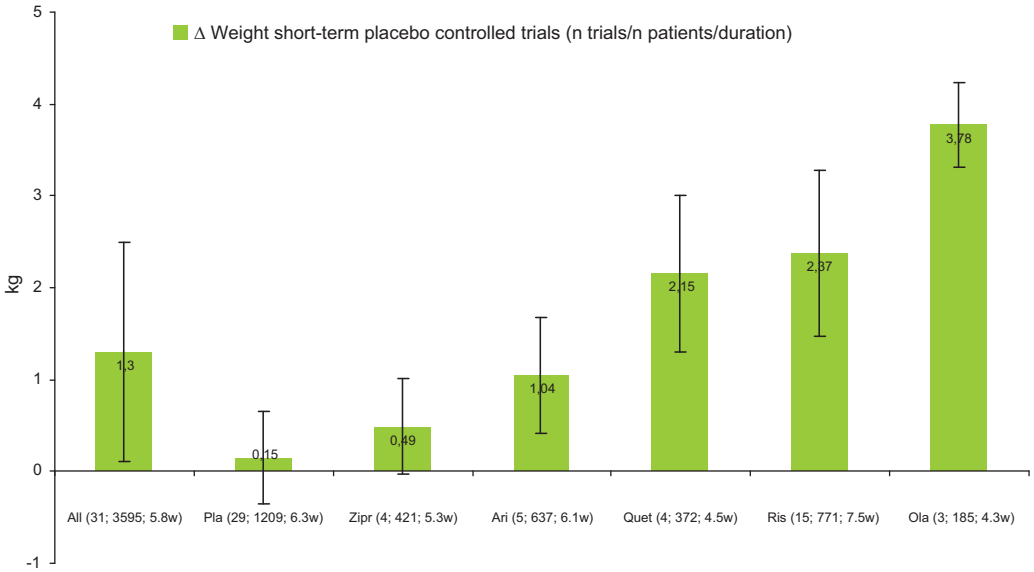

Fig. 2. Mean weight change in short-trem trials (31 studies) (mean change from baseline and standard deviations; number of studies, number of participants, mean duration of studies, w: weeks).

(aripiprazole, CI 8.3–16.8) (overall NNH for all SGA: 7 [CI 5.9–8.0]). The NNH of 36 (CI −0.9–6.5) for ziprasidone was not significantly different from placebo, but this results was only based on a single study in bipolar disorder. The NNH for aripiprazole was in part driven by data in youth with autism. Analysis of the NNH for patients with schizophrenia and bipolar patients only did not change the results for olanzapine (NNH 3, CI 2.1–3.1) nor risperidone (NNH 6, CI 4.7–7.5), but in these samples, aripiprazole did not differ from placebo anymore and was comparable to ziprasidone, with a NNH of 39 (CI −0.2 to 5.4).

A formal meta-analysis was possible in 24 studies including 3048 youth (1934 on an SGA and 1114 on placebo). In these trials of paediatric populations with varying ages and diagnoses, ziprasidone was associated with the lowest weight gain (−0.04 kg, 95% CI: −0.38 to +0.30), followed by aripiprazole (0.79 kg, 95% CI: 0.54 to 1.04), quetiapine (1.43 kg, 95% CI: 1.17 to 1.69) and risperidone (1.76 kg, 95% CI: 1.27 to 2.25) were intermediate, and olanzapine was associated with the most weight gain (3.45 kg, 95% CI: 2.93 to 3.97) (Fig. 3).

3.2. Metabolic adverse effects and metabolic syndrome components

Multiple prospective studies have reported that obesity, metabolic abnormalities and weight gain during childhood strongly predict obesity, metabolic syndrome (MetS), hypertension, cardiovascular morbidity, sleep apnoea, osteoarthritis and malignancy risk in adulthood [22,120].

MetS is a constellation of physical and laboratory features that is more common in obese patients and predisposes adults and children to atherosclerotic CVD. The occurrence of MetS in young individuals predicts early atherosclerosis and vascular disease as adults.

In children, normal values for the parameters that are part of the MetS change with age, height and gender, and therefore modified criteria have been proposed for use in children and adolescents (20,23,24). In children and adolescents, at least three of the five criteria must be met [20,130]. Currently, there exists no universally accepted definition of the MetS for children and adolescents [28].

The International Diabetes Federation (IDF) suggests that for children (10–16 years), MetS can be diagnosed by abdominal obesity and the presence of two or more clinical features. They use a threshold value for triglyceride level of 1.69 mmol/l (150 mg/dl) (Table 4) [130].

As shown in the weight gain section, one of the most pronounced adverse effects of SGA is weight gain [103]. The average increase in weight and body mass index is twice as high in patients started on SGA compared with first-generation antipsychotics, yet agents within each of these classes produce heterogeneous outcomes [30,116,117]. The odds of developing MetS in MetS free young adults were three-fold in patients started on SGA compared to FGA, and there were significant differences between SGA in their risk to induce MetS in first-episode patients [30].

The effects of SGA in children on glucose and lipids are less well studied (Table 4). Only a limited number of mostly recent studies directly evaluated the impact of SGA on these MetS components in young patients. The SGA associated with the largest weight changes also seem to be associated with the largest effects on glucose and lipids [25,93,98].

Diabetes mellitus is another much-feared consequence of significant weight gain and obesity. In patients receiving SGA, there may also be direct effects on insulin secretion [1]. There may be several underlying mechanisms: increased adipose tissue potentially results in insulin resistance, glucose intolerance and diabetes. The increase in fatty acids could alter glucose metabolism, or the pancreatic β-cell response is diminished [120]. A case-report describes the development of diabetes in a young patient (14 years) after several months of risperidone treatment, which was reversible after stopping the antipsychotic [76]. There is a short- and long-term risk for the development of diabetes. A worrisome finding was that in some patients, diabetes mellitus did not resolve after discontinuation of the antipsychotic [18,76]. In addition to diabetes, SGA have been associated with hyperlipidaemia. This is relevant, as research has shown that hypertriglyceridaemia is an independent risk factor for CVD [9,28,29,32,61,100,120].

3.3. Effect on thyroid function

There are only data available of the effect of quetiapine on thyroid function. Quetiapine has been noted to decrease serum total thyroxine (T4) in some studies. Although the mechanism of this effect is unknown, serum free thyroxine and thyroid

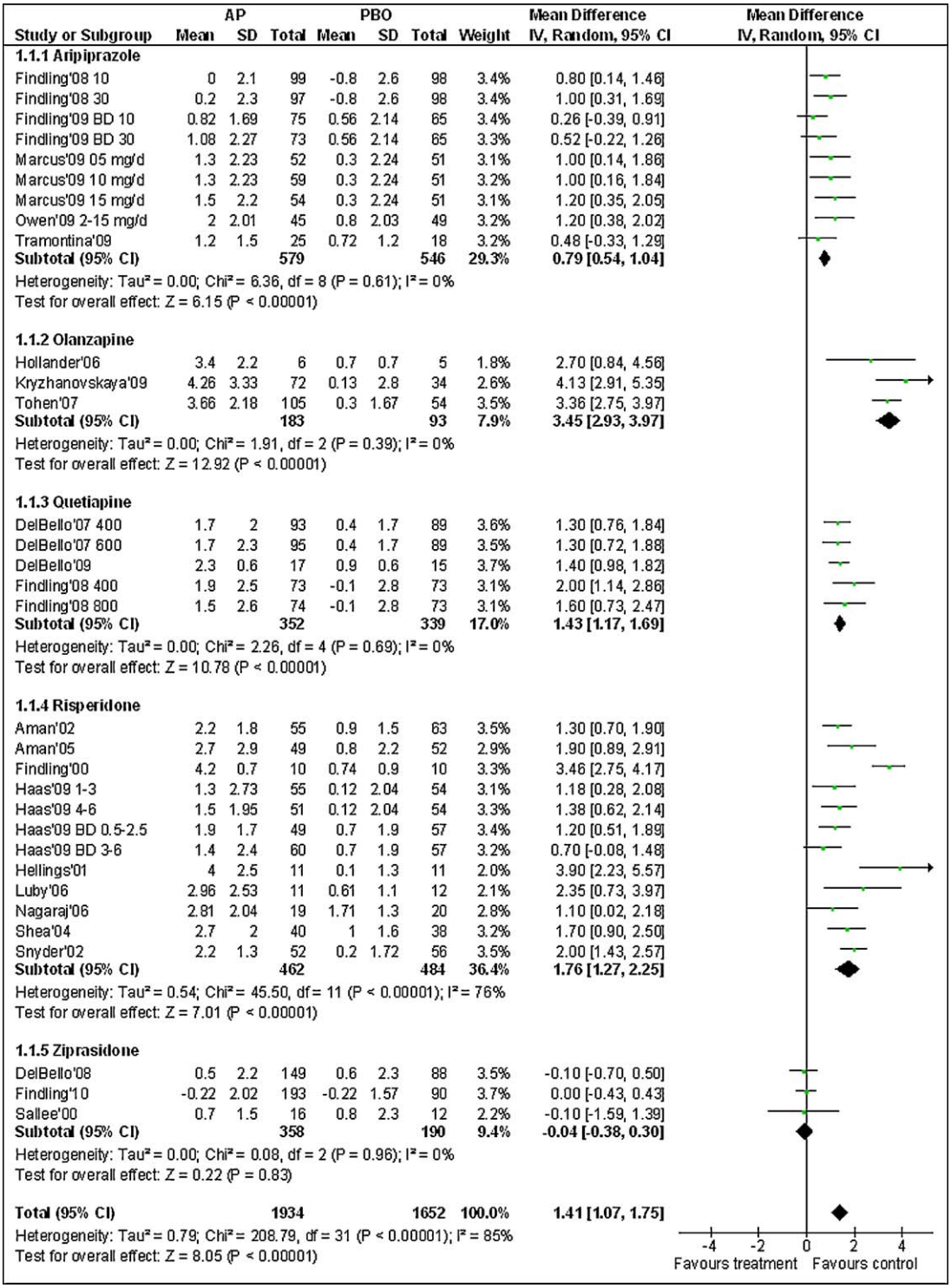

Fig. 3. Forest plot of weight change in kilogram in children and adolescents randomly treated with a second-generation antipsychotic or placebo.

stimulating hormone (TSH) generally remain within normal range in paediatric patients receiving quetiapine, suggesting that subjects remain euthyroid [20].

3.4. Hyperprolactinaemia

The changes in prolactin in the RCTs in young patients are generally consistent with data in adults: largest and dose-dependent increase with risperidone (seven studies), an increase with olanzapine (two studies), mixed results for quetiapine (four studies) and ziprasidone (three studies) and a decrease with aripiprazole (four studies) (Table 5).

Many SGA cause less hyperprolactinaemia than FGA, although this effect varies across agents and is dose-dependent [20,23,110]. Hyperprolactinaemia is most pronounced with by risperidone and paliperidone, followed by amisulpride and haloperidol [20,68,110]. Risperidone can substantially elevate prolactin levels in a dose-related fashion [7,45,110]. A transient increase was reported with

Table 4
The metabolic syndrome: criteria [20,23,130].

Adults	Children and adolescents
Abdominal obesity	Obesity
Waist circumference ≥ 102 cm in males	Waist circumference ≥ percentile 90
Waist circumference ≥ 88 cm in females	BMI ≥ percentile 95
Fasting serum triglyceride levels	Fasting serum triglyceride levels
≥1.69 mmol/l (≥ 150 mg/dl)	≥1.24 mmol/l (≥110 mg/dl)
	≥1.7 mmol/l ((≥150 mg/dl) IDF (10 to 16 years)
Fasting HDL-cholesterol	Fasting HDL-cholesterol
<1.03 mmol/l (<40 mg/dl) in males	<1.03 mmol/l (<40 mg/dl) (boys and girls)
<1.29 mmol/l (<50 mg/dl) in females	
Blood pressure ≥ 130/85 mmHg	Blood pressure ≥ percentile 90 (adjusted for sex and age)
Fasting glucose	Fasting glucose
≥5.6 mmol/l (≥100 mg/dl)	≥5.6 mmol/l (≥100 mg/dl)

IDF: international diabetes federation, waist obligatory criterion.

olanzapine and ziprasidone. Clozapine, quetiapine and sertindole seem not to provoke an increase of the serum concentrations of prolactin [20,44,45,59,60,80,119]. Different studies have shown a mean decreases in serum prolactin during treatment with aripiprazole [46,47,82,104]. The effect of SGA on prolactin is variable and is a consequence of the peripheral antidopaminergic effect [7,46,48,52,82,104,110]. This effect may be more pronounced in postpuberal children and adolescents than in adults. This may be caused by an age-related decrease in dopamine receptors [20,121]. Clinical symptoms of hyperprolactinaemia are presented in Table 6.

4. Monitoring of the metabolic adverse effects

Side-effects of antipsychotics must be monitored in paediatric patients, just as in adults [6,15,23,32,55]. It is important that screening is conducted regularly. In children and adolescents, adverse drug reactions related to antipsychotics seem to occur particularly in the first three months of therapy [1].

To gain insight into a patient's metabolic risk requires the acquisition of basic clinical data, including taking a personal and family history. Laboratory values (e.g. fasting glucose and lipid levels) should be monitored at baseline [6,15,20–24,31,32,55,88,103,120]. At the same time, body weight, height and sex- and age adjusted BMI *z* score and percentile values, as well as blood pressure should be measured.

Correll (2008) recommended checking cardiometabolic health parameters at baseline, 3, 6 and 12 months, with 6-monthly assessments thereafter, unless abnormalities appear [24]. The frequency of testing will depend on the presence of risk factors and detected abnormalities. When significant weight gain occurs or patients develop symptoms that are suggestive of new-onset diabetes, the frequency of the assessments must be increased. Fasting glucose and lipids should be monitored more often in children and adolescents than in adults because children can gain more weight relative to adults and also may be at greater risk for metabolic abnormalities. In adults, recent guidelines have recommended follow-up measurements at six weeks [32] and/or 12 weeks [32] after initiation of treatment and at least annually [32] or six-monthly [23–25] thereafter. A free online flowchart for screening and monitoring cardiometabolic risk in adults treated with antipsychotic medication was recently published in a joint statement from European psychiatrists, diabetologists and cardiologists (www.europsy.net/, position statements) [32]. These guidelines are summarised in Table 7, and are also be applicable in young patients, taking into account adapted threshold values of the specific variables [23,24,32].

4.1. Body weight

Monitoring weight change as such has limited use in youth because they are expected to gain weight as part of normal development. Weight *z*-score or, especially, BMI *z*-score change is a more accurate measure to follow. The threshold values are different from those used in adults [20,23,24]. A generally accepted definition of clinically significant weight gain during development does not exist, but a BMI increase of at least 0.5 *z*-scores (i.e., standard deviations) has been proposed [20] and applied [128].

Similarly, due to considerable differences in weight-to-height-ratio relationships during normal development, BMI is not useful to determine normal or abnormal weight categories. Normative tables by sex and age are available [20,128]. Children and adolescents between the 85th and less than the 95th percentile for BMI by age and sex are considered "overweight", while BMI percentiles by age and sex at or beyond the 95th percentile are considered "obese" (http://www.cdc.gov/obesity/defining.html) [20,24,128].

Independent of total adiposity, a central distribution of fat is believed to be a risk factor for poor health in both adults and children. Excess abdominal fat is associated with hyperlipidaemia, cardiovascular risk factors, type 2 diabetes and other morbidities. Accurate measurement of total and regional body fat is fundamental in order to detect as early as possible whether the child is deviating from normal values. Individuals with high waist circumference are more likely to have hypertension, diabetes, dyslipidemia and MetS. Evidence has supported that waist circumference is a better predictor of CVD and visceral fat than BMI [42]. However, although waist circumference percentile tables that are sex- and age- adjusted are available, the imprecision of this measure in general clinical practice is large in young patients and the routine measurement of waist circumference in youth is currently not endorsed (online: http://www.gghjournal.com/volume21/1/ab17.cfm) [20,23,24].

4.2. Glucose

Fasting glucose thresholds for prediabetes 5.55–6.94 mmol/l (100–125 mg/dl) and diabetes ≥6.99 mmol/l (≥126 mg/dl) are similar for paediatric and adult patients [20,24].

Symptoms that are suggestive of new-onset diabetes are weight loss, polyuria, polydipsia and change in mental status [20,23]. Also, signs and symptoms of diabetic ketoacidosis should be monitored on a regular basis: rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydratation, rapid respiration, clouding of sensorium, even coma [6,19].

Table 5
Changes in prolactin, glucose and lipids in randomised controlled trials of second-generation antipsychotics in patients <18 years.

Drug/study	Indication	Age range	Duration (weeks)	Effect on prolactin	Effect on glucose	Effect on lipids
Aripiprazole						
Findling et al. (2008) [46]	Schizophrenia	13 to 17	6	Prolactin decrease all arms, significant	No change	No change
Findling et al. (2009) [47]	Bipolar, mania mixed	10 to 17	4	Prolactin decrease all arms, significant	No change	No change
Marcus et al. (2009) [82]	Autism	6 to 17	8	Significant decrease	No change	No change
Owen et al. (2009) [104]	Autism	5 to 15	8	Significant decrease	No change	No change
Tramontina et al. (2009) [124]	Bipolar and ADHD	8 to 18	6	No data	No data	No data
Olanzapine						
Hollander et al. (2006) [64]	Pervasive developmental disorder	6 to 14	8	No data	No data	No data
Tohen et al. (2007) [123]	Bipolar, mania	13 to 17	3	Significant increase	Significant increase	Significant increase cholesterol and triglycerides
Kryzhanovskaya et al. (2009) [73]	Schizophrenia	13 to 17	6	Significant increase	No change	Significant increase triglycerides, trend for cholesterol
Quetiapine						
DelBello et al. (2007) [34]	Bipolar, mood	Mean 14.7	12	No change	No change	No change
DelBello et al. (2009) [35]	Bipolar, depressed	12 to 18	8	Non significant change	No change	Significant increase triglycerides
FDA (2010) [53]	Bipolar, mania S149	10 to 17	3	No change	No change	Significant increase cholesterol and triglycerides
FDA (2010) [53]	Schizophrenia, S112	13 to 17	6	Prolactin decrease all arms	No change	Significant increase cholesterol and triglycerides
Risperidone						
Findling et al. (2000) [43]	Conduct disorder	5 to 15	10	No data	No data	No data
Buitelaar et al. (2001) [14]	Behavioural, aggression	11 to 15	6	Significant increase	No data	No data
Hellings et al. (2001) [63]	Autism	8 to 16	16	No data	No data	No data
Van Bellinghen et al. (2001) [126]	Behavioural	6 to 14	4	No data	No data	No data
Aman et al. 2002 [4]	Conduct, behavioural	5 to 17	8	No data	No data	No data
Scahill et al. (2003) [112]	Tourette	6–62 (young mean 11.1)	8	No data	No data	No data
Snyder et al. 2002 [118]	Conduct, behavioural	5 to 12	6	Significant increase	No data	No data
Shea et al. (2004) [114]	Autism	5 to 12	8	No data	No data	No data
Aman et al. (2005) [5,7,85,86]	Autism	5 to 17	8	Significant increase	No data	No data
Luby et al. 2006 [81]	Autism	2.5 to 6	24	Significant increase	No data	No data
Nagaraj et al. (2006) [94]	Autism	2 to 9	24	No data	No data	No data
Armenteros et al. (2007) [8]	ADHD, aggression	7 to 12	4	No data	No data	No data
Haas et al. (2009) [56]	Bipolar, mania	10 to 17	3	Dose dependent increase, significant	No change	No change
Haas et al. (2009) [58]	Schizophrenia	13 to 17	6	Dose dependent increase, significant	No change	No change
Haas et al. (2009) [57]	Schizophrenia	13 to 17	8	Increase with both doses	No change	No change
Ziprasidone						
Sallee et al. (2000) [111]	Tourette	7 to 17	8	No change	No change	No change
DelBello et al. (2008) [35]	Mixed psychotic sample	10 to 19	3	Small increase	No change	Significant decrease cholesterol and triglycerides
FDA [51]	Bipolar mania	10 to 17	4	No change	No change	Significant decrease cholesterol and triglycerides
Findling et al. (2010) [50]	Schizophrenia	13 to 17	6	No data	No data	No data

Table 6
Signs and symptoms of hyperprolactinemia [20,59,71].

Signs and symptoms of hyperprolactinemia
Hypogonadism: amenorrhea, low oestrogen (females), low testosterone (males)
Stimulation of breast glandular growth (females and males)
Galactorrhea (females > males)
Gynaecomastia (males) and breast tension or tenderness (females)
Libido decreased (females and males)
Sexual dysfunction (males and females)
Osteoporosis (females and males)
Failure to enter or progress through puberty in children (unclear)
Hirsutism (females)
(Controversial) relationship to benign pituitary tumours

4.3. Serum lipids

In children and adolescents (2–18 years), a total cholesterol concentration of 4.40–5.15 mmol/l (170–199 mg/dl) is borderline abnormal and >5.17 mmol/l (≥200 mg/dl) is elevated [28]. For LDL, the values are respectively 2.84–3.34 mmol/l (110-129 mg/dl) and >3.36 mmol/l (≥130 mg/dl). A HDL concentration of <0.91 mmol/l (<40 mg/dl) is considered to be abnormal for children and adolescents of both sexes [28]. These thresholds are lower than in adults [24].

A triglyceride level of >1.69 mmol/l (≥150 mg/dl) is an abnormal value in young adults [28,130]. An abnormally high triglyceride level in youths is >1.24 mmol/l (≥110 mg/dl) [24].

4.4. Blood pressure

Proper cuff sizes are essential for assessing blood pressure accurately in children [20,65]. In youth, blood pressure need to be adjusted for age, sex, height and weight, for which normative tables are available (http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf).

4.5. Thyroid function

Patients receiving quetiapine should probably have thyroid function tests monitored at baseline, at three months and at 1 year, with additional measurements every three months if TSH is elevated; treatment with thyroxine is not needed, unless serum TSH rises above the normal range [20].

4.6. Prolactin

Regular assessment of menstruation, nipple discharge, gynaecomastia (also in boys), sexual functioning and pubertal development in patients receiving antipsychotic medication is essential. If problems appear temporally related to antipsychotic drug therapy, then check serum prolactin. If serum prolactin is elevated above the normal range, then inquire whether the female patient is taking any form of hormonal contraception and obtain a pregnancy test to rule out pregnancy because both can elevate prolactin levels. In addition, obtain TSH and serum creatinine (to rule out hypothyroidism and renal failure, which can also elevate prolactin) [20].

5. Management and treatment of metabolic adverse effects

Clinicians should be vigilant about the effect on weight gain and all components of the metabolic syndrome when using antipsychotics. In general, prevention of weight gain with non-pharmacologic approaches is preferable, including healthy lifestyle counselling (diet and regular exercise) at the time of treatment initiation and thereafter [125]. Not all antipsychotics are equal in their potential to induce cardiometabolic side-effects and that the least problematic agents should be used first whenever possible [37]. First line treatment options from a cardiometabolic point of view are aripiprazole or ziprasidone (both SGA) or molindone (FGA), as these thee agents have been found to induce the least adverse metabolic side effects. In paediatric populations, however, all antipsychotics have displayed some adverse metabolic effects, so it is unlikely that any truly metabolically neutral FGA or SGA agents exist. The consequence of this finding is that monitoring of adverse metabolic effects is indicated in every patient receiving antipsychotic treatment.

Options for management after weight gain has already occurred include potentially lowering doses or switching to alternative agents with lower risk (aripiprazole or ziprasidone) [10,99]. Alternatively, one could also add a healthy lifestyle intervention, or a medication that can alleviate specific adverse effects [24]. When there is an alternative treatment, the drug will probably be discontinued if an adverse effect becomes a problem that supersedes the benefits of medication [79]. The presented

Table 7
EPA clinical practice guidelines for screening and monitoring.

EAP/EASD/ESC clinical practice guideline		
Ask	Measure	Decide
Personal/family history	Height	Behavioural change (overweight/obesity, prediabetes…)
Cardiovascular disease	Weight	Smoking cessation
Diabetes	Waist circumference	Switch medication
Hypertension	Blood pressure	
Activity level	Fasting glucose	
Diet	Fasting lipids	
Smoking	Prolactine when treatment with prolactin elevating agents	Referral to specialised services when severe abnormalities are present

At minimum, the psychiatric provider should take responsibility for the monitoring of metabolic side effects of psychotropic agents

	Baseline	6 weeks[b]	12 weeks	At least annually thereafter[b]
Medical history	x			
Weight (BMI), waist[a]	x	x	x	x
Blood pressure	x	x	x	x
Fasting glucose	x	x	x	x
Fasting lipids	x	x	x	x
Lifestyle advice	x			x

Adapted from [32].

[a] During initial phase of treatment, it is important to measure weight and height weekly to identify patients who gain weight rapidly; assessment of waist is difficult to interpret in growing youth, if performed, sex- and age-adjusted percentile tables are necessary: http://www.gghjournal.com/volume21/1/ab17.cfm.

[b] US recommendations do not suggest routine glucose and lipid monitoring every 6 weeks and recommend glucose and lipid monitoring every 6 months [23,24].

monitoring and management recommendations in youth treated with antipsychotics are not treatment guidelines [20,24,32,83].

5.1. Body weight

Some studies have indicated that weight control programs focusing on nutrition, exercise and motivation are effective in minimizing weight gain [39,125]. The American Heart Association provided updated dietary recommendations for children (older than 2 years). These guidelines include recommendations that children and adolescents have a balanced caloric intake with sufficient physical activity to achieve an appropriate weight [28].

Therapies that have had some success in producing weight loss or at least stabilizing body weight in paediatric patients receiving antipsychotics include amantadine, metformin, orlistat and topiramate [16,20,23,72,120,126]. A recent systematic review and meta-analysis on the effectiveness of medication used to attenuate antipsychotic-related weight gain only found a significantly greater effect than with placebo for metformin, fefluramine, sibutramine, topiramate and reboxetine. The database was largest for metformin, but a significant weight reduction compared to placebo was only observed after weight gain had already occurred, not when given concurrently with starting the antipsychotic in a preventive fashion. Overall, the authors concluded that at present none of the treatments had sufficient evidence to be recommended for broad clinical use [84], and only two of the 32 trials had been conducted in paediatric patients.

One of these paediatric studies was a randomized, double-blind, placebo-controlled trial that examined metformin treatment of weight gain associated with SGA in children and adolescents. Weight was stabilized in subjects receiving metformin, whereas patients randomized to placebo continued to gain more weight [72]. Metformin therapy was found to be safe and effective in reducing weight gain, impaired insulin sensitivity (metformin decreases insulin resistance), and abnormal glucose metabolism that can result from treatment of children and adolescents with SGA. This is relevant as it can be particularly difficult to successfully institute behavioural and dietary modifications in subjects with psychiatric disorders [72]. A recent open label trial in youth (10–18 years) treated with SGA and metformin showed stabilisation of the weight, and also a significant decrease in triglyceride levels. However, metformin did not improve insulin sensitivity and showed a trend toward increasing both LDL and cholesterol. Nevertheless, the authors concluded that metformin holds promise as a treatment for weight gain in paediatric patients [115].

5.2. Dyslipidemia

Dyslipidemia should be treated initially with dietary measures. If this is not sufficient, drug therapy may be given with gemfibrozil, fenofibrate, a statin, fish oil or niacin [20]. Statins have recently been shown to be both effective and safe in antipsychotic induced dyslipidemia in adults [29,61]. Pharmacologic intervention in children younger than 8 years is only implemented if these patients have a dramatic elevation of cholesterol values ($>$12.93 mmol/l or $>$500 mg/dl) [28].

5.3. Hyperglycaemia and diabetes

Hyperglycemia and diabetes may be treated with diet, oral antidiabetic agents, or insulin, as needed, but it should also be remembered that diabetes induced by SGA agents may be reversible when the drug is stopped or switched to a metabolically more neutral agent [20].

5.4. Prolactin

If other possibilities of prolactin elevation are ruled out and side-effects are severe and persistent, switching to a non-prolactin elevating agent should be considered if dose reduction alone is insufficient. If switching is not an option, a dopamine agonist or partial agonist can be added.

6. Limitations

This review is based on a rather limited number of studies, which often did not present a comprehensive assessment of potential metabolic side-effects of SGA. The proposed clinical practice guidelines were not developed by a multidisciplinary group, did not involve stakeholders and were not supported by official medical societies. Patients were not involved in the creation of these recommendations and the guidelines were not tested in the targeted clinician group.

7. Discussion

The reviewed data suggest that olanzapine is the antipsychotic drug most likely to be associated with weight gain in children and adolescents across different indications, followed by risperidone and quetiapine. Across all studied samples, aripiprazole induced some weight gain, while ziprasidone was weight neutral compared to placebo. However, weight gain with aripiprazole was most pronounced in youth with autism, without available data in patients with autism spectrum disorders for quetiapine or ziprasidone. In the analysis of NNH limited to patients with schizophrenia or bipolar disorder, both aripiprazole and ziprasidone did not differ from placebo nor from each other. This difference in results suggests either that patients with autistic disorder are more vulnerable to weight gain, or that this vulnerability is related to the younger age of these patients or to the likely smaller degree of prior antipsychotic exposure and weight gain, leaving more room to detect the antipsychotic related weight gain. These results are generally similar to studies in adults with schizophrenia and schizophreniform disorders, showing that clozapine and olanzapine were the most likely to lead to weight gain, followed by quetiapine and risperidone. Aripiprazole and ziprasidone were relatively benign, but not without weight increase, especially in first episode patients and those without prior antipsychotic treatment [3,25,39,46,69,77,78,87,99,107,122]. Due to negative metabolic outcomes, recent treatment guidelines for adult patients with schizophrenia have suggested not to use clozapine and olanzapine as first-line agents [12].

At present, there are insufficient data to explore potential dose-related effects of the different antipsychotics in youngsters. Only one paediatric cohort study has examined this question in antipsychotic-naive youth treated for the first three months, finding that weight gain and metabolic adverse effects were dose-related with risperidone, whereas only metabolic adverse effects were dose related with olanzapine, while no dose relationship was observed with aripiprazole and quetiapine [25]. A recent systematic review in adults on the subject did not find strong evidence that metabolic changes were dose-related [113].

Patients who are previously unexposed to antipsychotics are particularly vulnerable to weight gain and this weight gain occurs rapidly within the first few weeks [25,122]. Making predictions on who is more likely to gain weight on a specific agent is difficult. Some clinical variables have been associated with a greater liability for weight gain: younger age, presence of overweight or obesity; being underweight, familial history of obesity, non-white ethnicity, tendency to eat when under stress, cannabis use [3,32]. Early

weight gain (≥7% body weight within the first six weeks of olanzapine treatment) appears to be a good predictor of subsequent significant weight gain [32,129]. In addition to lower baseline BMI, higher haemoglobin level, red blood cell count and hematocrit were statistically significant biochemical predictors of greater BMI increase and obesity development in (the first episode of) schizophrenia [11]. Furthermore, children and adolescents with mental health problems often have multiple risk factors, including poor nutrition, inadequate exercise, substance abuse and lack of adequate health care monitoring [127].

Mechanisms of weight increase associated with pharmacological treatment have not been fully understood. Potential mechanisms include disease related factors (changes in the metabolic rate, appetite changes), drug related factors (impact of drugs on serotonergic, histaminergic and noradrenergic transmission; satiety changes, sedation, dry mouth) and improvement related factors (dietary changes, changes in physical activity) [32,38–40].

A small study indicated that weight gain during risperidone treatment is reversible after medication discontinuation in children with disruptive disorders. But far more data are needed before an assumption can be made that this is the case for all children [79]. Of note, weight gain associated with SGA in children did not differ between those taking and those not taking stimulant co-medication [48,120].

Obesity has, besides the effect on medical morbidity, an impact on self-esteem, social development and compliance [39,67,106]. Weight gain is a serious complication in children and adolescents because weight gain is associated with health and psychosocial issues at a time when self-esteem and sexual functioning develop. Weight gain can also be associated with the development of eating disorders and depression [23].

Because of variable individual sensitivities, not every patient with hyperprolactinaemia develops symptoms. Antipsychotic-induced hyperprolactinaemia in children may normalize over time, but there are concerns about the potential for delayed pubertal development. Based on limited and solely medium term-data, most children and adolescents exposed to risperidone, which tends to raise prolactin the most, seem to progress normally through puberty [20,121]. In one study, 28% of the children had prolactin levels of more than two-times the upper limit of normal, while none of the children showed clinical signs of hyperprolactinaemia at 10 weeks [41]. Nevertheless, unless sufficiently large, long-term studies are completed in strictly peripubertal subjects that directly assess Tanner staging, it is not possible to fully rule out a potentially adverse effect of persistent prolactin elevation during development.

The exact effect of hyperprolactinaemia during puberty, an essential period for the development of bone mass, is largely unknown, although one might expect that hypogonadism, the shutdown of sex hormone production that can result from hyperprolactinaemia during this period would affect achievement of peak bone mass. On the other hand, the majority of peak bone mass is determined genetically, while up to 20% may be affected by factors such as the environment or hormones during puberty. Most of the studies in the endocrine literature addressing prolactinomas and changes in bone density involve prolactin levels much higher than the range one generally sees antipsychotic treatment [106]. Gynaecomastia can be a sign of hyperprolactinaemia in girls as well as in boys, but girls are more likely to develop this adverse effect [20,71].

The recent European guidelines on screening and monitoring for diabetes and CVD risk-factors mentioned the risks in children and adolescents, but did not formulate specific guidance for this population. These guidelines were a joint initiative of the European Psychiatric Association (EPA), the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC) [32].

The need for screening, monitoring and prevention of diabetes and other CVD-risk factors has been acknowledged in the psychiatric literature and some of the more recent general treatment guidelines for adults with severe mental illness. But the evaluation of screening practices by clinicians consistently shows that these are suboptimal [13,62,66,89–91,95,97]. The poor rate of screening was recently also confirmed in children treated with antipsychotics [92], although there is agreement that routine screening and monitoring of side-effects is warranted. Strategies need to be developed for implementing the existing guidelines in daily, routine clinical practice.

8. Summary and conclusion

The aim of this paper was to increase the awareness of health professionals caring for young patients that there is a need to screen regularly for cardiometabolic adverse effects in this vulnerable population. Prevention of these side-effects, including antipsychotic choice, is essential.

Evidence of efficacy and safety of the use of atypical antipsychotics in children and adolescents is growing, but still limited, especially regarding the cardiometabolic safety of the available treatment alternatives. However, the study of antipsychotic cardiometabolic safety is important for two main reasons. First, treatment with antipsychotics is often continued for long periods of time and during critical stages of child development. Second, exposure of a developing organism to a psychotropic medication, even for a short time, may have effects that are long-lasting or that emerge later in life. Research on short- and long-term safety of psychotropic drugs should be considered a priority in paediatric psychopharmacology [50,105].

Child psychiatrist and other mental health personnel prescribing antipsychotics have to coordinate the assessment and management within a shared care model with general and specialist health-care services. A good collaboration between child and adolescent psychiatrists, general practitioners and paediatricians is essential for the monitoring and management of severe adverse effects of antipsychotics in children and adolescents. Only by including such efforts can the intricately linked mental and physical health of youth be maximized.

Contributors

M. De Hert and M. Dobbelaere wrote the first draft of the paper. M. Dobbelaere did the initial systematic review of the literature. Data-extraction and analysis from the systematic review was done by M. De Hert and E. Sheridan. E. Sheridan did the meta-analysis. All authors contributed to the subsequent versions of the paper.

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