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SYSTEMATIC REVIEW

Weight Gain and Other Metabolic Adverse Effects Associated with Atypical Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-analysis

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Abstract

Objectives The aims of this study were to provide a systematic review and meta-analysis of the effects of atypical antipsychotics in children and adolescents on weight gain (primary objective) and other metabolic parameters (secondary objective).

Methods A systematic literature review and meta-analysis of double-blind, randomized, controlled trials were conducted. The data sources used were as follows: EMBASE, PubMed, BIOSIS, International Pharmaceutical Abstracts, The Cochrane database (Clinical Trials), Clinical Trials Government Registry, The metaRegister of Controlled Trials, WHO (World Health Organization) Clinical Trials Registry Platform, and PsycINFO®. Hand searching was also carried out by examining the reference lists of identified studies. Double-blind, randomized, controlled trials investigating the metabolic adverse effects (weight gain, lipid, glucose, and prolactin level abnormalities) associated with atypical antipsychotic use in children and adolescents aged $\leq$18 years were included, irrespective of whether the investigation of adverse effects was a primary or secondary endpoint.

Results We identified 21 studies of drug versus placebo that met the inclusion criteria, with a total of 2,455 patients, 14 studies for risperidone (1,331 patients), three for olanzapine (276 patients), and four for aripiprazole (848 patients). Compared with placebo, the mean weight increases for each drug were olanzapine 3.45 kg (95 % CI 2.93–3.98), risperidone 1.77 kg (95 % CI 1.35–2.20), and aripiprazole 0.94 kg (95 % CI 0.65–1.24). Regarding other metabolic abnormalities, eight studies reported statistically significant increases in prolactin with risperidone; two reported a statistically significant increase in glucose, total cholesterol, and prolactin with olanzapine; and three studies reported a statistically significant decrease in prolactin with aripiprazole. Data on lipid, glucose, and prolactin level changes were too limited to allow us to perform a meta-analysis.

Conclusions Olanzapine, risperidone, and aripiprazole were all associated with statistically significant weight gain. Olanzapine was associated with the most weight gain and aripiprazole the least. For the secondary outcome, although a number of active comparator trials were identified, data were not available for meta-analysis and were too limited to allow firm conclusions to be drawn.

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1 Introduction

Atypical antipsychotics (second-generation antipsychotics) have been regarded as a significant advance in psychopharmacotherapy because they have been reported as having a lower risk of extrapyramidal side effects (EPS) compared with the first-generation drugs [1–3]. In addition to their use in treating psychosis and mood disorder, mainly in adults and older teenagers, atypical antipsychotics have demonstrated their efficacy in the treatment of young people with disruptive behaviors in autism and intellectual impairment (mental retardation) in randomized controlled trials (RCTs) [1, 4, 5]. Although the use of atypical antipsychotics for the treatment of many psychiatric conditions in children and adolescents is growing, these drugs are often used off-label. A few short-term, placebo-controlled trials support the acute efficacy of risperidone, aripiprazole, olanzapine, or quetiapine in decreasing psychotic symptoms in adolescents and manic symptoms of bipolar disorder in children and adolescents [6–9].

In the last decade, the use of psychotropic drugs, especially atypical antipsychotics, has increased in children and adolescents [10–12]. A study using a research database in the USA showed that overall use of psychotropic medication in mental health patients aged 0–17 years increased from 59.5 % in 1997 to 62.3 % in 2000, with atypical antipsychotics having the highest change in utilization (138.9 %) over this period [13]. With this increased use there has been growing concern that certain drugs appear to be associated with metabolic dysfunction such as weight gain, diabetes mellitus, hyperglycemia and hyperlipidemia [11, 12]. These abnormalities may be at least partly due to the antagonism of atypical antipsychotics to various receptors in different neurotransmitter systems (serotonergic, dopaminergic, cholinergic, histaminergic, and others) [14–17].

Since childhood and adolescence involve important developmental periods of physical growth, together with motor, emotional, and cognitive development, the use of drugs that affect these aspects of development should be carefully considered and closely monitored [18]. These metabolic abnormalities are not only risk factors for increased morbidity and mortality, but may also impair patient adherence to treatment [19–22].

Several prospective studies have stated that weight gain and other metabolic abnormalities during childhood strongly predict obesity, metabolic syndrome, hypertension, cardiovascular disease, and osteoarthritis risk in adulthood [18–22].

The effects of atypical antipsychotics on glucose and lipid profiles in children and adolescents have been less well studied than have the effects in adults. Only a limited number of trials have evaluated the impact of these drugs in young patients [23]; in contrast, there have been several studies and meta-analyses in adults [24–26]. A meta-analysis by Allison et al. [25] in adults estimated that the mean weight gain after 10 weeks of treatment was 3.99 kg for clozapine, 3.51 kg for olanzapine, and 2.00 kg for risperidone. In another meta-analysis of adult data, Leucht et al. [26] found that clozapine and olanzapine were the most likely to be associated with weight gain, and abnormalities in glucose and lipids, followed by quetiapine and then risperidone. Regarding prolactin levels, risperidone and amisulpride were the most likely medications to be associated with an increase in these levels. However, data regarding weight gain and metabolic abnormalities in children and adolescents treated with antipsychotics are still limited [27, 28]. Our objective was to conduct a systematic review and meta-analysis of double-blind RCTs investigating the metabolic adverse effects of atypical antipsychotic medication prescribed to children and adolescents.

2 Methods

2.1 Literature Search

In order to identify RCTs and decrease location bias, we searched multiple databases including: EMBASE (1980–2010 Week 21), PubMed (1969–2010), BIOSIS (1969–2009 Week 27), International Pharmaceutical Abstracts (1970–May 2010), The Cochrane database (Clinical Trials), Clinical Trials Government Registry (http://www.clinicaltrials.gov), The metaRegister of Controlled Trials (www.controlled-trials.com), WHO (World Health Organization) Clinical Trials Registry Platform (http://www.who.int/ctrp/en/), and PsycINFO® (1978–2012) (http://www.apa.org/pubs/databases/psycinfo/index.aspx). In addition to this, the reference sections of all retrieved articles were manually searched for further relevant publications. The search strategy and terms are provided in Table 1.

2.2 Eligibility Criteria

We included double-blind RCTs investigating the metabolic adverse effects (weight gain, lipid, glucose, and prolactin level abnormalities) of atypical antipsychotics in children and adolescents aged ≤18 years. All such studies were included, irrespective of whether the investigation of adverse effects was a primary or secondary endpoint. All studies reporting the use of atypical antipsychotics, irrespective of the diagnosis or indication of drug used, were included, except studies of patients with anorexia nervosa, bulimia nervosa, or concurrent pre-existing medical conditions that might have affected weight gain (e.g.,

Table 1 Search strategy and terms

Subjects		Drug		Study design		Metabolic adverse effect
'Children' OR 'Child' OR 'Paediatric' OR 'Pediatric' OR 'Juvenile' OR 'School child' OR 'Youth' OR 'Young' OR 'Adolescents' OR 'Adolescence' OR 'Teenage'	AND	'Atypical antipsychotic drug(s)' OR 'Atypical antipsychotic medication(s)' OR 'New neuroleptic' OR 'Antipsychotic drug(s)' OR 'Second generation antipsychotic(s)' OR 'Antipsychotic(s)' OR 'Risperidone' OR 'Clozapine' OR 'Olanzapine' OR 'Aripiprazole' OR 'Quetiapine' OR 'Sertindole' OR 'Zotepine' OR 'Sulpiride' OR 'Amisulpride' OR 'Haloperidol' OR 'Ziprasidone' OR 'Paliperidone' OR 'Asenapine' OR 'Loperidone' OR 'Lurasidone'	AND	'Randomised controlled trials' OR 'Randomised controlled trial' OR 'Randomised controlled study' OR 'Randomised controlled studies' OR 'Randomised double blind placebo controlled trial' OR 'Randomised double blind placebo controlled study' OR 'Randomised double blind placebo controlled studies' OR 'Random allocation' OR 'Controlled clinical trial' OR 'Clinical trial' OR 'Clinical study' OR 'Double blind method' OR 'Double blind trial' OR 'Single masked method'	AND	'Weight gain' OR 'Obesity' OR 'Over weight' OR 'Metabolic side effects' OR 'Side effects' OR 'Side effect' OR 'Adverse effect' OR 'Adverse effects' OR 'Diabetes' OR 'Hyperinsulinemia' OR 'Hyperglycemia' OR 'Lipid abnormalities' OR 'Hyperlipidaemia' OR 'Dyslipidemia' OR 'Metabolic syndrome'

Cushing's syndrome, renal disease, or diabetes). There was no language restriction. We excluded open-label trials, crossover design trials, reviews, case reports, observational cohort studies, editorials, and studies published only in abstract form.

2.3 Outcomes

The primary outcome of the study was to determine whether there was a significant mean weight gain associated with atypical antipsychotic drug treatment in children and adolescents. The secondary outcome was to determine whether there were any other significant reported metabolic adverse effects, including raised prolactin, lipid abnormalities, hyperglycemia, diabetes, or metabolic syndrome.

2.4 Data Extraction and Quality Assessment

Two reviewers (N.B.A., Y.L.) carried out the electronic searches and reviewed the articles independently. Any articles that did not meet the eligibility criteria were excluded on initial review. We also extracted information on the methodological quality of the studies, including, for example, whether the trials were described as double-blind and who was blinded. Articles marked for potential inclusion were obtained electronically or in paper copy and assessed again for inclusion. Disagreement was resolved by consensus. All available studies meeting the inclusion criteria were included and appraised. A standardized proforma was used to record the details of the papers reviewed. All search results were merged using Reference Manager® (Thomson Reuters, New York, NY, USA) and examined. Duplicates and irrelevant reports were removed.

Details recorded in the proforma included indication of atypical antipsychotic use, interventions, trial duration, study design, country of study, mean age of participants, participants' sex, number of participants, and weight increase. The QUORUM (Quality of Reporting of Meta-analysis) was followed for reporting our review [29, 30]. For the assessment of the quality of the trials, the Jadad scale was used [31]. The scale is a 3-point questionnaire, each question to be answered with either 'yes' or 'no'. Each 'yes' would score a single point, each 'no' no point; there were to be no fractional points. The questions were about randomization, blinding, withdrawals, and dropouts. Additional points were given if the method of randomization was described in the paper, and was appropriate, and the method of blinding was described, and was appropriate. Therefore, a paper reporting a clinical trial could receive a Jadad score between 0 and 5; trials with a score of <3 were considered to be of poor quality and hence excluded from the analysis.

2.5 Analysis

We used a random effects model with Review Manager (RevMan 5.0.20; The Cochrane Collaboration, Oxford, UK) [32]. This was used because a random effects model does not assume identical effects across studies, and therefore allows for between-study heterogeneity [32].

The primary outcome analysis (mean weight gain) was based upon intent-to-treat data. Data of secondary outcomes (other metabolic events) were taken from the same trials. The mean weight gain, standard deviation (SD), and sample size of all trials were extracted by N.B.A. Where SDs were not reported, they were obtained from standards errors, *t* values, or *p* values that related to the differences between means in two groups, or data were obtained directly from the study authors where necessary. The degree of heterogeneity between studies was assessed using the DerSimonian and Laird Q test, and the I^2 statistic was used to describe the percentage of total variation across trials. A funnel plot was produced for the risperidone versus placebo group to assess publication bias, but could not be produced for the remaining groups because of the small number of studies identified.

3 Results

The initial electronic search identified 1,906 articles, of which 1,739 articles were excluded for the following reasons: duplicates ($n = 400$); study participants aged >18 ($n = 162$); open-label trials ($n = 208$); and other reasons, such as not relevant, case reports, reviews, comment, and editorial ($n = 969$) (Fig. 1). There were 167 articles that remained. Studies were classified into two groups: trials of drug versus placebo, and trials of drug versus drug.

3.1 Drug Versus Placebo

In this first group, initially 88 studies were included; however, 63 studies were excluded because they were either irrelevant or did not meet the inclusion criteria. The remaining 25 studies were further evaluated. An additional four studies were excluded for the following reasons: detailed data could not be obtained [33, 34]; treatment indication was anorexia nervosa [35]; and no direct comparison was made between the drug and placebo [36]. In total, 21 studies were included (Table 2).

3.2 Drug Versus Drug

For the second group, initially 79 studies were included; however, 68 studies were excluded because they were either irrelevant or did not meet the inclusion criteria. Only 11 studies were identified as relevant; however, they were further evaluated and all were excluded for the following reasons: weight was only reported at baseline [57], weight was not reported [58–62], or detailed data could not be obtained [63].

Therefore, no studies were left in the drug versus drug group, so we were unable to perform a meta-analysis of this comparison.

3.3 Results of Meta-Analysis

3.3.1 Primary Outcome

3.3.1.1 Risperidone Versus Placebo (14 Studies) Compared with placebo, the mean weight gain associated with risperidone was 1.77 kg (95 % CI 1.35–2.20) (Fig. 2). Risperidone was therefore associated with a statistically significant weight gain compared with placebo ($p < 0.00001$).

Figure 3 shows a funnel plot, used to estimate publication bias in the studies of risperidone versus placebo. The plot is symmetrical, implying absence of publication bias, except for two studies: one at the bottom of the figure (Van Bellinghen and De Troch [39]) and the study at the far right end (Findling et al. [37]). Bias could be due to a small sample size in both studies, which gives effect estimates that scatter more widely in the graph (Fig. 3) [29].

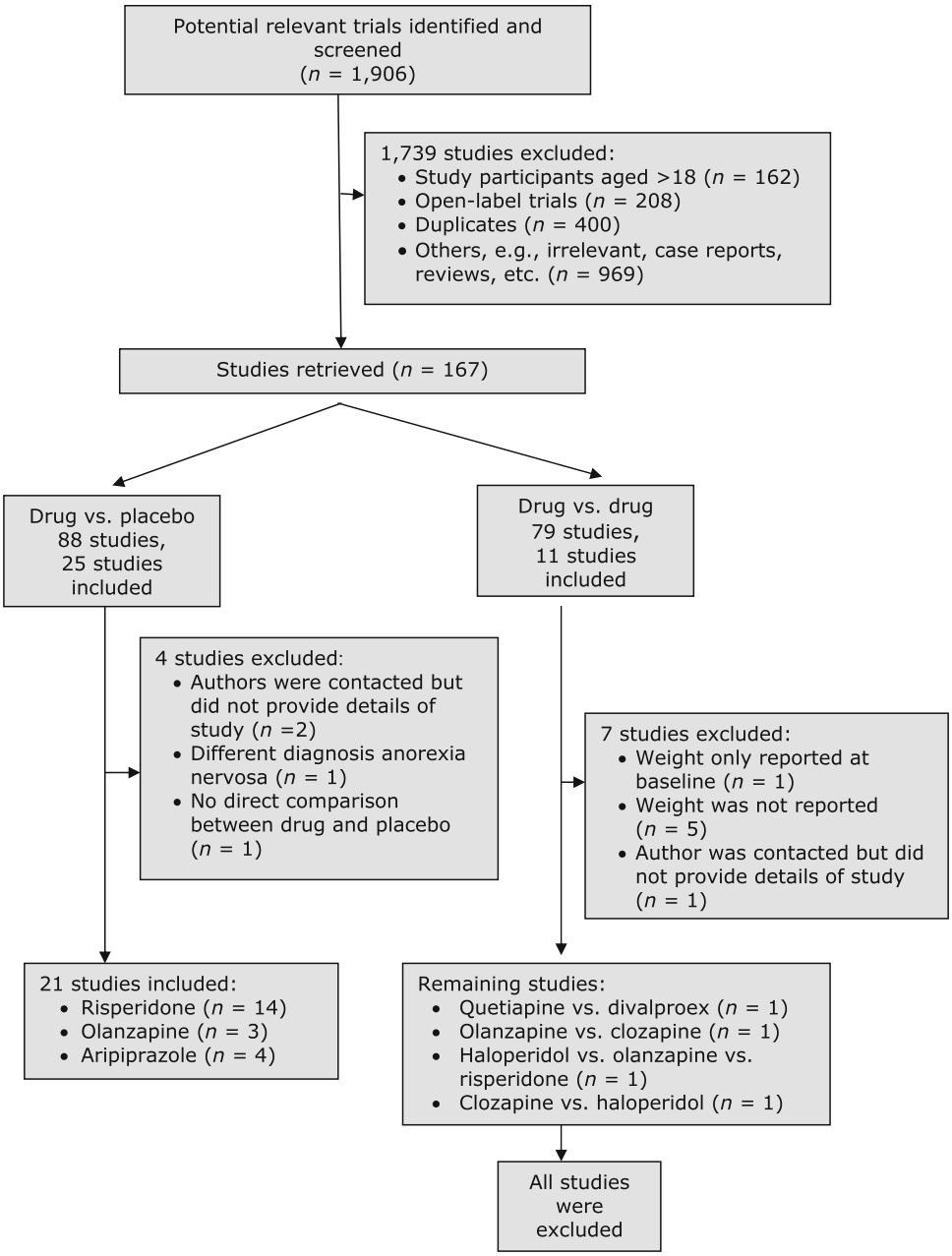
3.3.1.2 Olanzapine Versus Placebo (3 Studies) Compared with placebo, the mean weight gain associated with olanzapine was 3.45 kg (95 % CI 2.93–3.98) (Fig. 4). This implies that olanzapine is also associated with statistically significant weight gain compared with placebo ($p < 0.00001$).

3.3.1.3 Aripiprazole Versus Placebo (4 Studies) Compared with placebo, the mean weight gain associated with aripiprazole was 0.94 kg (95 % CI 0.65–1.24) (Fig. 5). This implies that aripiprazole was also associated with statistically significant weight gain compared with placebo ($p < 0.00001$).

3.3.2 Secondary Outcomes

Regarding other metabolic abnormalities, eight studies reported statistically significant increases in prolactin with risperidone; two reported a statistically significant increase in glucose, total cholesterol, and prolactin with olanzapine, and three studies reported a statistically significant decrease in prolactin with aripiprazole. Changes in prolactin, glucose, and lipids in the included randomized trials are shown in Table 3. For the secondary outcomes, although a number of active comparator trials were identified, insufficient data were available for meta-analysis.

Fig. 1 Review flowchart



3.4 Heterogeneity

The *p* value of the Chi-squared test in Fig. 2 shows evidence of statistical variability between studies, with the I^2 value showing considerable heterogeneity in the primary outcome variable (68 %). However, for the comparisons versus placebo shown in Figs. 4 and 5, there is no evidence of heterogeneity.

3.5 Quality of the Reports (Jadad Score)

In our meta-analysis, all trials included had a Jadad score of 4, except one study that had the full score of 5 (Table 2).

4 Discussion

The main finding from this review is that there is published evidence to indicate that treatment of young people aged ≤18 years with the atypical antipsychotic drugs risperidone, olanzapine, and aripiprazole is associated with statistically significant mean weight gain compared with placebo and that the effect appears to be greatest with olanzapine.

Regarding the other metabolic abnormalities, 13 studies reported statistically significant changes in lipid profile (triglyceride or cholesterol), glucose levels, and serum prolactin. In some of the included papers, it was not clear

Table 2 Summary of randomized controlled trials included in the meta-analysis

Source	Intervention	Indication	Age range (years)	No. of patients	Country	Duration (weeks)	Weight increase (kg ± SD)	No. of females	Jadad scale points (0–5)
Risperidone vs. placebo									
Findling et al., 2000 [37]	Ris (1.5–3.0 mg/day) or P	Conduct disorder	6–14	20	USA	10	Ris: 4.2 ± 0.7; P: 0.9 ± 0.74	1	4
Buitelaar et al., 2001 [38]	Ris (1.4–4 mg/day) or P	Disruptive behavior and aggression	11–15	38	Netherlands	6	Ris: 2.3 ± 2.58; P: 0.6 ± 2.58	5	4
Van Bellinghen and De Troch, 2001 [39]	Ris (mean total dose 1.2 mg/day) or P	Disruptive behavior	6–14	13	Belgium	4	Ris: 1.8 ± 2.07; P: 0.6 ± 2.07	8	4
Snyder et al., 2002 [40]	Ris (0.4–3.80 mg/day) or P	Disruptive behavior	5–12	110	Canada, USA, and South Africa	6	Ris: 2.2 ± 9.74; P: 0.2 ± 9.12	27	4
Aman et al., 2002 [41]	Ris (0.02–0.06 mg/kg/day) or P	Disruptive behavior	5–12	118	USA	6	Ris: 2.2 ± 1.8; P: 0.9 ± 1.5	21	4
Research Units on Pediatric Psychopharmacology Autism Network (RUPP), 2002 [42]	Ris (0.5–3.5 mg/day) or P	Autism and serious behavioral problems	5–17	101	USA	8	Ris: 2.7 ± 2.9; P: 0.8 ± 2.2	19	4
Shea et al., 2004 [43]	Ris (0.01–0.06 mg/kg/day) or P	PDD, disruptive behavior	5–12	79	Canada	8	Ris: 2.7 ± 2.0; P: 1.0 ± 1.6	18	4
Reyes et al., 2006 [44]	Ris (0.25–1.5 mg/day) or P	Disruptive behavior	5–17	335	Belgium, Germany, UK, Israel, Netherlands, Poland, South Africa, and Spain	26	Ris: 2.1 ± 2.7; P: –0.2 ± 2.2	45	4
Nagaraj et al., 2006 [45]	Ris (1 mg/day) or P	Autism	2–9	40	India	24	Ris: 2.81 ± 2.04; P: 1.71 ± 1.3	6	4
Armenteros et al., 2007 [46]	Ris (0.5–2.0 mg/day) or P	ADHD	7–12	25	USA	4	Ris: 0.9 ± 13.36; P: 0.6 ± 16.83	3	4
Anderson et al., 2007 [47]	Ris (mean 1.80–1.96 mg/day) or P	Autism	5–17	101	USA	8	Ris: 2.7 ± 2.9; P: 0.8 ± 2.2	19	4
Luby et al., 2006 [48]	Ris (0.5–1.5 mg/day) or P	Autism	2.5–6	24	USA	26	Ris: 2.96 ± 2.53; P: 0.61 ± 1.10	6	4
Haas et al., 2009 (a) [49]	Ris (1–3 mg/day) or P	Acute exacerbation of schizophrenia	13–17	160	USA	6	Ris: 1.4 ± 1.8; P: 0.12 ± 1.5	116	4
Haas et al., 2009 (b) [50]	Ris (0.5–2.5 mg/day or 3–6 mg/day) or P	Bipolar, mania	10–17	169	USA	3	Ris: 1.63 ± 2.08; P: 0.7 ± 1.9	87	4
Olanzapine vs. placebo									
Hollander et al., 2006 [51]	Ola (2.5–5 mg/day) or P	PDD	6–14	11	USA	8	Ola: 3.3 ± 2.2; P: 0.6 ± 0.6	2	4
Tohen et al., 2007 [52]	Ola (2.5–20 mg/day) or P	Bipolar mania	13–17	161	USA, Puerto Rico	3	Ola: 3.66 ± 2.18; P: 0.3 ± 1.67	–	4
Kryzhanovskaya et al., 2009 [53]	Ola (2.5–10 mg/day) or P	Schizophrenia	13–17	107	USA	6	Ola: 4.26 ± 3.33; P: 0.13 ± 2.8	32	4

Table 2 continued

Source	Intervention	Indication	Age range (years)	No. of patients	Country	Duration (weeks)	Weight increase (kg ± SD)	No. of females	Jadad scale points (0–5)
Aripiprazole vs. placebo									
Findling et al., 2008 [6]	Arip (10 or 30 mg/day) or P	Schizophrenia	13–17	302	USA, Europe, South Africa, South America, and Asia	6	Arip 10 mg/day: no change; Arip 30 mg/day: 0.2 ± 2.3; P: 0.8 ± 2.6	131	5
Tramontina et al., 2009 [54]	Arip (10 or 30 mg/day) or P	ADHD	8–17	43	Brazil	6	Arip: 1.19 ± 1.50; P: –0.7 ± 1.1	17	4
Owen et al., 2009 [55]	Arip (5, 10, or 15 mg/day) or P	Autism	6–17	98	USA	8	Arip: 2.0 ± 2.01; P: 0.8 ± 2.03	12	4
Marcus et al., 2009 [56]	Arip (5, 10, or 15 mg/day) or P	Autism	6–17	218	USA	8	Arip 5 mg/day: 1.3 ± 2.23; Arip 10 mg/day: 1.3 ± 2.23; Arip 15 mg/day: 1.5 ± 2.2; P: 0.3 ± 2.24	23	4

ADHD attention-deficit hyperactivity disorder, *Arip* aripiprazole, *Ola* olanzapine, *P* placebo, *PDD* pervasive developmental disorder, *Ris* risperidone, *SD* standard deviation, – indicates not reported

whether the authors were referring to clinical significance or statistical significance (Table 3). For serum prolactin, with long-term risperidone treatment in children and adolescents, levels tended to rise and peak in the beginning of treatment then steadily decline to values within or very close to normal range [64]. It was also noted that, in the aripiprazole study by Findling et al. [6], patients were required to discontinue prohibited medications, including mood stabilizers, antidepressants, and other psychotropics, at least 3 days before the initiation of treatment. For any discontinuing a medication that raised the prolactin level, this would contribute to the reduction in prolactin level on commencement of aripiprazole.

Recent studies suggest that hyperprolactinemia (at levels leading to hypogonadism) is associated with osteoporosis [65]. Childhood and adolescence involve important developmental periods of physical growth and bone mineralization, and hyperprolactinemia (which may lead to marked reduction in estrogen) can cause a decrease in bone density that may not improve later in life. Other unconfirmed potential risks from childhood hyperprolactinemia might include risk of breast cancer and pituitary tumors [23].

4.1 Comparison with Other Studies

Our meta-analysis revealed that olanzapine appeared to be the atypical antipsychotic associated with the greatest potential to induce weight gain compared with placebo. This finding is consistent with previous published studies of the use of atypical antipsychotics in adults [66–68] and young people [9, 24, 27, 28, 69–71].

In a study of 40 adult patients with borderline personality disorder randomly assigned to olanzapine or placebo, the mean baseline to endpoint weight gain was greater with olanzapine (3.71 kg) than with placebo (0.08 kg) [67]. In a prospective 12-week study assessing weight gain in 50 adolescents receiving olanzapine, risperidone, and haloperidol, the mean weight gain was 7.2 kg, 3.9 kg, and 1.1 kg, respectively, from baseline to endpoint [68].

4.2 Clinical Implications

The metabolic effects of antipsychotic drugs should be considered when planning the treatment strategy for individual patients. Baseline measurement of weight and height should be conducted, and any changes monitored. It has been recommended that plasma glucose, lipids, and prolactin should also be measured and regular follow-up should be individualized [65]. For example, according to NICE guidelines for mental health and behavioral disorders (2006) [72], baseline screening for weight and height should be monitored monthly for 6 months then every 6 months. Strategies for the management of drug-induced

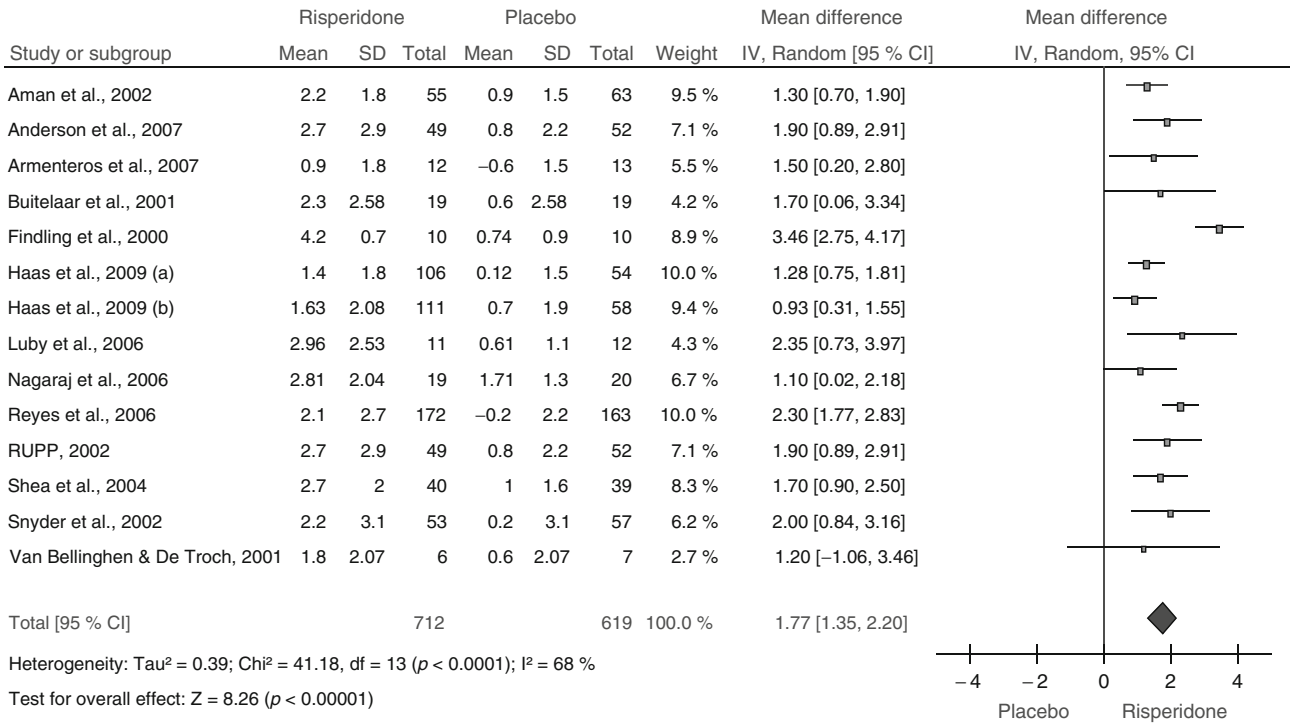


Fig. 2 Results of the meta-analysis of the primary outcome: weight gain induced by atypical antipsychotic drugs prescribed to children and adolescents. Risperidone versus placebo [37–50]. **a** Hass et al. [49]; **b** Hass et al. [50]. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

weight gain include therapeutic approaches, such as lifestyle change (diet, exercise) and pharmaceutical intervention. However, the prescription of additional medication to overcome the adverse effects of medication already prescribed should, if possible, be avoided.

The choice of the appropriate atypical antipsychotic drug should be based on treatment goals, the likely therapeutic benefit, the child's condition, possible adverse effects, and medication cost. Cochrane systematic reviews are carried out using strictly defined criteria. One relevant Cochrane review was found, although it should be noted that it was not specifically in young people. This was an evaluation of the effects of aripiprazole compared with other atypical antipsychotic drugs for patients with schizophrenia and schizophrenia-like psychosis. Four trials were examined in this review: two comparing aripiprazole against placebo and two aripiprazole with risperidone. Aripiprazole was less effective than olanzapine, but was associated with fewer adverse effects, such as weight gain and sedation. Compared with risperidone, there were no differences in efficacy; limited data were available on EPS, cholesterol, glucose, and weight gain [73]. In an add-on or switching study of aripiprazole in adults with psychosis, a significant reduction in prolactin was found [74], which was associated with a significant improvement in quality of life [75]. The evidence was, however, limited. No similar analyses were found for young people, where the numbers would be even smaller; it is consequently not possible to make clear recommendations with regard to the antipsychotic drug of choice in children and teenagers on the basis of Cochrane reviews.

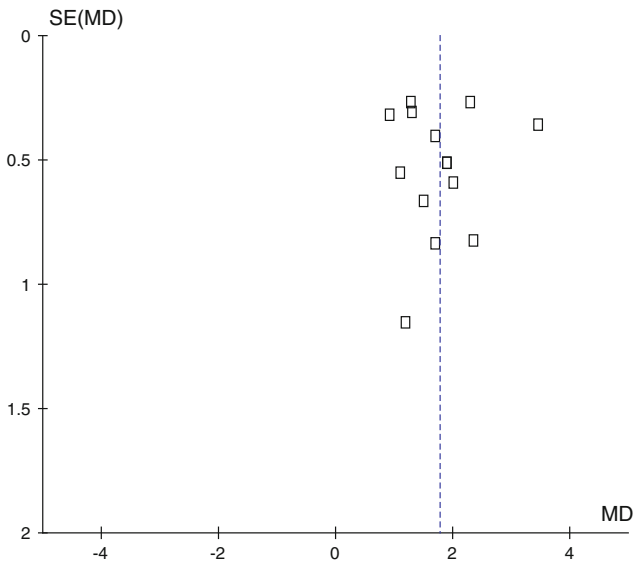


Fig. 3 Funnel plot of comparison: risperidone versus placebo; outcome: weight gain. *MD* mean difference, *SE(MD)* standard error of the mean difference

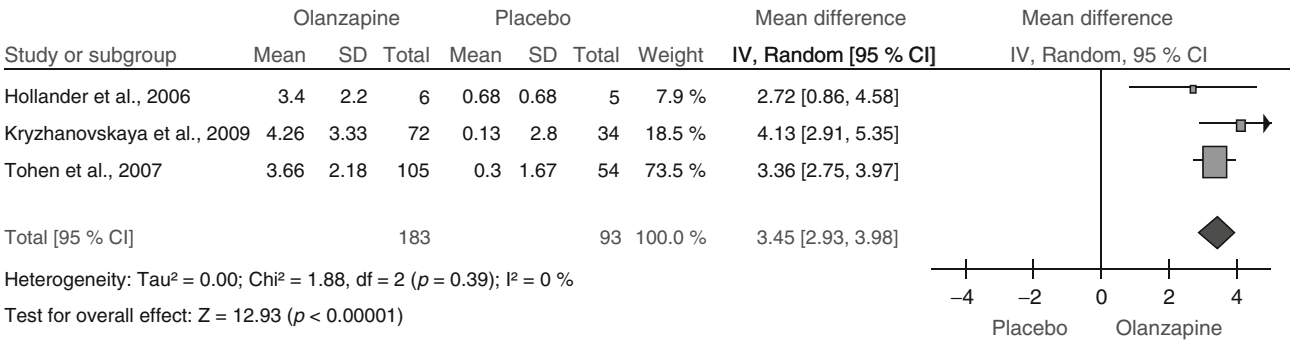


Fig. 4 Results of the meta-analysis of the primary outcome (weight gain): olanzapine versus placebo [51–53]. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

4.3 Limitations

This review is based on a limited number of studies, most of them of short duration. The majority of trials lasted for less than 10 weeks, which is sufficient to show change in weight gain, but may not be enough to show abnormalities in lipid profile. Although our results give a clear indication of a statistically significant mean weight gain associated with risperidone, olanzapine, and aripiprazole treatment in groups of young people, our mean weight gain results do not indicate changes in individuals, some of whom may gain large amounts of weight while others may gain none at all. As more data become available, it should be possible to deduce more definitive information on the metabolic adverse effects of these drugs.

5 Conclusions

This meta-analysis has demonstrated that there is a statistically significant association between mean weight gain and the administration of risperidone, olanzapine, and aripiprazole in young people. The mean weight gain appears to be greatest for olanzapine and least for aripiprazole. Weight gain can impair both physical health and psychological well-being; therefore, it will be important to determine factors that are associated with high risk of weight gain with atypical antipsychotics; these factors may include a genetic predisposition and lifestyle issues, particularly diet and exercise. The little data available on the secondary outcomes do not allow any firm conclusions to be drawn with regard to other metabolic changes. Although atypical antipsychotic medications have been studied for a range of psychiatric conditions in children and adolescents, the majority of these drugs are not licensed in children and many of the indications are for off-label use. This highlights a major gap in evidence-based psychiatric practice, especially as most trials involving children and adolescents were conducted on small sample sizes and with short treatment durations.

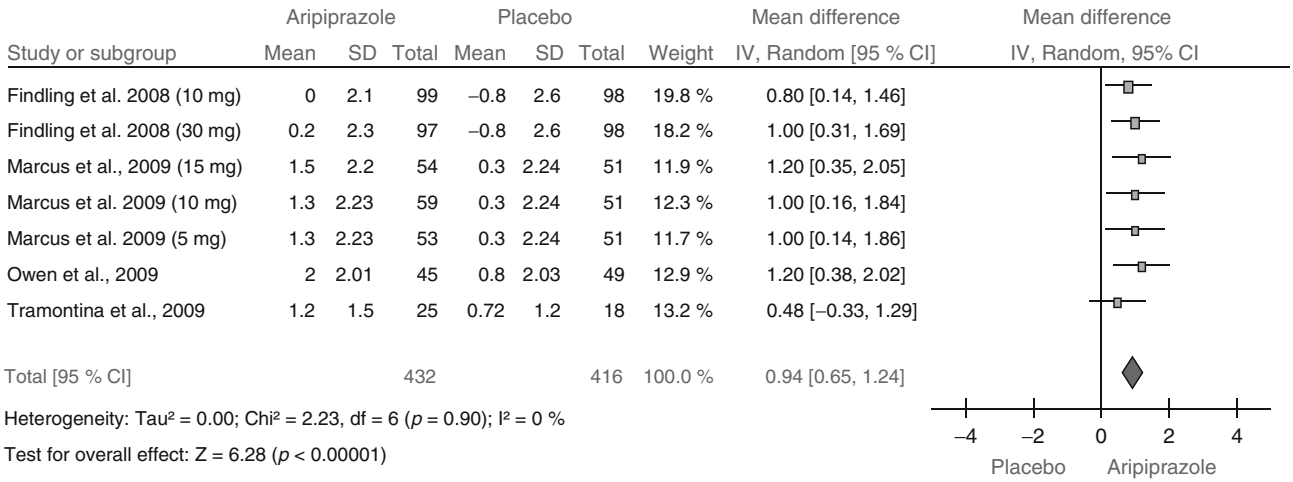


Fig. 5 Results of the meta-analysis of the primary outcome (weight gain): aripiprazole versus placebo [6, 54–56]. *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

Table 3 Summary of changes in lipids, glucose, and prolactin in randomized controlled trials included in the meta-analysis

Study, year	Effect on lipids	Effect on prolactin	Effect on glucose
Risperidone vs. placebo			
Findling et al., 2000 [37]	No data	No data	No data
Buitelaar et al., 2001 [38]	No data	Statistically significant increase ($p < 0.01$)	No data
Van Bellinghen and De Troch, 2001 [39]	No data	No data	No data
Snyder et al., 2002 [40]	No data	Statistically significant increase ($p < 0.003$ girls; $p < 0.001$ boys)	No data
Aman et al., 2002 [41]	No data	Statistically significant increase for boys ($p < 0.001$), but not for girls ($p = 0.13$)	No data
Research Units on Pediatric Psychopharmacology Autism Network (RUPP), 2002 [42]	No data	No data	No data
Shea et al., 2004 [43]	No data	No data	No data
Reyes et al., 2006 [44]	No data	Significant increase[a]	No change
Nagaraj et al., 2006 [45]	No data	No data	No data
Armenteros et al., 2007 [46]	No data	No data	No data
Anderson et al., 2007 [47]	No data	Statistically significant increase ($p < 0.0001$)	No data
Luby et al., 2006 [48]	No data	Statistically significant increase ($p < 0.05$)	No data
Haas et al., 2009 (a) [49]	No change	Dose-dependent significant increase[a]	No change
Haas et al., 2009 (b) [50]	No change	Dose-dependent significant increase[a]	No change
Olanzapine vs. placebo			
Hollander et al., 2006 [51]	No data	No data	No data
Tohen et al., 2007 [52]	Statistically significant increase ($p < 0.01$)	Statistically significant increase ($p < 0.001$)	Statistically significant increase ($p < 0.002$)
Kryzhanovskaya et al., 2009 [53]	Statistically significant increase ($p < 0.006$)	Statistically significant increase ($p < 0.002$)	No change
Aripiprazole vs. placebo			
Findling et al., 2008 [6]	No change	Statistically significant decrease: 10 mg ($p = 0.003$), 30 mg ($p < 0.0001$)	No change
Tramontina et al., 2009 [54]	No data	No data	No data
Owen et al., 2009 [55]	No change	Statistically significant decrease ($p < 0.001$)	No change
Marcus et al., 2009 [56]	No change	Statistically significant decrease ($p < 0.001$)	No change

[a] It was not clear from these papers whether the authors were referring to clinical or statistical significance

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Conflicts of interest and funding *F.M.C.B.* has received lecture fees, consultancy fees, research grants, and equipment grants from, and has been sponsored to attend conferences by, various pharmaceutical companies. He was previously editor-in-chief of a journal sponsored by GlaxoSmithKline. He has been asked to organize conferences supported by an unrestricted educational grant from Janssen-Cilag, a company marketing risperidone. None of these monies have been paid directly to F.M.C.B.; all monies since 2001 have been paid to his NHS Trust. F.M.C.B. has recently been sponsored to attend international epilepsy conferences by Eisai. No monies are currently being received from pharmaceutical companies, or from any source other than his employer, the NHS in the UK. *K.J.A.* has been on the Advisory Board for the Bristol-Myers Squibb and Otsuka Pharmaceuticals Ltd, and in addition, has received consultancy fees including payment for lectures and educational presentations from the same company. She was previously a member of various advisory boards, receiving consultancy fees and honoraria, and has received research grants from various companies, including Lundbeck and GlaxoSmithKline. She currently holds an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta. *I.C.K.W.* has received research funding and honoraria from various pharmaceutical companies, including Janssen-Cilag and Bristol-Myers Squibb (manufacturers of antipsychotic medicines). I.C.K.W. is currently receiving funding from the EU Commission to investigate the safety of risperidone in children. *M.L.M.* has received funding from pharmaceutical companies (Shire and Pfizer), but none of the funding is related to this study. The authors *N.B.A.* and *Y.L.* declare that they have no conflict of interest. N.B.A. is supported by a scholarship from the Ministry of Higher Education in the Kingdom of Saudi Arabia. No additional sources of funding were used to prepare this manuscript.

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