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Metabolic and Neurological Complications of Second-Generation Antipsychotic Use in Children

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Available evidence indicates that the use of antipsychotics, especially second-generation antipsychotics (SGAs), for children with mental health disorders has increased dramatically. Given the demonstrated metabolic and neurological adverse effects seen in adult patients on these medications, detailed evaluation of the risk for these adverse effects in children is appropriate.

Objective: The aim of the study was to assess the evidence for specific metabolic and neurological adverse effects associated with the use of SGAs in children.

Data Sources: MEDLINE (1996–May 2010) and EMBASE (1996–May 2010) databases were searched using highly sensitive search strategies for clinical trials in a paediatric population (children up to age 18 years).

Study Selection: We included any double-blind, randomized controlled trial (RCT) of SGA medications conducted specifically in a paediatric population for the treatment of a mental health disorder. This included the medications risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone and paliperidone. The primary outcomes assessed for this review were metabolic and neurological adverse effects, as measured using physical examination manoeuvres, rating scales or laboratory tests. A total of 35 RCTs were included in the analysis, but not all studies had data that could be used in the meta-analysis.

Data Extraction: Abstracts retrieved from the searches were reviewed independently by two different reviewers for potential relevant articles. Full-text articles were then read in detail independently by two different reviewers to see if inclusion criteria were fulfilled. Data were extracted independently by two review authors from included studies and entered onto pre-designed summary forms. Clinical trials were evaluated for methodological quality

using quality criteria developed by the US Preventive Services Task Force. Based on the fulfilment of quality criteria, studies were rated as good, fair or poor.

Data Synthesis: Meta-analysis was performed on the data for synthesis, and was carried out for commonly reported outcomes for each medication individually, in comparison with placebo or another drug. Odds ratios (ORs) with 95% confidence intervals for binary outcomes were used. For continuous outcomes, mean differences were used to analyze the data. Meta-analysis revealed that mean weight gain compared with placebo was highest for olanzapine at 3.47 kg (95% CI 2.94, 3.99) followed by risperidone at 1.72 kg (95% CI 1.17, 2.26), quetiapine at 1.41 kg (95% CI 1.10, 1.81) and aripiprazole at 0.85 kg (95% CI 0.58, 1.13). Olanzapine and clozapine treatment were associated with the highest rate of metabolic laboratory abnormalities in cholesterol and triglycerides. Prolactin elevation occurred with risperidone and olanzapine therapy. Higher odds of extrapyramidal symptoms compared with placebo were seen in children treated with risperidone (OR 3.55; 95% CI 2.04, 5.48) and aripiprazole (OR 3.70; 95% CI 2.37, 5.77). Elevated rates of extrapyramidal symptoms were also experienced with olanzapine use.

Conclusions: There is good evidence to support the existence of both metabolic and neurological adverse effects in children treated with these medications. Proper attention and vigilance to potential metabolic and neurological adverse effects is necessary, and should be considered part of the standard of care.

Background

The second-generation antipsychotics (SGAs) are a group of antipsychotic medications that include clozapine, olanzapine, risperidone, quetiapine, ziprasidone, paliperidone and aripiprazole. These medications are labelled 'atypical' in comparison with traditional antipsychotic medications, based on their chemical properties, which includes rapid dissociation from dopamine type 2 receptors, and blockade of serotonin type 2A receptors. The ability of these medications to dissociate rapidly from dopamine receptors leads to a lower (but not absent) risk of extrapyramidal signs and symptoms,[1] adverse effects that are common and troubling with traditional antipsychotic medications.[2] The perceived lower risk of neurological adverse effects with SGAs has led to routine use of these agents in adult patients with psychosis.

The atypical antipsychotics have been used 'off-label' in children for a number of mental disorders, including aggressive and oppositional behaviour in children with attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder and conduct disorder, behavioural problems or irritability related to autism spectrum disorders, tic disorders, mood disorders and psychosis. Randomized controlled trials (RCTs) have demonstrated efficacy for many of the atypical antipsychotics in these conditions.[3-9] At present, none of the SGAs has received official indications by Health Canada for the treatment of children under 18 years of age, while the US FDA has approved the use of risperidone and aripiprazole in children with schizophrenia, bipolar disorder and autism.

Available evidence indicates that the use of antipsychotics, especially SGAs, for children with mental health disorders has increased dramatically

in the US. Patel and colleagues[10] examined trends in prescribing antipsychotics to children within the Texas Medicaid Program from 1996 to 2000. They assessed the number of children with at least one Medicaid prescription claim for an antipsychotic per 1000 enrolees over a 5-year period, during which time there was a 160% increase in prescriptions. The prevalence of use of SGAs increased 494%. Olfson and colleagues[11] carried out further research into the characteristics of children treated with antipsychotic drugs in the US using the National Ambulatory Medical Care Survey.[11] They analyzed the national trends of visits from 1993 to 2002 that included prescription of antipsychotics. Office-based visits that included antipsychotic treatment increased from 201 000 visits in 1993 to 1 224 000 visits in 2002. Mental health visits involving prescription of an antipsychotic included patients with diagnoses of disruptive behaviour disorders (37.8%), mood disorders (31.8%), developmental disorders (17.3%) and psychotic disorders (14.2%).

In adult patients, SGAs are associated with metabolic effects, although the propensity of individual medications to induce these effects differs.[12] Data from uncontrolled observations, large retrospective database analyses and controlled experimental studies have found generally consistent evidence that clozapine and olanzapine treatment are associated with the greatest risk of clinically significant weight gain, and an increased risk of diabetes mellitus and dyslipidaemia. Studies of risperidone and quetiapine have shown more moderate levels of weight gain, and lower risks of diabetes and dyslipidaemia in comparison with clozapine and olanzapine. Ziprasidone is associated with minimal weight gain and, in limited studies, has not been found to induce diabetes or dyslipidaemia. One recently published prospective cohort study has been performed specifically to determine the association of SGAs with body composition and metabolic parameters in children.[13] After a median of 10.8 weeks of therapy, weight increased by 8.5 kg with olanzapine, 6.1 kg with quetiapine, 5.3 kg with risperidone and 4.4 kg with aripiprazole, in comparison with a minimal weight change of 0.2 kg in an untreated comparison group. Changes in cholesterol were also seen over this period; baseline to endpoint changes reached statistical significance for olanzapine and quetiapine for total cholesterol, triglycerides and non-high-density lipoprotein (HDL) cholesterol. In the risperidone group, triglyceride levels were significantly increased.

Over time, the notion that SGAs are associated with a lower risk of neurological adverse effects than first-generation antipsychotics has been called into question, leading to more in-depth analysis of clinical trial data. Miller et al.[14] performed an analysis of data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial to rigorously assess and compare the incidence of treatment-emergent parkinsonism, dystonia, akathisia and tardive dyskinesia associated with SGAs and perphenazine, a first-generation antipsychotic. In the CATIE study, adult patients with schizophrenia were assigned to treatment with olanzapine, perphenazine, quetiapine, risperidone or ziprasidone under double-blind conditions. Patients with tardive dyskinesia at baseline were excluded from randomization to perphenazine and were assigned to one of the four SGAs. Extrapyramidal symptoms (EPS) were measured using the Simpson Angus Scale (SAS), the Barnes Akathisia Rating Scale (BAS) and the Abnormal Involuntary Movement Scale (AIMS). These measures were collected at baseline, months 1 and 3, and quarterly thereafter until 18 months or time of treatment discontinuation. There were no significant differences in the incidence or change in rating scales for parkinsonism, dystonia, akathisia or tardive dyskinesia when comparing SGAs with perphenazine or when comparing between SGAs. A total of 1.1–4.5% of patients taking SGAs and 3.3% of patients taking perphenazine developed tardive dyskinesia during treatment. There were greater rates of concomitant antiparkinson medication among individuals taking risperidone and lower rates among individuals taking quetiapine. Rates of discontinuation because of parkinsonism were lower among people taking quetiapine and ziprasidone. There was a trend for a greater likelihood of concomitant medication for akathisia among individuals taking risperidone and perphenazine. Analyses of the FDA spontaneous

adverse event reporting postmarketing surveillance database have also shown that neurological adverse effects occur with olanzapine use, both in children and adults.[15]

Given the increasing frequency of use of SGAs in children, the demonstrated metabolic and neurological adverse effects seen in adult patients taking these medications, and emerging evidence in children, detailed evaluation of the risk for these adverse effects in children is appropriate. The objective of this systematic review and meta-analysis is to assess the evidence for specific metabolic and neurological adverse effects associated with the use of SGAs in children. This information will assist practitioners in understanding the potential risks of therapy with these medications in paediatric patients.

Methods

We included any double-blind, RCT of SGA medications versus placebo or an active comparator conducted specifically in a paediatric population (children up to 18 years of age) for the treatment of a mental health disorder, or that included a separate data analysis of paediatric participants if the study also included adults. The SGA medications were all assessed individually. This includes the medications risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone and paliperidone. The primary outcomes assessed for this review were metabolic and neurological adverse effects, as measured using physical examination manoeuvres, rating scales or laboratory tests. Specific outcomes of interests included the following:

- weight gain (kg);
- clinically significant weight gain (more than 7% of baseline bodyweight);
- waist circumference (cm);
- body mass index [BMI] (kg/m^2);
- blood pressure;
- heart rate;
- EPS, as measured through structured neurological examination or the use of an established rating scale, e.g. BAS, SAS, AIMS, Extrapyramidal Symptom Rating Scale (ESRS);
- electrocardiogram (ECG);
- fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides;
- blood sugar;
- prolactin;
- liver function tests (AST and ALT);
- thyroid-stimulating hormone and free thyroxine (T4).

To find relevant articles for the review, the MEDLINE (1996–May 2010) and EMBASE (1996–May 2010) databases were searched using highly sensitive search strategies for clinical trials in a paediatric population. Searches were carried out for each SGA medication individually. Abstracts retrieved from the searches were reviewed independently by two different reviewers for potential relevant articles. Full-text articles were then read in detail independently by two different reviewers to see if inclusion criteria were fulfilled. Disputes between reviewers regarding inclusion were resolved by discussion. Data were extracted independently by two review authors from included studies and entered onto predesigned summary forms. Extracted data were compared to ensure accuracy. Data were entered into Review Manager 5 (Cochrane IMS, http://ims.cochrane.org) by one author for meta-analysis, and checked by the second author for accuracy.

Clinical trials were evaluated for methodological quality using quality criteria developed by the US Preventive Services Task Force (USPSTF)[16] [see Appendix 1, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A51]. Based on the fulfilment of quality criteria, studies were rated as good, fair or poor. Two authors independently assessed methodological quality for each included study. The domains assessed included:

1. allocation concealment;
2. blinding;
3. sequence generation;
4. intent-to-treat analysis;
5. clear statement of intervention and outcomes;
6. assembly of comparable groups;
7. measurement instruments acceptable and applied equally;
8. appropriate attention to confounders in analysis.

Quality assessment did not include evaluation of reported secondary effects; therefore, studies rated good or fair did not necessarily have good reporting of adverse events.

Odds ratios (ORs) with 95% confidence intervals (CIs) for binary outcomes were used. For continuous outcomes, mean differences were used to analyze the data. All analyses included all participants in the treatment groups to which they were allocated. The reviewers attempted to contact study authors when data were missing from trial reports. When we were unable to obtain the missing information, we imputed the missing data with replacement values. When standard deviations were missing from trial data, we imputed the standard deviation from a trial with a similar duration, intervention and clinical population.

Clinical heterogeneity was assessed by comparing trial design and the distribution of important participant factors. By examining the I^2 index, an approximate quantity that describes the proportion of variation in point estimates that is due to heterogeneity of studies rather than to sampling error, statistical heterogeneity was assessed. In addition, a chi-squared test of homogeneity was also performed in order to determine the strength of evidence that heterogeneity is genuine.

Meta-analysis was performed on the data for synthesis and was carried out for commonly reported outcomes for each medication individually, in comparison with placebo or another drug. Both random-effects and fixed-effect models were used. Random effects models were used when the I^2 index approached 50%, which indicates a moderate degree of heterogeneity.[17] RCTs of 12 weeks or shorter in duration were combined, and RCTs of longer than 12 weeks were combined in separate analyses. The separate analyses were conducted to understand if differences occur with respect to adverse effects in short- versus long-term studies.

Results

Results for each SGA are described in separate sections. Overall, trial quality was high, with 32 of the 35 studies received a rating of good or fair by USPSTF criteria.

Risperidone

A total of 948 abstracts on risperidone were retrieved from searches performed using the MEDLINE and EMBASE databases. Of these, 70 full-text articles were reviewed and 19 were included in the analysis (see table IS and figure 1S, Supplemental Digital Content 1).

Trials Shorter than 12 Weeks

Ten RCTs on the use of risperidone versus placebo were shorter than 12 weeks; two in autistic disorder,[18,19] four in conduct or disruptive behaviour disorders,[20-23] two in aggression,[24,25] one in bipolar I disorder[26] and one in schizophrenia.[9] Trial duration ranged from 3 to 10 weeks and the trials were of overall high quality.

No standard deviations were provided for mean weight gain in the risperidone and placebo groups in two of the trials,[9,25] and we were unable to calculate standard deviations as no other statistical measures were provided (such as p-values or standard errors). In order to include these trials in the meta-analysis, we imputed the standard deviation from the Aman et al.[21] trial as the trials were of similar duration and the mean weight gain was of similar magnitude in both treatment groups in these trials.

Meta-analysis was performed on adverse effect data obtained from these ten trials. Mean weight gain was greater in patients treated with risperidone compared with placebo, with a mean difference of 1.72 kg (95% CI 1.17, 2.26; $p < 0.00001$) [see figure 1]. The odds of clinically significant weight gain were higher in risperidone-treated patients (OR 2.90), but this was not significantly different from that of placebo ($p < 0.08$). Prolactin levels were elevated in risperidone-treated children relative to placebo, with a mean difference of 20.70 ng/mL (95% CI 16.78, 24.62; $p < 0.00001$) [see figure 2]. Change in prolactin level from baseline to endpoint was also higher in risperidone-treated children, with a mean difference of 44.57 ng/mL (95% CI 32.24, 56.90; $p < 0.00001$). Risperidone-treated patients had significantly higher odds of EPS relative to placebo, with an OR of 3.35 ($p < 0.00001$) [see figure 3]. Laboratory testing for cholesterol, triglycerides and fasting

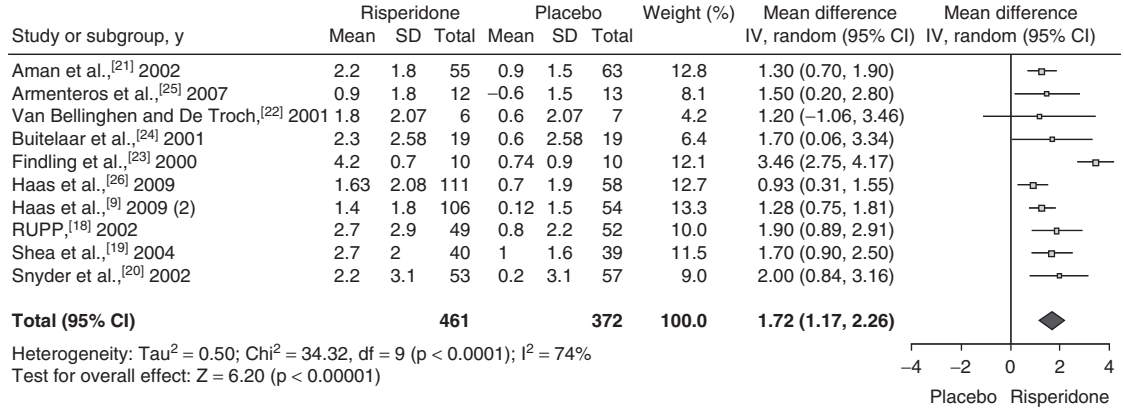

Fig. 1. Mean weight gain (kg), risperidone vs placebo (randomized controlled trials <12 weeks). **df** = degrees of freedom; **IV** = inverse-variance.

blood sugar were only performed and reported by Haas et al.[26] There were no clinically significant changes found within or between treatment groups on any of these laboratory measures. Haas et al.[9] reported that glucose metabolism-related treatment adverse events were absent. Reyes et al.[27] also indicated that there was no significant change in mean fasting glucose level.

Six of ten RCTs investigated change in blood pressure, with five of these studies[18,20,22,24,25] reporting no significant difference in blood pressure. One study[19] reported systolic blood pressure had increased by 4.0 mmHg in children treated with risperidone by study endpoint, compared with a mean decrease of 0.7 mmHg with placebo.

We identified two high-quality RCTs in children with psychotic disorders in which children were randomized to risperidone, olanzapine or a first-generation antipsychotic for 8 weeks.[28,29] Sikich et al.[28] randomized 50 children to risperidone, olanzapine or haloperidol, and Sikich et al.[29] randomized 119 children to risperidone, olanzapine or molindone.

Meta-analysis of the two studies with respect to data on olanzapine and risperidone show that the amount of weight gain is higher in olanzapine-treated subjects than risperidone-treated subjects, with a mean difference between groups of 2.41 kg (95% CI 0.98, 3.83; p = 0.0009) [see figure 4]. Change in BMI was also greater with olanzapine than risperidone, with a mean difference of 0.90 kg/m^2 (95% CI 0.42, 1.38; p = 0.0003) [see figure 5]. The change in BMI in both the olanzapine- and risperidone-treated groups was higher than that observed in patients treated with a first-generation antipsychotic medication. The number of subjects requiring anticholinergic therapy for EPS was high in both the olanzapine-

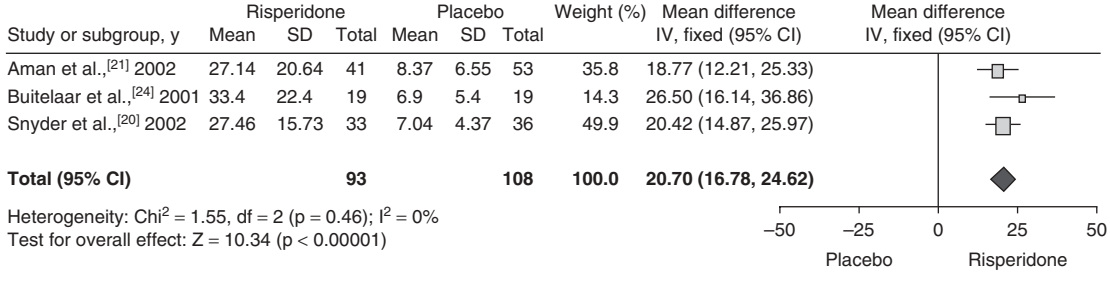

Fig. 2. Prolactin level at endpoint (ng/mL), risperidone vs placebo (randomized controlled trials <12 weeks). **df** = degrees of freedom; **IV** = inverse-variance.

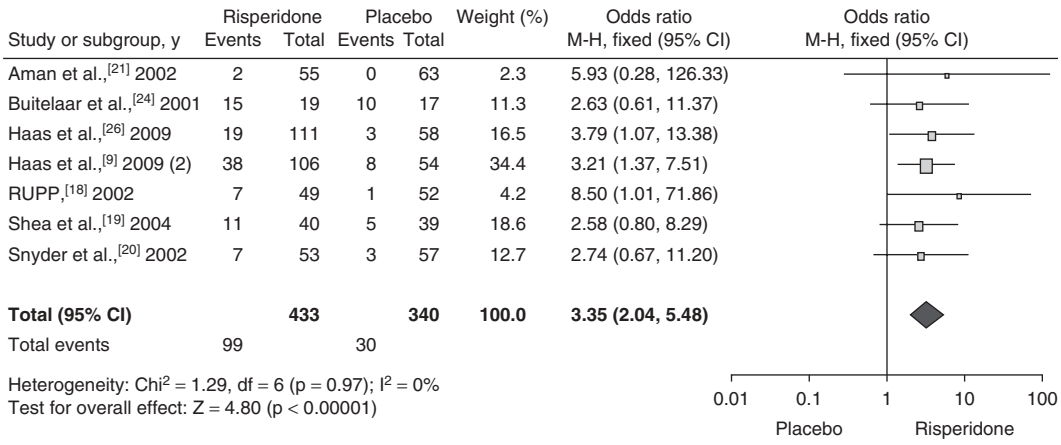

Fig. 3. Extrapyramidal disorder, risperidone vs placebo (randomized controlled trials <12 weeks). **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

and risperidone-treated groups, as well as the haloperidol group. In the study comparing these treatments with molindone, all molindone-treated subjects were treated prophylactically with benzatropine. While meta-analysis of the data shows higher odds of anticholinergic therapy with risperidone than olanzapine, the difference was not statistically significant.

Differences in result reporting precluded meta-analysis for the other outcomes. In the study by Sikich et al.[28] comparing risperidone and olanzapine with haloperidol, the mean SAS score changed significantly between baseline and endpoint in the haloperidol group only. Four subjects reported akathisia at endpoint – two receiving haloperidol and two receiving olanzapine. There was no difference between baseline and endpoint, or between groups, in HDL cholesterol, LDL cholesterol, triglycerides, glucose or prolactin. AST and ALT were statistically significantly higher at endpoint compared with baseline in risperidone-treated patients, but the clinical significance of the magnitude of difference is uncertain. In the study by Sikich et al.[29] comparing risperidone and olanzapine with molindone, the change in total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, insulin, homeostasis model assessment – insulin resistance (HOMA–IR), ALT, AST, prolactin and corrected QT interval (QTc) were given for each medication. In olanzapine-treated subjects, the changes in total cholesterol, LDL cholesterol, insulin, ALT and AST were significant compared with baseline values, and were significantly higher than in subjects treated with risperidone. Prolactin change from baseline was significant in risperidone-treated subjects, and was significantly greater than in subjects treated with olanzapine or molindone.

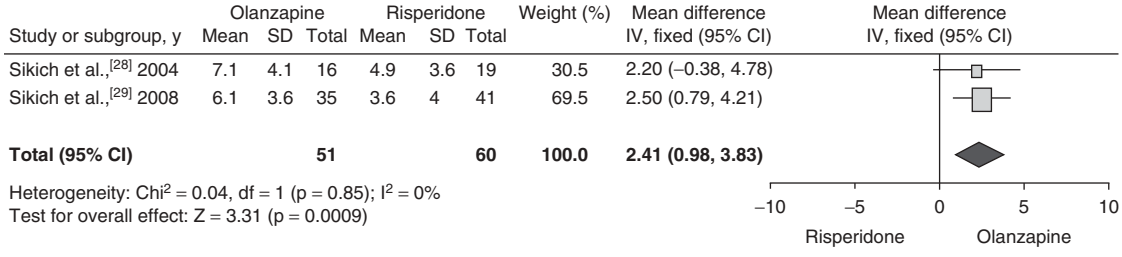

Fig. 4. Weight gain (kg), risperidone vs olanzapine. **df** = degrees of freedom; **IV** = inverse-variance.

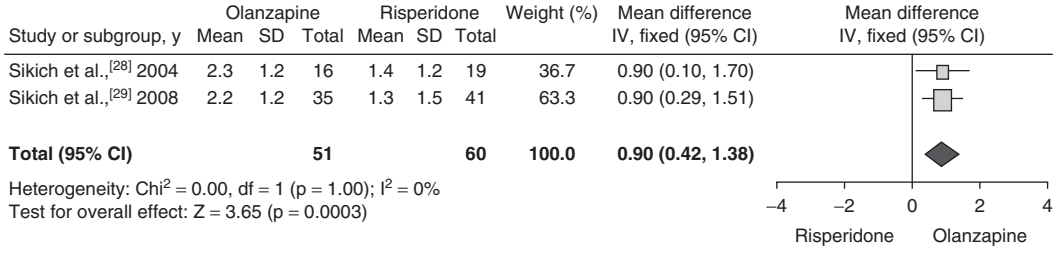

Fig. 5. Body mass index change (kg/m²), risperidone vs olanzapine. **df** = degrees of freedom; **IV** = inverse-variance.

Three RCTs were identified in which children were randomized to risperidone or an active comparator. Haas et al.[30] randomized children to high- (1.5–6 mg/day) or low-dose (0.15–0.6 mg/day) risperidone for the treatment of 257 adolescents with schizophrenia in an 8-week trial. Median doses were 4 mg/day in the high-dose group and 0.4 mg/day in the low-dose group. Sixteen of 125 patients in the high-dose group had their dose adjusted because of EPS, in contrast to no patients in the low-dose group. Overall, more patients in the high-dose group (41/125) experienced EPS than in the low-dose group (13/132). There were no clinically relevant changes in vital signs in either group and one patient experienced an increase from normal baseline QTc to a prolonged QTc. No clinically significant changes in glucose, cholesterol or triglyceride levels were observed. The mean change in weight from baseline was 3.2 ± 3.49 kg in the high-dose group and 1.7 ± 3.29 in the low-dose group. The proportion of patients who experienced weight gain as an adverse event was higher in the high-dose group (18%) compared with the low-dose group (5%).

Gilbert et al.[31] compared risperidone (mean dose 2.5 mg/day) with pimozide (mean dose 2.4 mg/day) in 19 children with Tourette's syndrome in a crossover trial where patients were treated for 4 weeks with each drug, separated by a washout period of 2 weeks. There was no significant difference between treatments with respect to weight gain (1.0 kg after 4 weeks of treatment with pimozide and 1.9 kg after 4 weeks of treatment with risperidone). The mean ESRS did not differ after treatment with each medication and there were no QTc intervals >450 ms.

Gaffney et al.[32] randomly assigned 21 children with Tourette's syndrome to risperidone or clonidine in an 8-week trial. Mean weight change was higher in risperidone-treated patients (2.1 ± 2.3 kg) than clonidine-treated patients (0.1 ± 5.9 kg) but this was not statistically significant. There were no significant differences between the risperidone and clonidine groups regarding changes in blood pressure or pulse, or ECG changes.

Longer Duration Trials

Three trials >12 weeks' duration comparing risperidone with placebo for the treatment of paediatric mental health disorders were identified.[27,33,34] Two of these trials included children with autistic disorder[33,34] and one trial included children with disruptive behaviour disorders.[27] All three trials were of 6 months' duration, with two trials being high in quality and one trial low in quality.

Mean weight gain was higher in patients treated with risperidone compared with placebo, with a mean difference of 1.95 kg (95% CI 1.14, 2.75; $p < 0.00001$) [see figure 6]. In the study by Reyes et al.,[27] endpoint levels of prolactin were 20.3 ± 21.3 ng/mL and 9.6 ± 9.5 ng/mL for risperidone-treated patients and placebo, respectively ($p < 0.00001$). Luby et al.[34] investigated the change in prolactin level from baseline to endpoint and found the increase in risperidone-treated patients to be significantly higher than placebo ($p < 0.001$). The increases in prolactin level were 33.38 ± 14.48 ng/mL and 11.11 ± 18.74 ng/mL for risperidone-treated children and placebo, respectively. Reyes et al.[27] and Nagaraj et al.[33] investigated the incidence of EPS. Children treated with risperidone had higher odds of EPS than those

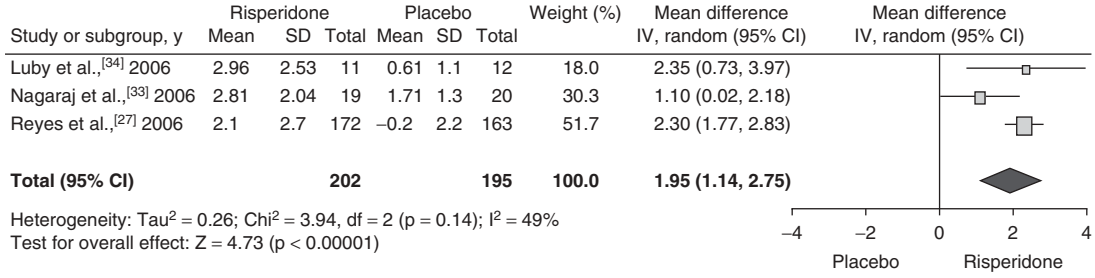

Fig. 6. Mean weight gain (kg), risperidone vs placebo (randomized controlled trials >12 weeks). **df** = degrees of freedom; **IV** = inverse-variance.

treated with placebo (OR 3.71); however, this difference was not significant (p = 0.07).

One RCT of 12 weeks' duration compared risperidone (mean dose 2.6 mg/day) with haloperidol (mean dose 2.6 mg/day) in 30 children with autistic disorder.[35] Change from baseline in EPS, as measured by the ESRS, was significant in the haloperidol group only. Metabolic adverse effects were not well described in the manuscript.

In summary, high-quality, short-term randomized trials of risperidone versus placebo support the existence of the following adverse effects in children treated with risperidone for <3 months: weight gain, increase in BMI, increase in blood pressure (minor), EPS and elevation in prolactin. In comparison with olanzapine, children receiving risperidone gain less weight and have fewer metabolic laboratory abnormalities but have more neurological adverse effects. RCTs longer than 3 months in duration provide evidence of weight gain, elevation in prolactin and EPS associated with risperidone use.

Olanzapine

A total of 640 abstracts pertaining to olanzapine were retrieved through the MEDLINE and EMBASE searches. Of these, 24 full-text articles were reviewed and 7 were included in the analysis (see table IIS and figure 2S, Supplemental Digital Content 1). The results of two trials comparing olanzapine with risperidone are described in full in the Risperidone section, and the results of two trials comparing olanzapine with clozapine are described in the Clozapine section.

We identified three RCTs of olanzapine versus placebo in children; one in bipolar disorder,[36] one in schizophrenia,[5] and one in pervasive developmental disorder.[37] These trials ranged in duration from 3 to 8 weeks and were of high quality.

Meta-analysis was performed on adverse effect data reported from these three trials. Weight gain was higher in olanzapine-treated subjects compared with placebo, with a mean difference of 3.47 kg (95% CI 2.94, 3.99) between groups (see figure 7). The odds of clinically significant weight gain was higher in olanzapine-treated children, with an OR of 10.66 (p < 0.003) of a >7% increase in baseline weight. BMI increased in olanzapine-treated subjects, with a mean difference of 1.28 kg/m^2 (95% CI 0.96, 1.59) compared with placebo (see figure 8). The odds of high triglycerides anytime during treatment were higher in children taking olanzapine compared with placebo, with an OR of 5.13 (95% CI 2.78, 9.45) [see figure 9]. There was no difference in the change in fasting glucose from baseline between treatment groups. Compared with baseline, fasting total cholesterol increased in children receiving olanzapine compared with placebo, with a mean difference of 3.67 mg/dL (p = 0.001) [see figure 10]. Olanzapine-treated subjects had much higher odds of an elevated prolactin any time during treatment compared with placebo, with an OR of 30.52 (p < 0.00001) [see figure 11]. Children treated with olanzapine had a greater change in AST from baseline, with a mean difference of 8.98 U/L (95% CI 5.19, 12.78), and a greater change in ALT from baseline, with a mean difference of 22.5 (95% CI 14.26, 30.74). The odds of a clinically significant increase in ALT was higher in olanzapine-treated children, with an OR of 18.74 (p = 0.0005) [see figure 12]. There was no

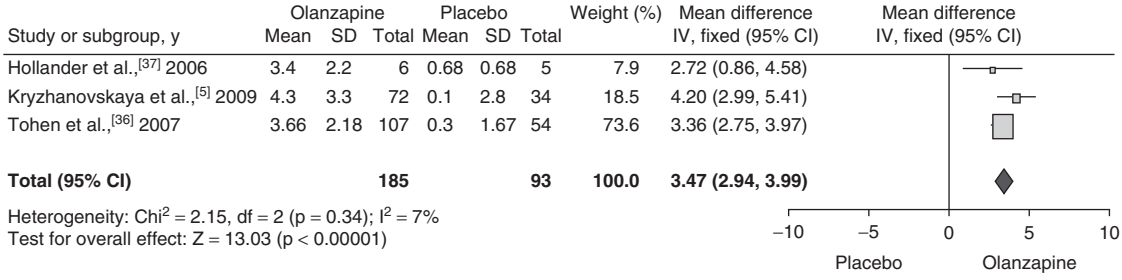

Fig. 7. Weight gain (kg), olanzapine vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

significant difference between treatment groups in the change in QTc interval from baseline.

With respect to EPS, all studies reported using the AIMS, SAS and BAS, but only one study provided raw data on scale scores. According to all study reports, there were no differences in the rate of abnormal movements between groups. However, data from the trials by Sikich et al.[28,29] (described above in the Risperidone section) found a high rate of EPS in olanzapine-treated patients. Blood pressure was measured in all three trials. Hollander et al.[37] measured blood pressure, but no raw data were presented. Kryzhanovskaya et al.[5] reported no significant differences in blood pressure. In contrast, Tohen et al.[36] reported a significant baseline-to-endpoint increase in supine systolic blood pressure. An increase of 3.61 mmHg in olanzapine-treated patients and a decrease of 2.28 mmHg in the placebo group (p = 0.001) was seen.

In summary, short-term randomized trials of olanzapine demonstrated an increased risk of the following adverse effects in children treated with olanzapine for <3 months: weight gain, clinically significant weight gain, increased BMI, EPS, increase in blood pressure (minor), and elevation in triglycerides, total cholesterol, LDL cholesterol, insulin, prolactin, AST and ALT. In comparison with risperidone, olanzapine results in greater weight gain and metabolic laboratory abnormalities, but fewer EPS (see Risperidone section). In comparison with clozapine, olanzapine results in similar levels of weight gain and metabolic laboratory abnormalities (see Clozapine section).

Quetiapine

A total of 353 abstracts relating to quetiapine were retrieved from the MEDLINE and EMBASE searches. Of these, 17 full-text articles were reviewed and four were included in the analysis (see table IIIS and figure 3S, Supplemental Digital Content 1).

Three studies of quetiapine versus placebo in children with mental health disorders were identified, one for adjunctive treatment in adolescents with mania[3] one for depressed adolescents with bipolar disorder[38] and one for conduct disorder.[39] These trials ranged from 6 to 8 weeks in duration and were of high quality.

The only adverse effect data reported in all three trials were regarding mean weight gain and

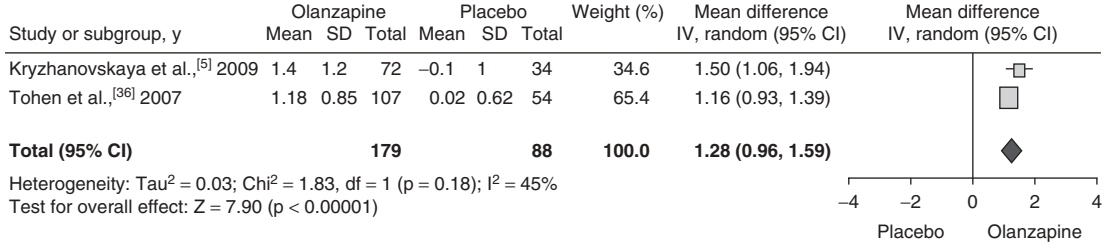

Fig. 8. Change in body mass index (kg/m²), olanzapine vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

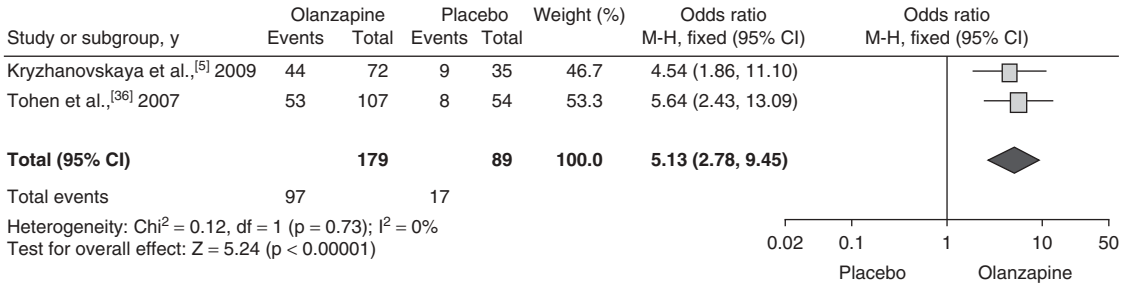

Fig. 9. High triglycerides any time during treatment, olanzapine vs placebo. **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

change in prolactin levels during therapy. These data were combined using meta-analysis. Weight gain was significantly higher in those treated with quetiapine, with a mean difference of 1.41 kg (95% CI 1.01, 1.81) compared with placebo (see figure 13). The mean change in prolactin levels was not significantly different between treatment groups.

The effect of treatment on lipids and blood glucose were described in the study by DelBello et al.[38] They reported a significant change in fasting triglycerides in children treated with quetiapine versus placebo, with a mean increase of 30 mg/dL in quetiapine-treated patients compared with a mean decrease of 14 mg/dL in subjects treated with placebo (p = 0.003). There were no significant group differences in the change in fasting total cholesterol, LDL cholesterol, HDL cholesterol or glucose from baseline to the end of therapy. They also reported the incidence of shifts from normal to abnormal levels of fasting metabolic parameters during study participation by treatment assignment. This was almost significant for triglycerides, which went from normal (<110 mg/dL) to high (>110 mg/dL) in 4 of 17 quetiapine-treated children, and in 0 of 15 placebo-treated children (p = 0.07).

With respect to EPS, the studies by DelBello et al.[3,38] both used the SAS, BAS and AIMS, and did not report any differences between placebo and quetiapine on these measures. Connor et al.[39] reported no difference between groups on the AIMS. All studies reported no significant difference in QTc intervals between patients treated with quetiapine and placebo.

The effect of quetiapine on blood pressure and heart rate was studied in all three trials. DelBello et al.[38] reported a significant increase in supine systolic blood pressure at endpoint in the quetiapine group (mean change +6 mmHg) compared with the placebo group (mean change −6 mmHg). Heart rate was significantly higher in quetiapine-treated patients (mean change +11 beats per minute [bpm]) compared with placebo (mean change −3 bpm). Standing systolic and diastolic blood pressures were also significantly higher in the quetiapine-treated group. Two study patients in the quetiapine group who had normal blood pressure at baseline developed hypertension (defined as systolic blood pressure >120 mmHg, or diastolic

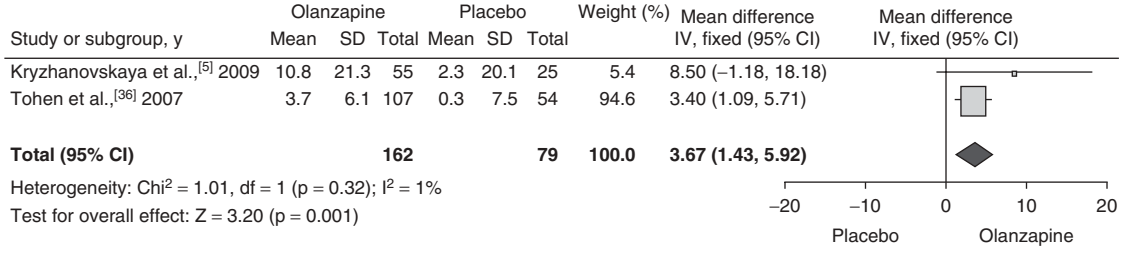

Fig. 10. Change in fasting total cholesterol from baseline (mg/dL), olanzapine vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

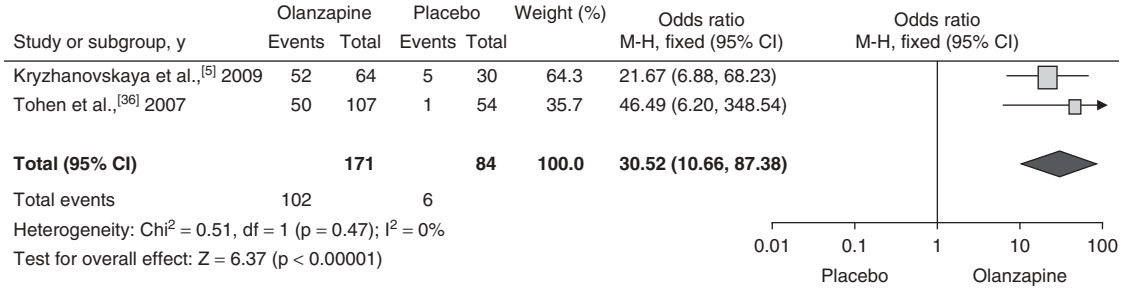

Fig. 11. Elevated prolactin any time during treatment, olanzapine vs placebo. **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

blood pressure >80 mmgHg) at study endpoint. DelBello et al.[3] reported no changes in blood pressure or heart rate, and Connor et al.[39] reported a significantly higher average sitting pulse of 8.6 bpm in quetiapine-treated subjects.

Our search identified one 4-week RCT of quetiapine versus divalproex in adolescent mania.[40] This study was not incorporated into the meta-analysis because of significant non-statistical clinical heterogeneity. Fifty patients were randomized equally to divalproex (mean dose not stated) or quetiapine (mean dose 412 mg/day). No group differences were observed for change from baseline to endpoint in EPS, vital signs, QTc interval or weight gain. Mean weight gain in the quetiapine group was 4.4 ± 5.0 kg compared with 3.6 ± 6.0 kg in the divalproex group ($p = 0.2$).

In summary, short-term RCTs of quetiapine provide good-quality evidence of the following adverse effects in children treated with quetiapine for <3 months: weight gain, increase in blood pressure and heart rate (minor), and elevated triglycerides.

Aripiprazole

The MEDLINE and EMBASE searches retrieved 175 abstracts on aripiprazole. Of these, nine were selected for review of the full-text article and five met our inclusion criteria (see table IVS and figure 4S, Supplemental Digital Content 1).

Five RCTs on the use of aripiprazole for paediatric mental health disorders were identified: two trials in children with autistic disorder,[7,41] one trial in children with bipolar disorder,[42] one trial in children with combined bipolar disorder and ADHD[43] and one trial in children with schizophrenia.[4] These trials ranged from 4 to 8 weeks in duration and were of high quality.

Meta-analysis was performed on adverse effect data obtained from these five trials. Mean weight gain was higher in aripiprazole-treated patients compared with placebo, with a mean difference of 0.85 kg (95% CI 0.57, 1.13; $p < 0.00001$) [see figure 14]. The odds of clinically significant weight gain was higher in aripiprazole-treated patients, with an OR of 3.66 ($p = 0.0003$). Aripiprazole-treated patients

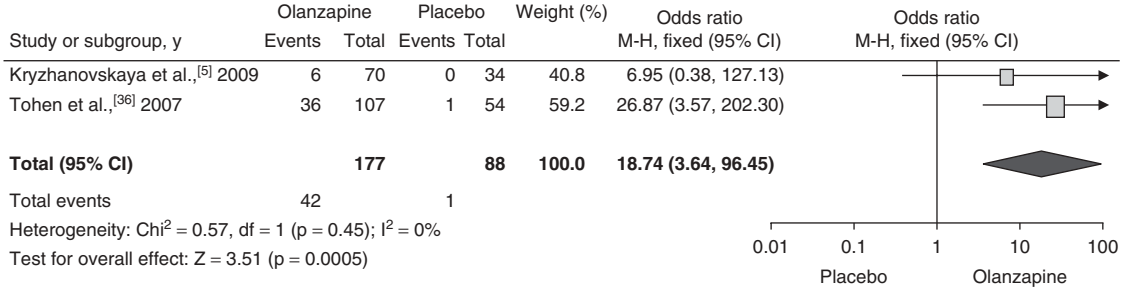

Fig. 12. Clinically significant elevation in ALT, olanzapine vs placebo. **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

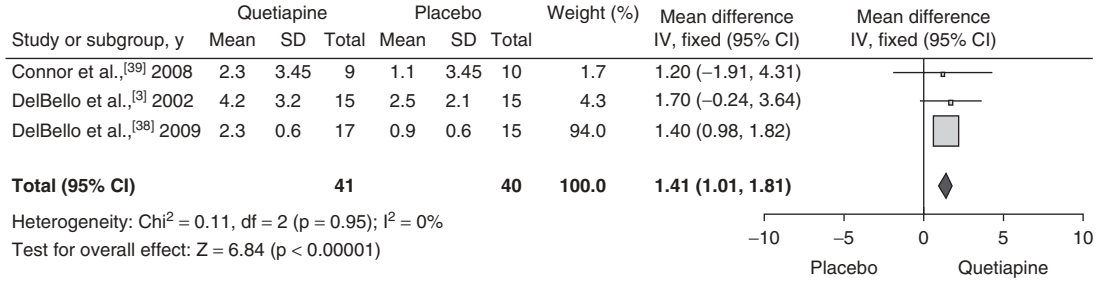

Fig. 13. Mean weight gain (kg), quetiapine vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

had a significantly greater increase in BMI post-treatment compared with placebo, with a mean difference of 0.27 kg/m^2 (95% CI 0.11, 0.42) [see figure 15]. The incidences of elevated fasting blood glucose, elevated triglycerides, elevated LDL cholesterol or total cholesterol, or low HDL cholesterol were not significantly different between treatment groups. Aripiprazole-treated patients had a significantly greater decrease in prolactin levels after treatment, with a mean difference of −5.03 ng/mL (95% CI −7.80, −2.26) relative to placebo (see figure 16). Aripiprazole-treated patients had higher odds of EPS compared with the placebo group, with an OR of 3.70 ($p < 0.00001$) [see figure 17]. The rate of abnormal QTc intervals on ECG testing was not different between groups. No significant changes in blood pressure or heart rate were reported.

In summary, short-term RCTs of aripiprazole provide good quality evidence of the following adverse effects in children treated with aripiprazole for <3 months: weight gain, clinically significant weight gain, increase in BMI and EPS. There is good evidence that metabolic laboratory abnormalities do not occur with short-term aripiprazole treatment, and that prolactin levels decrease with aripiprazole treatment.

Clozapine

A total of 370 abstracts pertaining to clozapine were retrieved from the MEDLINE and EMBASE searches. Of these, eight were read in full and three were included in the analysis (see table VS and figure 5S, Supplemental Digital Content 1).

Data on short-term adverse effects of clozapine are available from three RCTs of clozapine for paediatric schizophrenia, all with an active comparator. These trials ranged in length from 6 to 12 weeks and were of high quality. Two trials compared clozapine with olanzapine[44,45] and one trial compared clozapine with haloperidol.[6]

Shaw et al.[44] compared clozapine with olanzapine in 25 children with schizophrenia in an

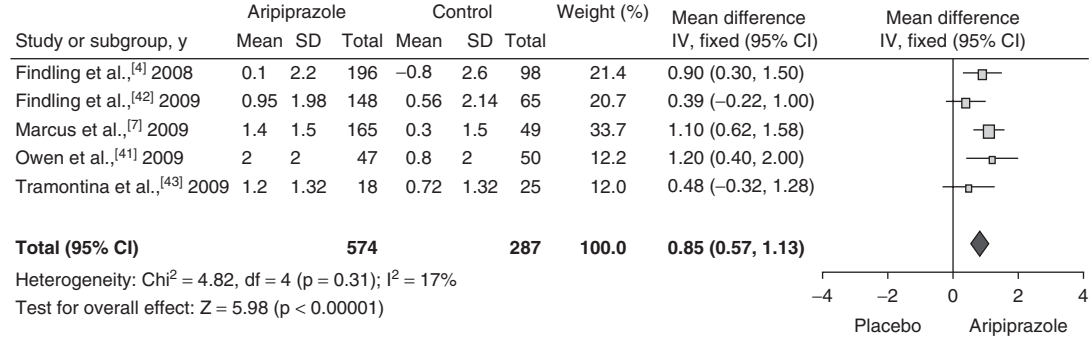

Fig. 14. Mean weight gain (kg), aripiprazole vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

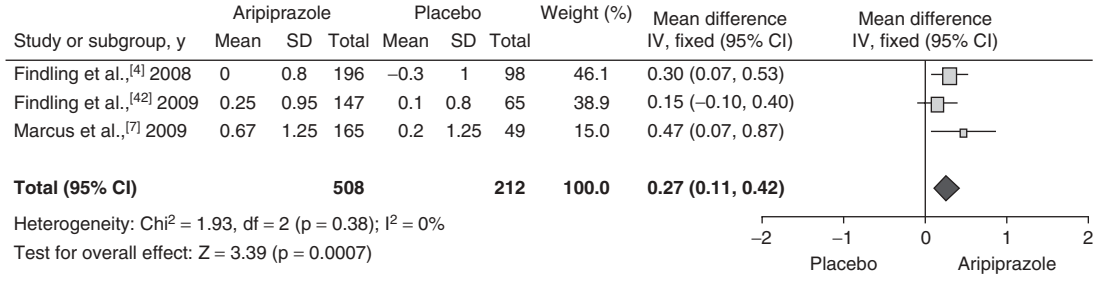

Fig. 15. Change in body mass index from baseline (kg/m^2), aripiprazole vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

8-week trial. The mean daily doses of clozapine and olanzapine were 327 mg and 18 mg, respectively. Both medications resulted in clinical improvement. Mean weight gain with clozapine was 3.8 ± 6.0 kg, while the mean weight gain with olanzapine was 3.6 ± 4.0 kg (p = 0.96). Change in BMI was 1.6 ± 2.5 kg/m^2 with clozapine and 1.4 ± 1.6 kg/m^2 with olanzapine (p = 0.76). There were no differences in median AIMS or SAS scores. One of 12 patients receiving clozapine developed elevated triglycerides and total cholesterol requiring treatment. Two of 12 patients in the clozapine group and 1 of 13 patients in the olanzapine group experienced a drop in absolute neutrophil count.

In a 12-week trial, Kumra et al.[45] compared clozapine with olanzapine in 39 children with schizophrenia. The mean dose of clozapine at endpoint was 403 mg and 26 mg for olanzapine. At baseline, 16 of the 18 clozapine-treated patients and 16 of the 21 olanzapine-treated patients were overweight or obese. At trial endpoint, this increased to 17 of 18 clozapine-treated patients and 17 of 21 olanzapine-treated patients. Three of the 18 clozapine-treated patients had a >7% increase in bodyweight compared with baseline, as did 2 of 21 olanzapine-treated patients. Four of 18 clozapine-treated patients and 5 of 21 olanzapine-treated patients had fasting triglycerides >110 mg/dL at trial endpoint.

In a 6-week trial, Kumra et al.[6] compared clozapine with haloperidol in 21 children with schizophrenia. The mean final daily dose of clozapine was 176 mg and 16 mg for haloperidol. Mean weight gain was 0.9 ± 6.47 kg in clozapine-treated patients compared with 0.94 ± 2.89 kg in haloperidol-treated patients. Four of ten clozapine patients had a drop in absolute neutrophil count. One of the 11 haloperidol-treated patients developed neuroleptic malignant syndrome. Total score on the AIMS did not change in either group.

In summary, high-quality, short-term RCTs demonstrated the following adverse effects in

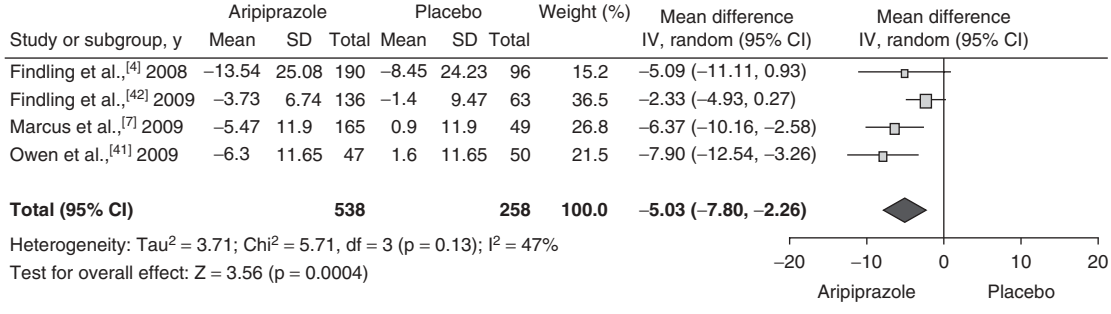

Fig. 16. Mean change in prolactin (ng/mL), aripiprazole vs placebo. **df** = degrees of freedom; **IV** = inverse-variance.

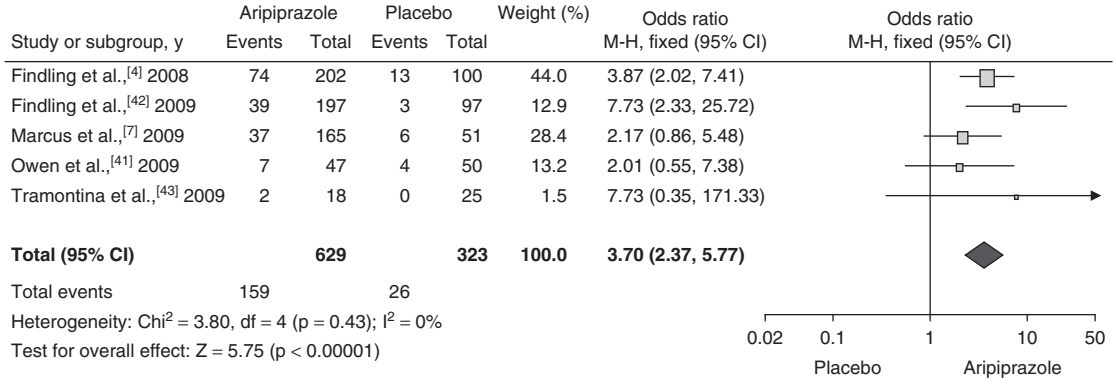

Fig. 17. Extrapyramidal disorder, aripiprazole vs placebo. **df** = degrees of freedom; **M-H** = Mantel-Haenszel.

children taking clozapine for <3 months: weight gain, increase in BMI, elevated triglycerides and a decrease in absolute neutrophil count. In comparison with olanzapine, similar changes in weight and BMI were seen with clozapine treatment.

Ziprasidone

A total of 160 abstracts pertaining to ziprasidone were obtained from the MEDLINE and EMBASE searches. Of these, five full-text articles were reviewed in detail, and one met our inclusion criteria (see table VIS and figure 6S, Supplemental Digital Content 1).

Data on short-term adverse effects of ziprasidone are available from one 8-week RCT in children with Tourette's syndrome.[8] Twenty-eight children were randomized to ziprasidone (mean daily dose 28.2 mg) or placebo. Mean weight gain was similar in the two groups, with 0.7 ± 1.5 kg gained in the ziprasidone group and 0.8 ± 2.3 kg gained in the placebo group at trial endpoint. Mean serum prolactin levels were also similar between groups at trial endpoint. There were no clinically significant effects in the mean SAS, BAS or AIMS in either group. One of the 16 ziprasidone-treated patients developed akathisia, which resolved with lowering of the medication dosage. No clinically significant differences between the treatment groups were observed in assessment of vital signs or ECG parameters.

In summary, data on the use of ziprasidone in children are scarce.

Paliperidone

Twelve abstracts pertaining to paliperidone were retrieved from the MEDLINE and EMBASE searches. Of these, none met our inclusion criteria.

Discussion

Multiple RCTs have established the efficacy of many of the SGAs in paediatric mental health disorders. It is clear that these medications offer real benefits to children living with mental illness and have been a useful addition to the treatment options available for paediatric schizophrenia, bipolar disorder, disruptive behaviour disorders, autism and Tourette's syndrome. The present review of adverse effect data from RCTs has confirmed the existence of both metabolic and neurological adverse effects in children treated with these SGAs. The risk of metabolic adverse effects appears greatest with olanzapine, followed by clozapine and quetiapine. Risks for metabolic adverse effects appear lower for risperidone and aripiprazole, while data on ziprasidone in children are scarce. The risk of neurological adverse effects of treatment appears greatest with risperidone, olanzapine and aripiprazole. Neurological adverse effects appear very uncommon in children treated with quetiapine and clozapine, but there are not enough paediatric data on ziprasidone to reach satisfactory conclusions.

With respect to the noted metabolic adverse effects of SGA treatment, the long-term health

consequences of obesity and dyslipidaemia in children are concerning. A prospective cohort study of 2195 children followed for 21 years has shown that youth determinants of adult metabolic syndrome include obesity, high triglycerides, high insulin, high C-reactive protein and a family history of hypertension and type 2 diabetes.[46] Young adults who are overweight at age 5 years have more than twice the odds (OR 2.6, 95% CI 1.29, 5.22) of developing diabetes by age 21 years compared with those with a normal BMI at age 5 years.[47] Obesity, high LDL cholesterol and low HDL cholesterol in childhood are associated with a decrease in carotid artery elasticity in adulthood, an early pathophysiological change relevant to the development of atherosclerosis.[48] The social and emotional consequences of obesity in a child who may already be seen as different because of their mental health disorder is also worth considering. A prospective study has demonstrated that women with metabolic syndrome in childhood have higher levels of depressive symptoms in adulthood than women free of childhood metabolic syndrome.[49]

Given the evidence for metabolic adverse effects in children treated with SGAs, and the long-term sequelae of these problems, monitoring of all children prescribed SGAs is appropriate. There has been a notable lag, however, in the translation of research evidence into changes in clinical practice. Data from the US suggest that metabolic testing rates have shown little change following the 2003 FDA warning on diabetes risk for SGAs and recommendations from the American Psychiatric Association (APA) in 2004 that all patients receiving SGAs have glucose and lipid testing. In the evaluation of 109 451 individuals receiving Medicaid who began taking an SGA (sample included 25% children), initial testing rates (pre-warning) were low (glucose 27%, lipids 10%). The FDA warning and APA recommendations were not associated with an increase in glucose testing among SGA-treated patients and was associated with only a marginal increase in lipid testing rates (1.7%; $p < 0.02$).[50]

Despite initial claims that the SGAs had few neurological adverse effects, this appears only true for quetiapine and clozapine. Paediatric trial data support the presence of neurological complications in children treated with risperidone, olanzapine and aripiprazole. Potential neurological complications include acute dystonic reactions, parkinsonism, tardive dystonia, tardive dyskinesia and akathisia. While these neurological complications will often be relieved with cessation of the offending agent, both tardive dyskinesia and tardive dystonia can be very difficult to treat and can be permanent in some patients. A high degree of vigilance is necessary in identifying neurological complications of therapy and treating them promptly.

Limitations of the current review include the short duration of most RCTs, with the majority of placebo-controlled trials lasting 10 weeks or less. While 10 weeks is an adequate timeframe to demonstrate weight gain and increases in BMI, abnormalities on lipid testing may take longer to become apparent, especially with medications where weight gain occurs more slowly. Many of the risperidone trials did not include metabolic laboratory testing as part of their study protocol. It is possible that selective outcome reporting occurred and that this information was collected but not reported. RCTs may underestimate metabolic and neurological adverse effects that occur in a real-world setting as these trials usually forbid polypharmacy, which is frequent in paediatric mental health disorders. Evaluation of open-label, longer duration trials of SGAs is appropriate to delineate chronic adverse effects associated with SGA use. Open-label and observational trials can provide useful evidence on harms associated with medication use. We have performed a systematic review of open-label trials, which we were unable to include in the current manuscript as the great volume of information precludes publishing the data in a single manuscript. We found the open-label studies reported similar adverse effects to the RCTs, but the magnitude of change was often larger due to the longer study periods involved.

Conclusions

We have good evidence to support the existence of both metabolic and neurological adverse effects

in children treated with these medications. Proper attention and vigilance to potential metabolic and neurological adverse effects is necessary and should be considered part of the standard of care.

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