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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CRD summary
The review concluded that there was evidence to support that second-generation antipsychotic use in children was associated with metabolic and neurological adverse effects. Limitations in the evidence, in particular the short-term duration and small sample sizes of the included trials, and potential for missing trials mean that the authors' conclusions should be considered tentatively.

Authors' objectives
To determine whether the use of second-generation antipsychotics in children was associated with specific metabolic and neurological adverse effects.

Searching
MEDLINE and EMBASE were searched from 1996 to May 2010; search terms were not reported. Searches were carried out for each of the second-generation antipsychotic agents separately.

Study selection
Eligible double-blind randomised controlled trials (RCTs) compared second-generation antipsychotic medications with placebo or an active comparator in a paediatric population (18 years old or younger) for the treatment of mental health disorders. The primary outcomes of interest were metabolic and neurological adverse effects (measured by physical examination, rating scales or laboratory tests). Trials with adult participants were included only if separate data for the paediatric population were reported.

Trial interventions included risperidone, olanzapine, quetiapine, clozapine, aripiprazole and ziprasidone. Most interventions were compared with placebo but some trials included an active comparator (olanzapine, haloperidol, pimozide, clonidine, risperidone, divalproex and clozapine). Trial duration lasted less than three months (range three to 12 weeks) in most trials, but three trials had a duration of six months. Populations varied across trials and included children with schizophrenia, autistic disorder, conduct or disruptive behaviour disorders, aggression, bipolar, pervasive developmental disorder, mania, combined bipolar with ADHD and Tourette's syndrome.

Two reviewers independently selected trials for inclusion in the review and any disagreements were resolved by discussion.

Assessment of study quality
Two reviewers independently assessed trial quality using criteria developed by the USA Preventative Services Task Force. The domains assessed included: allocation concealment, blinding, sequence generation, intention-to-treat analysis, a clear statement of interventions and outcomes, assembly of comparable groups, use of acceptable measurement instruments applied equally and appropriate attention to confounders in analysis. Each trial was rated as good, fair or poor.

Data extraction
Two reviewers independently extracted data that allowed for the calculation of odds ratios with 95% confidence intervals for binary outcomes and mean differences for continuous outcomes. When standard deviations were missing from trial data the standard deviation of a comparable trial was imputed, or where other data were missing, these were imputed with replacement values. The reviewers attempted to contact the authors of the primary studies when data were missing or additional information was required.

Methods of synthesis
Trials were pooled using a fixed-effect model for each outcome. Separate analyses were performed for each agent. Where there was evidence of statistical heterogeneity a random-effects model was used. Statistical heterogeneity was
assessed using $X^2$ and $I^2$ (an index approaching 50% was considered significant). Clinical heterogeneity was assessed by comparing trial design and the distribution of participant factors. Analyses were also performed according to duration of trial (12 weeks or shorter versus trials longer than 12 weeks).

**Results of the review**

Thirty-five RCTs were included in the review (number of participants not stated). Overall, trial quality was considered to be high (32 trials received a rating of good or fair).

**Risperidone** (19 RCTs): Trial durations ranged from three weeks to six months and trial quality ranged from low to good. In trials shorter than 12 weeks, significant increased risk was found (compared with placebo) for weight gain (10 RCTs), body mass index, blood pressure (minor), extrapyramidal symptoms (seven RCTs) and elevated prolactin (three RCTs). Trials of 12 weeks or more demonstrated a significant increase in weight gain (three RCTs) when compared with placebo. Outcomes with only one RCT were also stated in the review.

**Olanzapine** (seven RCTs): Trial durations ranged from three to eight weeks and were of good quality. Compared with placebo, significant increased risk was found for weight gain (three RCTs), clinically significant weight gain, increased body mass index (two RCTs), extrapyramidal symptoms, increased blood pressure (minor) and elevation in triglycerides (two RCTs), total cholesterol (two RCTs), low-density lipoprotein cholesterol, insulin, prolactin (two RCTs), aspartate and alanine transaminase (two RCTs). Compared with risperidone, greater weight gain and metabolic laboratory abnormalities were found with olanzapine (two RCTs). Compared with clozapine, no significant between group differences were found in terms of weight gain and metabolic laboratory abnormalities.

**Quetiapine** (four RCTs): Trial durations ranged from six to eight weeks and were of good quality. Significant increased risk was found for weight gain (three RCTs), increase in blood pressure and heart rate (minor) and elevated triglycerides compared with placebo.

**Clozapine** (three RCTs): Trials durations ranged from six to 12 weeks and were of good quality. All comparisons were with an active comparator: olanzapine (two RCTs, see above) and haloperidol (one RCT). A greater proportion of patients receiving clozapine demonstrated a decrease in absolute neutrophil count compared with haloperidol. No change in either group in total score on the Abnormal Involuntary Movement Scale was found. In addition, a similar mean weight gain in both groups was also found.

**Aripiprazole** (five RCTs): Trial durations ranged from four to eight weeks and were of good quality. Significant increased risk was found for weight gain (five RCTs), clinically significant weight gain, increase in body mass index (three RCTs) and extrapyramidal symptoms compared with placebo (five RCTs). Evidence of metabolic laboratory abnormalities were not found and prolactin levels were found to decrease (four RCTs).

**Ziprasidone** (one RCT): No significant between group differences were observed for the main endpoints in this eight week trial in children with Tourette's syndrome.

**Paliperidone**: no trials meeting the inclusion criteria were found.

**Authors' conclusions**

There was evidence to support that second-generation antipsychotic use in children was associated with metabolic and neurological adverse effects.

**CRD commentary**

The review question was supported by clear inclusion criteria. Two electronic databases were searched; index terms were not reported nor was it clear whether this search was restricted by language. No attempt was made to identify unpublished trials. Appropriate steps were taken to minimise the likelihood of reviewer error and bias for the selection of trials, data extraction and validity assessment. Trial quality was assessed using relevant criteria. Although individual results were not reported the overall quality of the included trials was considered to be high.

Trials were pooled using appropriate methods. Statistical heterogeneity was assessed and significant heterogeneity was found in some analyses, all relating to weight gain. Not all estimates were fully reported which made it more difficult to assess the reliability of these results. Many of the summary estimates were based on few included RCTs. Other
Limitations included limited patient details, small sample trials and short study duration (less than 10 weeks). Given the limitations of the evidence and the potential for missing trials the authors' conclusions should be considered tentatively.

**Implications of the review for practice and research**

**Practice:** The authors stated that attention and vigilance to potential metabolic and neurological adverse effects was required and should be considered part of standard care.

**Research:** The authors did not state any implications for research.

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