Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis
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CRD summary
The review found that second-generation antipsychotics commonly caused adverse short-term metabolic effects and extrapyramidal syndrome in children and adolescents and that adverse effect profiles varied across the different drugs. Post-hoc determination of methods, suboptimal study-quality assessment and reliance on indirect comparisons suggest that these conclusions require cautious interpretation.

Authors' objectives
To assess the short-term adverse effects of second-generation antipsychotics in children and adolescents.

Searching
The reviewers searched MEDLINE and EMBASE (1996 to October 2010) and the clinical trial registries of the Food and Drug Administration and European Medicines Agency. Search terms were reported. Reference lists of retrieved studies and reviews were checked.

Study selection
Eligible studies were short-term (up to 12 weeks) controlled trials of adverse effects associated with second-generation antipsychotics in children and adolescents. Studies needed to include at least 10 participants in each arm and have control groups that received medication or placebo. Studies that used cross-over, retrospective, combination or discontinuation designs (not further defined) were excluded. Outcomes of interest were adverse events reported by the largest number of studies.

Children and adolescents in the included studies had schizophrenia, bipolar disorder, behavioural problems (comorbid with autism or an intellectual disorder), Tourette syndrome or conduct disorder. The mean age of participants ranged from five to 17 years and just over one in four studies were restricted to adolescents. In most studies most participants were white males. Antipsychotics used were aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone. Doses varied between and within studies. Most studies included a washout period. Outcomes reported in the review were weight, metabolic parameters (glucose, cholesterol, triglycerides), prolactin, somnolence or sedation and extrapyramidal syndrome (including akathisia). Most studies were set in USA and were industry funded.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The quality of reporting of adverse effects was assessed by allocating one point where detailed data were given (such as mean and standard deviation for continuous variables) and zero points when data were incomplete or absent. The score could range from 1 to 13 points.

Two reviewers independently assessed study quality.

Data extraction
The reviewers extracted event rates (binary data) and mean changes from baseline (continuous data) from each study. Missing data were not imputed.

Two reviewers independently extracted the data, checking the original report in cases of disagreement. Primary study authors were contacted to request missing information.

Methods of synthesis
A Bayesian multiple treatment comparison meta-analysis was conducted using the Markov chain Monte-Carlo method. Binary data were combined using a logistic regression model. Continuous data were combined using a natural scale.
Findings were expressed as odds ratios for binary data and mean differences in change from baseline for continuous data, each with 95% credible intervals (CI). Sensitivity analyses were of randomised studies and different choices of low-information prior distributions.

Results of the review
The review included 41 studies (4,015 participants, range nine to 302). The meta-analysis reportedly included 93 arms: between four and 25 arms for each active intervention and 23 control arms (untreated or placebo). Quality of reporting was rated as moderate (mean score of 5 points out of 13).

Clozapine data were only sufficient for analyses of weight gain and somnolence; other drugs were assessed for all outcomes. Findings reported here showed a significant difference between the intervention group and placebo or no treatment; findings for other comparisons were not significant.

Weight gain was reported by 25 studies (62 arms, 3,401 participants). Aripiprazole, clozapine, olanzapine, quetiapine and risperidone were associated with significant gain. Odds ratios for risk of weight gain ranged from 3.77 (CI 0.37 to 16.27) for ziprasidone to 15.1 (CI 6.56 to 31.1) for olanzapine. Mean weight gain ranged from 0.89 to 3.99kg (30 studies, 66 arms, 3,221 participants) and was highest for olanzapine (mean gain 2.99kg). Ziprasidone was associated with a mean weight loss of -0.1kg, which was not statistically significant.

Metabolic outcomes were reported by 10 studies (27 arms, 1,655 to 1,784 participants). Risperidone and olanzapine significantly increased glucose (mean increases ranged from 2.09 to 3.7mg/dL). Quetiapine and olanzapine significantly increased cholesterol (mean increases ranged from 4.46 to 10.77mg/dL) and triglycerides (mean increases ranged from 19.5 to 20.18mg/dL).

Increases in prolactin were reported by 12 studies (26 arms, 1,180 participants). Risperidone, olanzapine and ziprasidone statistically significantly increased the risk of a meaningful increase in prolactin (odds ratios 15.6 to 38.63). Sedation and somnolence were reported by 29 studies (66 arms, 3,348 participants) and all drugs significantly increased the risk (odds ratios 5.44 to 54.82). Extrapyramidal syndrome (including akathisia) was reported by 28 studies (63 arms, 3,258 participants) and ziprasidone, olanzapine, aripiprazole and risperidone all significantly increased the risk (odds ratios 3.71 to 20.56).

Credible intervals were reported for all analyses. The findings of sensitivity analyses did not differ substantially from those of the main analyses.

Authors' conclusions
Second-generation antipsychotics commonly caused adverse short-term metabolic effects and extrapyramidal syndrome in children and adolescents. Adverse effect profiles varied across the different drugs.

CRD commentary
The objectives of the review were clear. Inclusion criteria were altered post hoc and all longer-term studies were excluded on the grounds that they would likely be follow-ups from industry-funded trials. As inclusion was restricted to studies that reported the adverse events most frequently reported in other studies, review outcomes also appeared to be determined post hoc. Relevant sources were searched for published and unpublished studies. It was unclear whether the search was restricted by language. Steps were taken to limit possible reviewer bias and error by having more than one reviewer independently assess study quality and extract data; it was unclear whether this also applied to study selection. The authors assessed study quality only on whether adequate statistical details were reported for their outcomes of interest. Without information about other factors (such as comparability of the groups and blinding of outcome assessment) it was difficult to determine the quality of data included in the review.

Meta-analysis relied largely on indirect comparisons of uncertain reliability due to clinical and methodological heterogeneity between the studies. It was unclear whether the studies were statistically homogeneous. The review authors acknowledged that there were few data and wide credible intervals for some comparisons and studies were of short duration.

Post-hoc determination of the review's inclusion criteria, suboptimal quality assessment and reliance on indirect comparisons suggest that the authors' conclusions require cautious interpretation.
Implications of the review for practice and research

**Practice:** Guidelines for use of second generation antipsychotics in children and adolescents should advise careful clinical and biological monitoring of adverse effects. These drugs should be prescribed only for evidence-based indications.

**Research:** The authors stated that long-term multi-arm comparative studies of second generation antipsychotics in children and adolescents were needed urgently and should report on both efficacy and adverse effects. Other research that the authors recommended were longer-term studies of quetiapine and olanzapine, investigation of prolactin levels and osteoporosis risk in females taking risperidone, olanzapine and ziprasidone and how moderators (other than gender) contribute to adverse event rates. They noted that higher standards of reporting of adverse effects were needed.

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