Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis

De Hert M, Yu W, Detraux J, Sweers K, van Winkel R, Correll CU

CRD summary
This review found preliminary evidence that lurasidone might be less likely to increase weight than other newly approved second-generation antipsychotics, for treating schizophrenia and bipolar disorder, and that asenapine and iloperidone might cause short-term metabolic adverse effects, but more evidence was needed. These conclusions require very cautious interpretation, due to poor reporting and methodological limitations in the review.

Authors’ objectives
To assess the effects of new second-generation antipsychotics (asenapine, iloperidone, lurasidone and paliperidone), for treating schizophrenia and bipolar disorder, on body weight and other metabolic outcomes.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL and EMBASE were searched for articles from 1966 to March 2012, without language restriction. For iloperidone and lurasidone, the US Food and Drug Administration (FDA) drug approval database was searched. Search terms were reported. The reviewers checked the reference lists of relevant studies, and sought additional studies from the drug manufacturers.

Study selection
Eligible studies were randomised controlled trials (RCTs) comparing asenapine, iloperidone, lurasidone or paliperidone head-to-head or versus placebo, in patients with schizophrenia or bipolar disorder. Trials had to report weight gain, glucose, cholesterol, triglycerides or other lipid variables, in the short term (up to 12 weeks) or longer term (13 to 52 weeks), or both.

In the included trials, over 85% of participants had schizophrenia, and the others had bipolar disorder. For the primary analysis of weight outcomes (mean weight change and percentage weight change) all trials were placebo controlled. A secondary analysis of weight and other metabolic outcomes used data from trials with active comparators or single-arm studies. No studies compared the new second-generation antipsychotics head-to-head. There were primary trials for all four drugs, and FDA regulatory approval data for iloperidone and lurasidone. The outcomes were weight increase from baseline of 7% or more; change from baseline in mean weight; total, low-density and high-density lipoprotein cholesterol; triglycerides; and glucose. Most trials (all those of iloperidone and lurasidone) lasted less than 12 weeks (range three to 52).

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Trial quality was assessed using the Jadad scale, for the adequacy of reported randomisation, double-blinding, and withdrawals or dropouts. The maximum score was 5 points. The authors did not state how many reviewers performed the assessment.

Data extraction
The data were extracted from primary trials and regulatory approval studies. Where these overlapped, only one source was used. The relative risks and 95% confidence intervals were calculated for binary data, and mean differences (between groups, in change from baseline), with 95% confidence intervals, were calculated for continuous data. The number needed to harm was calculated. Only data from the relevant drug arm were extracted from non-placebo-controlled trials.

The authors did not state how many reviewers extracted the data.
Methods of synthesis
The trial data were combined, using a random-effects model, to calculate pooled relative risks and numbers needed to harm, for binary data, or weighted mean differences, for continuous data, with 95% confidence intervals. The main meta-analysis included only placebo-controlled trial data and reported weight outcomes. The second meta-analysis included all trial data and reported weight and metabolic outcomes.

Where the data were skewed (for some metabolic variables) an exploratory meta-analysis was conducted. Where the trials had multiple arms, the placebo arm was used several times. Statistical heterogeneity was assessed with $I^2$, and publication bias was assessed with Egger's test. For indirect comparisons, where two antipsychotics were compared with placebo, a lack of overlap in the two confidence intervals was interpreted as evidence of a significant difference between the two antipsychotics.

Results of the review
The authors stated that 56 trials were included, with 21,691 participants, and 42 of these trials (15,942 participants) were placebo controlled and suitable for pooling. All 56 trials were analysed for metabolic outcomes. Trial quality was satisfactory overall, with a mean Jadad score of 3.9 points (range 2 to 5).

Compared with placebo, a weight gain of at least 7% was significantly more likely in groups taking asenapine either short term (RR 4.09, 95% CI 2.25 to 7.43; five RCTs; NNH 17) or long term (RR 2.05, 95% CI 1.21 to 3.46; three RCTs; NNH eight), those taking iloperidone short term (RR 3.13, 95% CI 2.08 to 4.70; four RCTs; NNH 11), and those taking paliperidone either short term (RR 2.17, 95% CI 1.64 to 2.86; 12 RCTs; NNH 20) or long term (RR 1.76, 95% CI 1.06 to 2.90; two RCTs; NNH 20). Short-term lurasidone was not significantly associated with weight gain (six RCTs).

Compared with placebo, the mean short-term weighted mean difference in weight change was 0.49kg (95% CI 0.17 to 0.81; five RCTs) with lurasidone, 1.16kg (95% CI 0.83 to 1.49; three RCTs) with asenapine, 1.24kg (95% CI 0.91 to 1.57; 15 RCTs) with paliperidone, and 2.50kg (95% CI 1.92 to 3.08; one RCT) with iloperidone. Where reported, heterogeneity was absent, except for the analysis of paliperidone ($I^2=91%$).

Compared with placebo, long-term asenapine and paliperidone were associated with significant weight gain. The mean long-term weighted mean difference in weight change was 1.30kg (95% CI 0.62 to 1.98; three RCTs) with asenapine, and 0.50kg (95% CI 0.22 to 0.78; four RCTs) with paliperidone. Where reported, heterogeneity was absent, except for the analysis of paliperidone ($I^2=68%$).

When all 56 studies were pooled, no clinically meaningful differences were detected between the intervention and placebo, for most outcomes. Short-term iloperidone (one RCT) was associated with a statistically significant increase in total cholesterol (+11.60mg per decilitre, dL; 95% CI 4.98 to 18.22), and high-density (+3.6mg/dL, 95% CI 1.58 to 5.62) and low-density (+10.30mg/dL, 95% CI 4.94 to 15.66) lipoprotein cholesterol. Short-term lurasidone was associated with an increase in high-density lipoprotein cholesterol (+1.50mg/dL, 95% CI 0.56 to 2.44; five RCTs), and long-term asenapine was associated with an increase in total cholesterol (+6.53mg/dL, 95% CI 1.17 to 11.89; one RCT).

When the drugs were ranked for weight outcomes, all except lurasidone were associated with a significant likelihood of short-term weight gain, compared with placebo. There was no clear evidence of publication bias.

Authors' conclusions
There was preliminary evidence that lurasidone might be less likely to increase weight than other newly approved second-generation antipsychotics, for treating schizophrenia and bipolar disorder, and that asenapine and iloperidone might cause short-term metabolic adverse effects, but more evidence was needed.

CRD commentary
The objectives and inclusion criteria were clear, but the authors included some single-arm studies that did not meet the criteria for study design. Different inclusion criteria were used for two of the four interventions, with regulatory approval data included. Relevant sources were searched for published and unpublished trials, without language restrictions. It was unclear whether sufficient steps were taken to minimise the risk of reviewer bias and error in study selection, validity assessment and data extraction. The Jadad scale assessed some quality criteria, but did not assess...
allocation concealment and follow-up rates.

It was not entirely clear how many trials were included in the review, as some had overlapping samples or were extensions of other trials; there was some inconsistency in the text on study numbers. It was also unclear at times which trials were included in each analysis. Few participant characteristics, such as age, were reported. The authors acknowledged that some data that were pooled were very skewed, and there was high heterogeneity for two analyses ($I^2=68\%$ and 91\%). The confidence intervals were wide and there were very few data for some analyses. The placebo groups for several trials were used multiple times in the same analysis. The use of indirect comparisons to rank different interventions was of questionable validity as it was unclear whether the trial characteristics were sufficiently similar for meaningful comparisons to be made.

The authors' conclusions require very cautious interpretation, due to poor reporting and methodological limitations in the review.

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

**Practice:** The authors stated that newly approved second-generation antipsychotics should be used with caution, and that body weight and metabolic variables should be carefully monitored, especially in children, adolescents and people being treated for a first episode.

**Research:** The authors stated that RCTs and active-controlled clinical trials were needed to assess the metabolic safety of newly approved second-generation antipsychotics. Trials should assess the adverse effects of these drugs so that they can be ranked with other available antipsychotics.

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