Comparing tolerability of olanzapine in schizophrenia and affective disorders: a meta-analysis

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CRD summary
This review concluded that patients with schizophrenia might be more likely to gain weight while on olanzapine, than patients with bipolar disorder. The uncertain quality of the evidence, the lack of direct comparisons, and the differences between trials, limit the reliability of the pooled results. The authors' conclusions should be considered with caution.

Authors' objectives
To investigate olanzapine-induced metabolic adverse effects and extrapyramidal symptoms, in patients with schizophrenia, compared with those in patients with affective disorders.

Searching
EMBASE, PubMed, PsycINFO and ClinicalTrials.gov were searched to 2010, without language restrictions. Search terms were reported. The reference lists of review articles were searched and cross-referencing was used to identify further studies.

Study selection
Open-label or double-blind randomised controlled trials (RCTs) of oral olanzapine monotherapy for the treatment of adult patients (aged 18 to 65 years) with schizophrenia or affective disorders (including bipolar disorder) were eligible for inclusion if they lasted at least three weeks. Trials had to report data on the metabolic or extrapyramidal adverse effects. Fixed and flexible dosing trials were eligible, but trials of patients with schizoaffective disorder were excluded.

The included trials studied olanzapine in patients with schizophrenia or bipolar disorder. The patients' mean age ranged from 26.7 to 43.1 years across trials. The mean daily dose of olanzapine ranged from 5mg to 20.1mg. Treatment duration varied from three to 104 weeks. There was a higher percentage of male patients in the schizophrenia trials (67.5%), than in the bipolar disorder trials (46.5%).

Two reviewers independently undertook study selection.

Assessment of study quality
The authors did not state that they assessed trial quality.

Data extraction
The data were extracted on metabolic and extrapyramidal adverse effects, and used to calculate the mean changes for continuous outcomes or event rates for dichotomous outcomes, together with 95% confidence intervals.

One reviewer extracted the data and study authors were contacted, if necessary.

Methods of synthesis
Random-effects meta-analysis was used to calculate pooled mean changes and event rates, with 95% confidence intervals. The data were analysed separately for schizophrenia and for bipolar disorders. $I^2$ was used to assess statistical heterogeneity, sensitivity analysis was used to assess confounding factors, and logistic regression was used to determine any association between the gender ratio and the tolerability outcome.

Results of the review
A total of 33 trials were included, with 4,831 patients. Nineteen trials were of patients with schizophrenia (2,389 patients), and 14 trials were of patients with bipolar disorder (2,442 patients).

Metabolic effects: Olanzapine was associated with a statistically significantly greater weight gain in patients with schizophrenia than in patients with bipolar disorder (mean weight gain 3.14kg in 18 trials versus 2.28kg in 13 trials;
There were no significant differences between patients with schizophrenia and those with bipolar disorder, in cholesterol change (six trials for schizophrenia; seven trials for bipolar disorder), in glucose change (seven trials for schizophrenia; eight trials for bipolar disorder), and in triglyceride change (two trials for schizophrenia; four trials for bipolar disorder).

**Extrapyramidal effects:** There was no significant difference with olanzapine between patients with schizophrenia and those with bipolar disorder in the incidence of akathisia (11 trials for schizophrenia; eight trials for bipolar disorder), parkinsonism (six trials for schizophrenia; seven trials for bipolar disorder), and medication for Parkinson's disease (eight trials for schizophrenia; four trials for bipolar disorder).

There was evidence of statistical heterogeneity in all analyses (I²>50%). Sensitivity analyses indicated some differences between genders, with company sponsorship, and with different treatment duration; the full results were presented.

**Authors’ conclusions**
Patients with schizophrenia might be more likely to gain weight while on olanzapine, than patients with bipolar disorder.

**CRD commentary**
The inclusion criteria for the review were broadly defined and four relevant data sources were searched for articles in any language. Publication bias was not assessed and cannot be ruled out. Attempts were made to reduce reviewer error and bias during study selection, but the same attempts were not reported for data extraction. Quality assessment, using a standard checklist, was not undertaken and few trial details were provided, making it difficult to determine the reliability of the evidence.

There were differences across the trials in the doses, trial duration and age of patients. The data were combined using random-effects meta-analysis, with substantial statistical heterogeneity reported for all analyses, which may mean that the data were not suitable for pooling. The authors noted that their results were limited by the lack of trials that directly compared the effects of olanzapine in patients with schizophrenia versus those with affective disorder.

The uncertain quality of the evidence, the lack of direct comparisons, and the differences between trials, limit the reliability of the pooled results. The authors’ conclusions should be considered with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that their review supported the recommendation for regular screening and accurate monitoring of patients who were prescribed antipsychotics.

**Research:** The authors stated that prospective controlled trials of olanzapine-induced adverse effects comparing patients with different psychiatric disorders were needed. The effects of previous antipsychotic exposure, ethnicity, and initial treatment weight on the olanzapine-induced adverse events needed investigation.

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