Time to all-cause treatment discontinuation of olanzapine compared to other antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis

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CRD summary
The review concluded that olanzapine appeared to have lower time to all-cause discontinuation rates in both RCTs and observational studies than most first and second generation antipsychotics, except for clozapine. The mixed quality of the evidence base and the small number of studies for some comparisons limits the reliability of the authors’ conclusions.

Authors' objectives
To compare olanzapine with other antipsychotics for the treatment of schizophrenia in terms of time to all-cause medication discontinuation and all-cause treatment discontinuation rate.

Searching
MEDLINE, EMBASE, Science Citation Index, The Cochrane Library (Issue 4) and the Cochrane Schizophrenia Group Register were searched from inception to April 2009 for articles in any language. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) and observational studies that compared olanzapine with any other oral antipsychotic in adult patients with schizophrenia or a related condition were eligible for inclusion. Studies had to have a minimum of 12 weeks follow-up and report data on all-cause medication discontinuation or all-cause treatment discontinuation.

The included trials studied olanzapine with a variety of antipsychotics, including haloperidol, clozapine, ziprasidone, perphenazine and risperidone. Most studies were in patients diagnosed with schizophrenia or schizoaffective disorder using the Diagnostic and Statistical Manual of Mental Disorders and/or the International Classification of Diseases criteria. Patients were mainly adult out-patients with a relatively chronic course of illness. The proportion of male patients ranged from 28.8% to 96.4%.

Two reviewers independently undertook study selection and disagreements were resolved by consensus.

Assessment of study quality
Quality assessment was undertaken using the Higgins and Green checklist for RCTs, and the Downs and Black checklist for observational studies.

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Data extraction
Data were extracted on outcomes and used to calculate relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs). Intention-to-treat data were used, when possible.

Two reviewers extracted the data and disagreements were resolved by consensus.

Methods of synthesis
Random-effects (inverse variance) meta-analysis was used to calculate pooled relative risks or hazard ratios, with 95% confidence intervals. Missing data were imputed. Data were pooled separately for RCTs and observational studies. Subgroup analyses were undertaken on the basis of comparator drug. $I^2$ was used to assess statistical heterogeneity. Sensitivity analysis was conducted on the basis of olanzapine dosages, allocation concealment, time period, imputation of data and study sponsorship. Publication bias was assessed using funnel plots and Egger’s linear regression.

Results of the review
A total of 60 RCTs (33,360 patients) and 27 observational studies (202,591 patients) were included. The mean duration of follow-up ranged from 12 weeks to two years. The quality of the RCTs was variable; 70% did not report an adequate generation of allocation sequence, 77% did not report adequate allocation concealment, and only 20% were double-blind. The quality of the observational studies ranged from 4 to 23/33 (median 13). The study sample size ranged from 20 to 18,154 patients in the RCTs and 50 to 63,214 patients in the observational studies.

**Time to all-cause medication discontinuation** (results taken from text)

In RCTs, olanzapine was significantly better than aripiprazole (HR 0.81, 95% CI 0.71 to 0.93; two RCTs), quetiapine (HR 0.68, 95% CI 0.56 to 0.83; six RCTs), risperidone (HR 0.77, 95% CI 0.70 to 0.86; 12 RCTs), ziprasidone (HR 0.73, 95% CI 0.59 to 0.90; six RCTs) and perphenazine (HR 0.68, 95% CI 0.48 to 0.97; three RCTs). There were no significant differences between olanzapine and clozapine (four RCTs), amisulpride (three RCTs) or haloperidol (two studies) in RCTs. Observational studies showed some similar results, but there were some differences; full results presented in the review.

**All-cause medication discontinuation rates** (results taken from text)

In RCTs, olanzapine was associated with significantly less discontinuation rates than aripiprazole (RR 0.87, 95% CI 0.80 to 0.93; six RCTs), quetiapine (RR 0.69, 95% CI 0.58 to 0.82; nine RCTs), risperidone (RR 0.86, 95% CI 0.81 to 0.92; 23 RCTs), ziprasidone (RR 0.81, 95% CI 0.78 to 0.83; six RCTs), haloperidol (RR 0.75, 95% CI 0.66 to 0.85; 16 RCTs), perphenazine (RR 0.78, 95% CI 0.64 to 0.95; three RCTs) and sulpiride (RR 0.56, 95% CI 0.32 to 0.96; one RCT). There were no significant differences between olanzapine and clozapine (eight RCTs) or amisulpride (four RCTs). Observational studies showed some similar results; full results were presented in the review.

There was evidence of significant statistical heterogeneity for several of the analyses. There was no evidence of publication bias apart from one analysis with observational studies. The dose of olanzapine did not alter results. Other analyses were reported.

**Authors' conclusions**

Olanzapine appeared to have lower time to all-cause discontinuation rates in both RCTs and observational studies than most first and second generation antipsychotics, except for clozapine.

**CRD commentary**

Inclusion criteria for the review were clearly defined and several relevant databases were searched for articles in any language. Publication bias was assessed and was reportedly not detected for most analyses. Attempts were made to reduce reviewer error and bias throughout the review. Quality assessment indicated that the quality of the evidence base was mixed, although some of the quality issues could have been due to poor reporting.

Data were pooled using meta-analysis and statistical heterogeneity was assessed; some analyses had high levels of statistical heterogeneity and/or a small number of studies. Overall, the mixed quality of the evidence base and the small number of studies for some comparisons limits the reliability of the pooled results; hence, the authors’ conclusions should be interpreted with a degree of caution.

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

**Practice:** Authors stated that there was a need to balance the risks and benefits of antipsychotic medications in the individual patient.

**Research:** Authors stated that comprehensive meta-analyses that compared antipsychotics head-to-head and include a large number of RCTs and observational studies could help further determine the differential effectiveness of antipsychotics in the treatment of schizophrenia.

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