Tolerability of atypical antipsychotics in the treatment of adults with schizophrenia or bipolar disorder: a mixed treatment comparison of randomized controlled trials

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CRD summary
The authors concluded that antipsychotics had mixed tolerability profiles, with different treatments being better tolerated depending on the outcome assessed. The conclusions reflect the evidence presented, and despite some methodological weaknesses are likely to be reliable.

Authors’ objectives
To compare the tolerability profiles of atypical antipsychotics in adults with schizophrenia or bipolar disorder.

Searching
BIOSIS Previews, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE and PsycINFO (searches completed December 2007) were searched for English-language papers and abstracts. No restriction on year of publication was applied. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared any atypical antipsychotic with at least one other atypical antipsychotic in adult patients with schizophrenia or bipolar disorder were eligible for inclusion. Trials that compared atypical antipsychotics with placebo or conventional antipsychotics (such as haloperidol) were excluded. Outcomes considered were: functional health dimensions (usual activities); general well-being (mood and anxiety); range of symptoms associated with antipsychotic medications (such as tiredness, weaknesses, weight gain); extrapyramidal symptoms-related events (such as akathisia, tremor); and discontinuations (all-cause, due to adverse events or lack of efficacy).

Most studies enrolled patients with schizophrenia. Antipsychotics evaluated were: olanzapine, aripiprazole, risperidone, quetiapine, and ziprasidone. Most studies assessed the following direct comparisons: olanzapine-risperidone; quetiapine-risperidone and; olanzapine-quetiapine.

Two reviewers independently assessed studies for inclusion. The authors did not state how disagreements were resolved.

Assessment of study quality
Study quality was assessed according to methods described in Cochrane Handbook for Systematic Reviews of Interventions. Key criteria assessed were randomisation and concealment of treatment allocation. Studies were rated A (clearly adequate), B (possibly adequate) or C (clearly inadequate).

Two reviewers independently assessed study quality. Disagreements were resolved by a third party.

Data extraction
Data on antipsychotic medications and outcome measures were extracted. Intention-to-treat data were calculated where they were not reported.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Summary estimates for the effects of each treatment compared with baseline treatment (risperidone) was calculated using odds ratios (ORs) and 95% credible intervals (CrIs). Treatment effects were compared using a random-effects mixed treatment Bayesian Markov Chain Monte Carlo simulation. Subgroup analyses were performed to examine the
differential effects of treatments on dizziness and nausea. Sensitivity analysis was performed to assess the impact of selected studies on the risk of extrapyramidal symptoms. Statistical heterogeneity within pairwise comparisons was measured using prespecified standard deviations (SD) values: <0.1 = none/little; 0.1 to 0.5 = some; 0.5 to 1.0 = moderate; 1.0 to 2.0 = high; and >2.0 = very high.

Results of the review
Forty-eight RCTs (50 publications) were included. Data on sample sizes were not reported. Quality of studies were rated as either A or B.

The following outcomes were statistically significant compared with risperidone: decreased bodily anxiety or restlessness with quetiapine (OR 0.51, 95% CrI 0.29 to 0.79); decreased extrapyramidal symptoms with quetiapine (OR 0.44, 95% CrI 0.13 to 0.91); increased weight gain with olanzapine (OR 2.14, 95% CrI 1.76 to 2.63); and decreased weight gain with ziprasidone (OR 0.47, 95% CrI 0.32 to 0.66).

There were significantly fewer all-cause discontinuations with olanzapine (OR 0.72, 95% CrI 0.62 to 0.83) and significantly more all-cause discontinuations with quetiapine (OR 1.29, 95% CrI 1.04 to 1.55) and ziprasidone (OR 1.28, 95% CrI 1.02 to 1.58).

Further results were reported in the paper.

Heterogeneity was moderate or low for all outcomes except tiredness, where evidence of high heterogeneity (SD=1.3) was found.

Authors’ conclusions
Atypical antipsychotics had mixed tolerability profiles. Different treatments were better tolerated depending on the outcome assessed.

CRD commentary
The review addressed a clear question. Several relevant databases were searched. Non-English publications were excluded and unpublished papers were not sought, which raised the possibility of language and publication biases. Appropriate steps were taken to minimise bias and errors during study selection and quality assessment; it was unclear whether such steps were taken during data extraction. No demographic characteristics of patients were reported, which limited inferences on generalisability of results. Study quality was assessed using appropriate criteria. Statistical methods used to combine data appeared appropriate. The authors acknowledged a number of limitations, which included limited data on outcomes assessed and differences in definitions of outcomes and dosing of antipsychotic agents. The conclusions reflect the evidence presented and despite some methodological limitations are likely to be reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

Funding
Medical writing support (AM) funded by AstraZeneca UK Ltd.

Bibliographic details

PubMedID
19698898

DOI
10.1016/j.clinthera.2009.07.004
Original Paper URL
http://dx.doi.org/10.1016/j.clinthera.2009.07.004

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Antipsychotic Agents /adverse effects /therapeutic use; Bipolar Disorder /drug therapy; Humans; Randomized Controlled Trials as Topic; Schizophrenia /drug therapy

AccessionNumber
12009108994

Date bibliographic record published
20/01/2010

Date abstract record published
16/06/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.