Comparing tolerability profile of quetiapine, risperidone, aripiprazole and ziprasidone in schizophrenia and affective disorders: a meta-analysis

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CRD summary
The authors concluded that the evidence did not justify using a particular antipsychotic medication based on diagnosis to minimise certain potential side effects. There was potential for review bias and concerns about the indirect nature of the comparisons and generalisability of the findings. However, the authors acknowledged some of the limitations and their conclusions and research recommendations seem appropriately cautious.

Authors' objectives
To compare the tolerability of four second-generation antipsychotics in the treatment of schizophrenia and affective disorders.

Searching
PubMed, EMBASE and PsycINFO were searched up to 2010 without language restrictions. Search terms were reported. ClinicalTrials.gov was searched. Reference lists of relevant articles were checked for further studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared side effects of four antipsychotics (quetiapine, risperidone, ziprasidone and aripiprazole) in the treatment of patients (aged 18 to 65 years) with schizophrenia or affective disorders. Eligible trials had to administer antipsychotics as oral monotherapy at fixed or flexible doses for at least three weeks. Outcomes of interest were metabolic side effects (such as change of weight, blood glucose and cholesterol levels) or extrapyramidal side effects (such as akathisia and parkinsonism).

Studies were excluded if they were of patients with schizoaffective or schizophreniform disorders, outcome data were incomplete or unavailable and if patients were treated with depot antipsychotics.

Studies of affective disorders were of patients with major depressive disorder or bipolar I or II disorder (with or without manic or mixed episode). The mean age of patients ranged between 26.7 and 50.6 years. Most patients were male. Mean doses of the different antipsychotics varied across studies. Treatment duration ranged from four to 78 weeks in patients with schizophrenia and from three to 52 weeks in patients with affective disorders.

Two reviewers independently screened studies for inclusion.

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

Data extraction
One reviewer extracted means and standard deviations of metabolic side effects and event rates for extrapyramidal side effects. Effect size estimates and 95% confidence intervals were calculated separately for patients with schizophrenia and patients with affective disorders. Primary authors were contacted for missing or additional data.

Methods of synthesis
A random-effects model was used to combine effect size estimates and 95% confidence intervals (CIs) for each outcome and by patient group. Mean differences (MD) were reported.

Statistical heterogeneity was assessed using the I² statistic ($I^2 > 50\%$ indicated considerable heterogeneity) and explored based on age, sex ratio, treatment dose and treatment duration (short-term < 12 weeks versus long-term > 12 weeks).

Results of the review
Forty studies (47 treatment arms) in patients with schizophrenia and 33 studies in patients with affective disorder were
included in the review.

Metabolic changes:

There were no statistically significant differences in weight changes in patients with schizophrenia and affective disorder for quetiapine (22 studies), aripiprazole (10 studies) and risperidone (15 studies).

There was a statistically significant increase in blood cholesterol levels with quetiapine in patients with schizophrenia (MD 8.05mg/dL, 95% CI 5.20 to 10.91; four studies) and a significant decrease in levels in patients with affective disorders (MD -2.76mg/dL, 95% CI -4.60 to -0.93; seven studies). The difference in cholesterol levels was statistically significantly different between the two patient groups. Similar findings were reported for low density lipoprotein.

Aripiprazole decreased levels of cholesterol in both patient groups (four studies); the difference between the two patient groups was not statistically significant.

Quetiapine (15 studies) and aripiprazole (four studies) increased blood glucose levels in both patient groups. The difference between the two patient groups was not statistically significant.

Quetiapine increased triglyceride levels in both patient groups (11 studies). The difference between the two patient groups was not statistically significant.

Extrapyramidal side effects:

Incidence of akathisia was higher in patients with affective disorders for quetiapine (11 studies) and ziprasidone (10 studies) but differences compared to patients with schizophrenia were not reported to be significant.

There was a statistically significant increase in incidence rates for aripiprazole treatment when both patient groups were combined (effect estimate 0.11, 95% CI 0.08 to 0.14; 16 studies). Analysis by patient group showed a statistically significant higher incidence rate in patients with affective disorders.

Incidence of parkinsonism did not significantly differ between the two patient groups when treated with quetiapine (19 studies), risperidone (nine studies) or ziprasidone (nine studies) and aripiprazole (11 studies). Findings on antiparkinson medication use were reported in the review.

All outcomes showed considerable statistical heterogeneity which was explored in the review using subgroup analyses, and the results were reported in the review.

Authors' conclusions

The evidence did not justify using a particular antipsychotic medication preferentially based on diagnosis to minimise certain potential side effects.

CRD commentary

The review question and related inclusion criteria were stated clearly. Several appropriate sources were searched for relevant articles without language restrictions. The search was up to 2010 and the authors acknowledged that further literature had been published since then. Study selection was performed in duplicate but only one reviewer performed the data extraction so reviewer error and bias could not be ruled out. Study quality was not assessed.

There was a lack of trials that directly compared outcomes in patients with schizophrenia and affective disorders. The included study designs were not stated clearly so it was unclear whether studies met inclusion criteria. The authors acknowledged that comparisons between the two patient groups were indirect and they highlighted that the studies did not examine the impact of previous exposure to antipsychotics and that this might affect the generalisability of the findings. Therefore, the methods used to compare differences between groups did not seem appropriate. There was evidence of clinical and statistical heterogeneity across studies (acknowledged by the authors) and it may not have been appropriate to combine study data.

There was potential for bias in the review and concerns regarding the statistical methods, the indirect nature of the
comparisons and generalisability of the findings. The authors acknowledged limitations of the review and their conclusions seem appropriately cautious.

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

**Practice:** The authors stated that it was important that prescribers consider side effects as the efficacy of treatment may be reduced due to the presence of certain side effects. Patients with severe mental illness needed to be informed of the different side effects and should be monitored regularly.

**Research:** The authors stated that future research should assess long-term safety of other antipsychotic drugs and the effects of treatments on patients with different categories of affective disorders (such as major depression disorder and bipolar I or II). They also stated that prospective controlled trials were needed to directly compare treatment differences in patients with schizophrenia and affective disorders.

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