Use of atypical antipsychotic agents in bipolar and schizoaffective disorders: review of the empirical literature  
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Authors' objectives
To examine the use of atypical antipsychotic agents in bipolar and schizoaffective disorders using a review of the empirical literature.

Searching
A search of the electronic database MEDLINE (no dates) was conducted. The bibliographies of retrieved articles were checked and cross-referenced. This was augmented by a review of abstracts presented at numerous professional meetings since the introduction of the first atypical antipsychotic clozapine, in 1989.

Study selection
Study designs of evaluations included in the review
All prospective studies providing statistical comparison data. The authors state that the studies are limited to mainly open-label, uncontrolled designs, but individual study designs included in the review were not stated in the majority of cases.

Specific interventions included in the review
Atypical antipsychotic agents approved by the Food and Drug Administration (FDA) as of March 1998. Studies should also clearly identify whether the agent was used as an adjunct to other mood-stabilising agents or as monotherapy. Studies included in the review examine the effects of clozapine (monotherapy), risperidone (monotherapy and adjunct therapy) and olanzapine (monotherapy and adjunct therapy). Dose regimens not stated.

Participants included in the review
Patients with bipolar or schizoaffective disorders (no further details reported).

Outcomes assessed in the review
The main outcome measure was treatment response rate (% no. of patients) using a rating scale such as the Clinical Global Impression Scale (CGI) or the Young Mania Rating Scale (YMRS). Other rating scales included in the review were the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression Scale of Improvement (CGI-I), the Global Assessment of Functioning Scale (GAF); Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP) and the Montgomery-Asberg Depression Rating Scale (MADRS). The definition of response to treatment was based n that defined by the individual studies. For risperidone mania induction (% no. of patients) was also reported.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

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

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. Data tables presented in the review include information regarding bibliographic details, the number of participants, outcome measure(s), results (% improvement) and the type of therapy (i.e. monotherapy or adjunct).
Methods of synthesis

How were the studies combined?
A narrative summary was used, with studies grouped according to the agent under investigation. A weighted average value was reported for each agent in terms of the % improvement in the rating scale score(s).

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review

Eleven studies. The type of study design was not reported in most cases.

Clozapine (2 studies, 42 patients):
One study showed a 65% response rate (% improved) to clozapine in terms of CGI-I scores and the other a 72% response rate in terms of YMRS and BPRS scores. Both studies looked at monotherapy. Overall a weighted average response rate of 69% was reported.

Risperidone (6 studies, 65 patients):
Four studies used CGI scores, two used YMRS, two used BPRS, one HAM-D and one used GAF scores. The response rate (% improved) ranged from 0% to 64% with an overall weighted average of 51%. Two of the studies looked at monotherapy and the remainder looked mainly at adjunct therapy. In terms of mania induction four studies reported no incidences and the other two studies (both monotherapy) reported rates of 50% (n=4 patients) and 40% (n=2 patients) to give an overall weighted average rate of 9.2%.

Olanzapine (3 studies, 226 patients):
One study used CGI-BP scores, one used YMRS, and one used BPRS and MADRS scores. The response rate (% improved) ranged from 49% to 57% (data not reported for one study) with an overall weighted average of 50%. Two of the studies looked at monotherapy and one looked at adjunct therapy.

Authors' conclusions

Although conclusions cannot be definitively derived from the effectiveness literature discussed in this review the atypical antipsychotic agents do seem to have somewhat clearer advantages in terms of safety for the treatment of bipolar and schizoaffective disorders, advantages which are reflected in the minimal risks of TD and the lower rates of EPS than with typical antipsychotic agents. If future randomised, naturalistic, and/or double-blind studies provide better efficacy data, these agents may prove to play an important role in the treatment of these complex conditions.

CRD commentary

This was a clearly presented review with clear inclusion criteria. However, only one database was searched and although this was supplemented with a manual search of conference abstracts, relevant data might have been missed and publication bias may be a problem.

Little methodological detail was provided in the review, particularly with regards to how the studies were selected and the data extracted. The data tables showed some relevant information about the studies, but the study design was unclear in the majority of cases and there was little information on the participants in terms of their age, gender and disease status. In addition, no information on the number of drop-outs and incidence of adverse events was provided. In view of the nature of the treatments and the type of patients under investigation, it is probable that there was a high level of non-compliance and loss to follow-up in the studies, but this was not reported in the review. It would also appear that the studies were not judged in terms of their validity.

In terms of the results of the studies, the definition of response to treatment appeared to vary between studies i.e. in one study response was defined as a 50% decrease in YMRS, in another a moderate-to-marked response on the CGI.
Combining the results to give a weighted average response rate is therefore misleading. In view of these comments the authors' findings should be interpreted with caution, although their recommendations for further research would appear valid.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that 'the current literature needs to be clarified with prospective controlled studies', firstly comparing 'each individual antipsychotic with typical antipsychotics' as 'adjuncts to mood stabilisers' in 'mania, mixed episodes, and rapid-cycling'. Also 'studies in acute depression, whether bipolar or unipolar, either open or double-blind, given as monotherapy in comparison with an antidepressant (in the case of unipolar depression) or as adjunctive treatment with a mood stabiliser compared to adjunctive placebo (in the case of bipolar depression), should be conducted'. 'Direct studies in bipolar disorder comparing risperidone with olanzapine or clozapine would also be useful, especially if they are randomised and double-blind'. Finally, 'studies on continuation and maintenance treatment, rather than only on short-term treatment, are also needed, at least in the naturalistic setting, but preferably also in a prospective manner with control groups receiving typical antipsychotic agents'.

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