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## Treating generalized anxiety disorder with second generation antipsychotics: a systematic review and meta-analysis

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### CRD summary

This review found second-generation antipsychotics were not superior to placebo as augmentation for refractory generalised anxiety disorder. Despite issues with adverse effects and tolerability, quetiapine monotherapy was efficacious compared to placebo for uncomplicated generalised anxiety disorder. The reported data appeared to support the review conclusions, but the paucity of data and study limitations suggest a cautious interpretation is required.

### Authors' objectives

To determine the efficacy and tolerability of second-generation antipsychotics as augmentation or monotherapy for generalised anxiety disorder.

### Searching

MEDLINE, EMBASE, PsycINFO and The Cochrane Library were searched up to November 2009 for studies published in any language. Search terms were reported. Reference lists of retrieved articles were screened. Current Controlled Trials was searched. The authors searched meeting abstracts of the American College of Neuropsychopharmacology (2004 to 2009), European College of Neuropsychopharmacology (1999 to 2009) and American Psychiatric Association (1996 to 2009).

### Study selection

Randomised double-blind placebo or active comparator trials of mixed or flexible doses of second-generation antipsychotics for generalised anxiety disorder in adults (>18 years) were eligible for inclusion in the review meta-analysis. Open label trials were summarised in the review. Eligible patients needed a primary diagnosis of generalised anxiety disorder. Patients with other Axis I and Axis II disorders were included unless specified in the individual study protocol. Studies that exclusively assessed adults older than 65 years old were excluded.

Included augmentation studies were for refractory generalised anxiety disorder and assessed quetiapine (120mg/day), risperidone (1.1mg/day) and olanzapine (87mg/day). Failed previous treatments were antidepressant with or without benzodiazepine that lasted four to 12 weeks. All of the monotherapy trials assessed quetiapine and all of these except one assessed different doses of between 50mg/day and 300mg/day; one study used flexible doses (mean dose 125mg/day). Study duration ranged from six to 12 weeks.

Mean dose of second-generation antipsychotic (where reported) ranged from 1.12mg/day to 386mg/day. All studies except one defined generalised anxiety disorder according to the Diagnostic and Statistical Manual Fourth Edition, Text Revision (2000). Duration of illness was often not defined. Reported mean durations ranged from 11.4 to 24.9 years. Included patients had mostly received at least six to 12 weeks of antidepressant with or without benzodiazepine. Primary outcomes were: clinically significant response, mostly defined as number of participants with a reduction of at least 50% from baseline in Hamilton Anxiety Rating Scale (HAM-A); remission (mostly defined as HAM-A score of 7 or less); and all-cause discontinuation. Secondary outcomes included change in HAM-A.

Two authors selected the studies for inclusion. Disagreements were resolved through discussion.

### Assessment of study quality

Study quality was assessed using the Cochrane Collaboration Risk of Bias tool. The authors did not report how many reviews performed the validity assessment.

### Data extraction

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction. Where necessary, study authors and pharmaceutical manufacturers were contacted for further data.

Intention-to-treat data were used to calculate relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences for continuous outcomes.

### Methods of synthesis

Studies were grouped according to comparison and outcome. For monotherapy, comparison patients who received 150mg/day were combined; an additional study used flexible doses. Pooled relative risks and mean differences, with 95% CIs, were calculated using a random-effects analysis. Number needed to treat (NNT) and number needed to harm (NNH) were calculated where relevant. The level of statistical heterogeneity was assessed using  $X^2$  and  $I^2$ . Heterogeneity was defined as statistically significant where  $I^2$  was greater than 50%.

Where significant heterogeneity was detected, further analyses were planned a priori to identify outliers by excluding each individual study in sequence. Other planned a priori analyses included effects of different doses of quetiapine XR, patient gender, duration, illness severity and presence of psychiatric comorbidity. Tests of interaction were performed with two-tailed significance set at 0.05.

A funnel plot to assess publication bias was planned a priori, but there were too few studies.

### Results of the review

Nine RCTs (2,295 participants) were included in the meta-analysis. Eight open-label non-comparative studies met the inclusion criteria and were described in supplemental tables (available online). The overall quality of the augmentation studies was low. Quality was unclear for the monotherapy studies (only one of four studies could be assessed).

Augmentation studies (five RCTs, 912 participants): There was no statistically significant difference between second-generation antipsychotics and placebo for clinical response and remission. There was a significant increase in risk of all-cause discontinuation associated with second-generation antipsychotics (RR 1.43, 95% CI 1.04 to 1.96). There were no statistically significant differences between second-generation antipsychotics and placebo for change in Hamilton Anxiety Rating Scale score from baseline and with weight gain.

Monotherapy studies (four RCTs, 1,383 participants): A statistically significant difference in clinical response was reported in favour of second-generation antipsychotics in comparison with placebo (RR 1.31, 95% CI 1.20 to 1.44). Statistically significant differences in favour of second-generation antipsychotics were reported for remission (RR 1.44, 95% CI 1.23 to 1.68) and reduction in Hamilton Anxiety Rating Scale score (RR 3.66, 95% CI 5.13 to 2.19; one RCT). However, in comparison with placebo there was a statistically significant increase in risk of all-cause discontinuation (RR 1.30, 95% CI 1.09 to 1.54) and weight gain (2.21b, 95% CI 1.16 to 3.24; one RCT). There was no evidence of significant statistical heterogeneity.

Further data reported in the review included a summary of data from open-label studies.

### Authors' conclusions

Second-generation antipsychotics were not superior to placebo as augmentation for refractory generalised anxiety disorder. Despite issues with adverse effects and tolerability, quetiapine monotherapy was efficacious in comparison with placebo for the treatment of uncomplicated generalised anxiety disorder.

### CRD commentary

This review assessed a clearly defined research question. Several relevant sources were searched. It appeared that the authors included only published data, which risked publication bias, although manufacturers were contacted for further information. There were no language restrictions, so the risk of language bias was likely to be low. Risks of reviewer error and bias were unclear: two reviewers independently assessed studies for inclusion, but no such precautions were taken for study selection and quality assessment. Study quality was assessed using relevant criteria, but findings for individual studies were not reported.

The authors commented that, where reported, the included studies were of short duration and had small sample sizes, high attrition rates and a number of other risks of bias that may have limited the reliability of the findings. The reliability of the statistical pooling was unclear as the studies appeared to clinically differ in a number of respects (particularly regarding populations and interventions), although the level of statistical heterogeneity was reported as low. The paucity of studies precluded planned analyses to investigate the effect of heterogeneity.

The reported data appear to support the review conclusions. However, the paucity of data and methodological limitations of the included studies suggest a cautious interpretation is required.

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

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

**Research:** The authors stated that further studies of agents and combinations with other medications and cognitive behavioural therapy were required in patients with generalised anxiety disorders.

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