Review: Atypical antipsychotics are effective adjuncts for treatment resistant depression but increase discontinuation due to adverse effects

**QUESTION**

**Question:** How effective are atypical antipsychotics as adjunctive therapy for treatment resistant depression?

**Outcomes:** Primary outcome: remission rates using the Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcomes: discontinuation rates and response rates.

**METHODS**

**Design:** Systematic review with meta-analysis.

**Data sources:** Studies in any language were searched for in MEDLINE, PubMed, the Cochrane database and EMBASE from inception; as well as abstracts of multinational psychiatric meetings since 2000, and the clinical trial registries of antipsychotic manufacturers or direct contact with manufacturers not having such registries. The search date was not reported.

**Study selection and analysis:** Double-blind, randomised, placebo-controlled trials of an antipsychotic as an adjunct to an antidepressant for treatment resistant depression using and assessing either the HAM-D or MADRS as their primary outcome were included. Exclusions: trials in bipolar disorder, psychotic major depression, minor depression, alcohol or substance abuse, comorbidity, dysthymic disorder or seasonal affective disorder. Outcomes were meta-analysed using a random-effects model after testing for heterogeneity.

**MAIN RESULTS**

Ten randomised controlled trials of 1500 outpatients were included (4 using olanzapine in combination with fluoxetine; 4 using quetiapine in combination with an SSRI or SNRI; and 2 with risperidone plus various antidepressants). Trial durations ranged from 4–12 weeks. Adjunctive antipsychotic treatment increased remission and response rates compared with adjunctive placebo (RR for remission: 1.75, 95% CI 1.36 to 2.24; p<0.001; RR for response: 1.35, 95% CI 1.13 to 1.63; p = 0.001). Tests for heterogeneity were non-significant for both remission and response rates. Overall rates of discontinuation were not significantly different between antipsychotic and placebo groups (RR 1.18, 95% CI 0.93 to 1.49; p = 0.133). However, discontinuation due to adverse effects was higher with antipsychotics than placebo (RR 3.38; 95% CI 1.98 to 5.76; p<0.001).

**CONCLUSIONS**

Antipsychotics (olanzapine, quetiapine and risperidone) are effective adjunctive treatment for depression that has failed to respond to an adequate trial of standard treatment. However, they do increase discontinuation due to adverse effects. No studies of adjunctive aripiprazole or ziprasidone were identified so results may not apply to these drugs.

**ABSTRACTED FROM**


**Notes:** Studies used different depression scales and defined remission using different cut-offs (4 studies used HAM-D score <8; 3 used MADRS score <9 and 3, MADRS score <11). All included studies defined response as a 50% reduction in primary depression scale score from baseline.

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