**Therapeutics**

**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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When dealing with treatment resistant depression, one of the most compelling clinical issues is to decide whether to switch to another antidepressant or to augment antidepressant treatment with an agent belonging to a different class. In this meta-analysis the benefit of adjunctive treatment of standard antidepressants with an atypical antipsychotic for treatment resistant depression was assessed. Despite some interesting findings, careful consideration of the analysis is needed before drawing conclusions for clinical practice. Firstly, a number of definitions exist for clinically significant treatment resistance, and we do not know which criteria were adopted in the included studies. A table with patients’ baseline characteristics would have let readers know which patient populations were included, and whether combining the results of different studies was clinically reasonable. Secondly, results from individual trials were not presented, and given the lack of these data the forest plots cannot confidently be interpreted and it is impossible to replicate the analysis. This omission is particularly relevant to this meta-analysis, as 7 out of 10 included studies were conference proceedings, and discrepancies have been documented between the results of the meeting abstract and the subsequent full-length publication. The main clinical finding of the meta-analysis is that adjunctive treatment of standard antidepressants (mainly fluoxetine) with some atypical antipsychotics (olanzapine, risperidone, quetiapine) might be more effective in terms of response and remission. However, tolerability is a crucial issue in augmentation strategies; the greater the number of drugs taken, the greater the risk of adverse events. As the authors stated in the text, a higher proportion of discontinuations due to adverse effects was found in the augmentation group. Furthermore, the duration of the trials included in this analysis (between 4 and 12 weeks) does not allow assessment of the real burden of side-effects associated with this augmentation strategy. This is especially true for the side-effect profile of atypical antipsychotics, which tend to become evident in the long term.
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