



Overcoming Resistance: Antipsychotics for difficult to treat depression

CLINICAL QUESTION

In patients with treatment-resistant depression, is adding an atypical antipsychotic to current therapy safe and effective?

BOTTOM LINE

About 30% of patients using atypical antipsychotics as adjunctive therapy achieve a response in treatment-resistant depression compared to ~20% on placebo at 6-8 weeks. Somnolence, akathisia, and weight gain are most commonly reported adverse events occurring in 5-20% versus 1-5% for placebo.

EVIDENCE

- 5 systematic reviews (7-32 Randomized Controlled Trials [RCTs], 2037-8349 patients), from the last 5 years versus placebo in patients with $\geq 1-2$ past antidepressant treatment failures. Adjunctive aripiprazole, brexpiprazole, cariprazine, and quetiapine accounted for 90% of patients (risperidone ~5%).¹⁻⁵ Results statistically significant unless indicated. After ~6-8 weeks:
 - Response ($\geq 50\%$ depression score reduction):^{1,2}
 - 24%-37% versus 18%-27% (placebo), Number Needed to Treat (NNT)=10-12.
 - Remission:²⁻⁵
 - 17-31% versus 12-18% (placebo), NNT=10-22.
 - Inconsistent/non-significant results for quetiapine and cariprazine.
 - Risperidone NNT=6, data at high risk-of-bias.

- Adverse events:
 - Discontinuation due to adverse events:²⁻⁴
 - 3-10% versus 1-3% (placebo), Number Needed to Harm (NNH)=15-58.
 - NNH=15 (cariprazine), 16 (quetiapine), 52-57 (aripiprazole), 57-58 (brexpiprazole).
 - Inadequate risperidone data.
 - Akathisia:^{2,3}
 - 8-20% versus 2-6% (placebo), NNH=7-20
 - NNH=7 (aripiprazole), 9 (cariprazine), 17-20 (brexpiprazole).
 - Quetiapine and risperidone similar to placebo.
 - Somnolence:^{2,3}
 - 4-19% versus 1-5% (placebo), NNH=6-32.
 - NNH=6 (quetiapine), 23 (cariprazine), 26-32 (brexpiprazole).
 - Aripiprazole and risperidone similar to placebo.
 - Weight gain ($\geq 7\%$ body weight):²
 - 4-8% versus 1-3% (placebo), NNH=19-45.
 - NNH=19 (aripiprazole), 34 (quetiapine), 45 (brexpiprazole).
 - Cariprazine and risperidone similar to placebo.
- Limitations: Most RCTs industry-funded; varying definitions of treatment resistance; uncertain long-term benefits/harms (example: weight gain, other metabolic complications); small sample sizes limit risperidone conclusions; inconsistent reporting of olanzapine.

CONTEXT

- Alternative strategies for treatment resistance include cognitive behavioural therapy (response NNT=5, remission NNT=10),⁶ add-on antidepressants (bupropion similar to aripiprazole for remission),⁷ or lithium (response NNT=5, remission similar to placebo based on limited data).^{1,8}
- Uncertain dose-response relationship. Lower doses may be as effective while minimizing adverse effects.^{9,10}
- Cost/30 days (currently approved for depression in Canada):^{11,12}
 - Brexpiprazole 1-3mg \$110.
 - Aripiprazole 2-15mg \$25-40.
 - Quetiapine XR 150-300mg \$15-30.

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Authors do not have any conflicts of interest to declare.

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