



WHAT'S THE EVIDENCE?

Atypical Antipsychotics in Schizophrenia: Combination and High-Dose Strategies

In Canada, the most frequently prescribed atypical antipsychotics combinations include Risperdal, Seroquel, and Zyprexa. *Yet, not a single randomized controlled trial (RCT) was found* to support the efficacy or safety of these combinations despite a comprehensive systematic review by the Canadian Agency for Drugs and Technologies in Health (CADTH).

The available evidence identified few clinical advantages and uncertain harms when using combination or high-dose strategies for patients with schizophrenia who have an inadequate response to an antipsychotic.

No advantages found

Combination strategy: The evidence examining the use of two antipsychotics simultaneously compared with monotherapy is limited to 13 RCTs of short duration. Meta-analyses of these trials by CADTH revealed no clinically important differences in response rate, schizophrenia symptoms, extrapyramidal side effects, akathisia, metabolic side effects, or hospitalization rates between monotherapy and combination therapy. With insufficient evidence to accurately assess harms, the risks associated with atypical antipsychotic combination therapy are largely unknown.

High-dose strategy: Ten RCTs of short duration examined higher-than-recommended atypical antipsychotic dosing compared with standard dosing. No consistent evidence was found to suggest that going beyond the maximum recommended dose led to improved outcomes, and the potential harms of this approach are uncertain.

See *Optimal Use Recommendations for Atypical Antipsychotics*, 2011 at www.cadth.ca.

Action if inadequate response

Review diagnosis, explore adherence,
rule out substance abuse

inadequate response

Increase/decrease dose within
recommended range

inadequate response

Switch to different antipsychotic

if inadequate response
after second antipsychotic

Consider a 4- to 6- month
trial of clozapine



See Canadian Psychiatric Association. Clinical Practice Guidelines, Treatment of Schizophrenia. Can J Psychiatry, 2005;50 (13 Suppl 1).

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CADTH is an independent, not-for-profit agency funded by Canada's federal, provincial, and territorial governments.