Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia: Systematic Review

Adapted from A Systematic Review of Combination and High-Dose Atypical Antipsychotic Therapy in Patients with Schizophrenia [CADTH Optimal Use Report; Volume 1, Issue 1B]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011.

For more information on this project, visit http://www.cadth.ca/en/products/optimal-use/atypical-antipsychotics-for-schizophrenia.

Introduction

Schizophrenia is a mental illness that requires lifelong treatment and is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and low motivation. Antipsychotic medications are effective at relieving the symptoms of schizophrenia, and they form the foundation of treatment. These medications fall into two classes: the typical, or first-generation, antipsychotics (TAPs); and the atypical, or second-generation, antipsychotics (AAPs). At the time of this review, seven AAPs were available in Canada:

- aripiprazole
- clozapine
- olanzapine
- paliperidone
- quetiapine
- risperidone
- ziprasidone.

Approximately one-third of patients with schizophrenia have a poor response to antipsychotic medications. Although not recommended in most clinical practice guidelines, the use of AAPs at doses higher than recommended or combination of an AAP with another antipsychotic medication are strategies that are sometimes used in clinical practice to treat patients who have an inadequate response to standard doses of a single AAP. These strategies may be associated with increased risks for adverse effects, as well as increased costs. Annual expenditures on antipsychotics in Canada by 11 publicly funded drug plans in 2009 were approximately C$421.9 million, while C$62.3 million was spent by privately funded drug plans. The Canadian Agency for Drugs and Technologies in Health’s (CADTH’s) analysis of current utilization data found that combination therapy and high dose AAP monotherapy accounted for 20% to 38% of total antipsychotic expenditures in 2009.

Objective

The objective of this study was to assess the efficacy and safety of AAP combination therapy and high-dose treatment strategies in adolescents and adults with schizophrenia.

The following research questions were addressed:

1. What is the comparative clinical effectiveness (including clinical benefits and harms) of using combination therapy with AAPs (i.e., more than one AAP or AAP[s] plus TAP[s]) compared with AAP monotherapy for the treatment of adolescents and adults with schizophrenia for whom treatment with a single AAP or typical antipsychotic at recommended doses is inadequate?

2. What is the comparative clinical effectiveness (including clinical benefits and harms) of using high-dose AAP therapy compared with standard dose antipsychotic therapy for the treatment of adolescents and adults with schizophrenia for whom treatment with an AAP or TAP at recommended doses is inadequate?

Following careful evaluation of the evidence, the COMPUS Expert Review Committee (CERC) produced four recommendations on the use of AAP combination and high-dose treatment strategies in adolescents and adults with schizophrenia inadequately controlled on
standard-dose antipsychotic monotherapy (recommendation report)\(^7\) to guide Canadian health-care providers and policy-makers. CADTH also studied current practice (current practice report)\(^8\) and current utilization\(^6\) related to the prescribing of AAPs for patients with schizophrenia to guide knowledge exchange efforts around this work.

**Methods**

The project protocol\(^9\) presents, in detail, the methodology for the systematic review.

The population of interest for this review was adolescents (aged 13 to 17 years) and adults (aged 18 years and older) with schizophrenia or schizoaffective disorder who were inadequately managed with one or more AAPs at recommended doses. For the systematic review, a literature search was conducted on June 16, 2010 in medical databases and restricted to English or French publications. Monthly alerts were monitored until publication of the report. A search of grey literature (literature that is not commercially published) was also conducted. Studies were selected independently, by two reviewers, based on set criteria, with discrepancies resolved through discussion or the judgment of a third reviewer. Ultimately, the systematic review encompassed 30 unique randomized controlled trials (RCTs).

Meta-analyses were performed, where appropriate, to obtain pooled estimates of effect. Monthly RCT alerts were maintained until May of 2011. Four studies meeting the inclusion criteria were identified via these alerts, but sensitivity analyses incorporating the new data from these trials did not significantly affect the results of the analyses.

**Results**

The selected RCTs studied the following treatment strategies:

- Dual antipsychotic therapy involving either one or two AAPs (compared with AAP monotherapy); these included trials of clozapine-based combination therapy versus clozapine monotherapy, and non-clozapine AAP combinations versus AAP monotherapy. No trials were identified comparing non-clozapine combination therapy with clozapine monotherapy.
- High-dose, non-clozapine AAP therapy (compared with standard-dose clozapine and non-clozapine antipsychotics).

Of the 30 included RCTs, only one\(^10\) was conducted in adolescents (aged 10 to 18 years). Baseline duration of illness for the adult studies ranged from 7\(^11\) to 22\(^12\) years (weighted mean [SD] 15.6 [4.8]). A broad range of antipsychotic doses were used in the included trials. Common outcome measures included schizophrenia symptom scales (e.g., Positive and Negative Symptoms Scale [PANSS], Brief Psychiatric Rating Scale [BPRS] scores, Clinical Global Impression [CGI]), response rate, cognition, withdrawals, and serious adverse events. No evidence was available for relapse or remission rates.

**Combination Treatment Strategies**

**a) Clozapine-based antipsychotic combination therapy versus standard dose clozapine-monotherapy**

Eleven RCTs\(^13\)-\(^24\) compared combination therapy involving clozapine (CLZ) versus CLZ monotherapy. There were no statistical differences between groups for any outcome, with the exception of the Clinical Global Impression Improvement (CGI-I) scale, where slightly greater improvement was seen in the CLZ combination arm compared with CLZ monotherapy at 16 weeks.

The four studies that reported efficacy scores (PANSS-total score) were inconsistent in their findings. One study\(^17\) showed a small, statistically significant benefit with CLZ monotherapy, whereas another study\(^14\) showed a small, statistically significant benefit with CLZ combination therapy. The other two studies\(^16,20\) did not show a statistically significant difference between CLZ combination therapy and CLZ monotherapy.

More serious adverse events occurred with CLZ combination therapy compared with CLZ...
monotherapy (11/216 versus 0/194). For the majority of other harms outcomes, there were no statistically significant differences between groups, although withdrawal due to adverse events (8/200 versus 4/180) and akathisia (6/138 versus 0/113) occurred numerically more frequently in the CLZ combination arm.

Regarding body weight, four trials comparing either risperidone \(^{16,17,21}\) or aripiprazole \(^{13}\) combined with clozapine with clozapine alone did not show a statistically significant difference. However, one study \(^{20}\) of patients who had gained more than 2.5 kg on CLZ monotherapy prior to the start of the trial reported a significant difference in body weight reduction with aripiprazole combined with CLZ, despite similar clozapine doses between arms. Total cholesterol was statistically significantly lower with CLZ combination than CLZ monotherapy, as was low-density lipoprotein or LDL cholesterol.

Five studies reported prolactin levels: three trials \(^{17,19,25}\) reported statistically lower prolactin levels with CLZ monotherapy, while two trials \(^{13,21}\) indicated a non-significant difference.

b) Non-clozapine antipsychotic combination therapy versus non-clozapine monotherapy

One RCT \(^{26}\) lasting 16 weeks compared risperidone or quetiapine plus aripiprazole with risperidone or quetiapine plus placebo.

There were no statistically significant differences between groups for any efficacy-related outcomes for this comparison. Regarding harms, there were fewer serious adverse events in patients using combination therapy (8/169 versus 19/153), and prolactin levels showed a statistically significant decrease from baseline with combination therapy, compared with monotherapy. No significant differences were observed for other harms outcomes.

High-Dose AAP Treatment Strategies

c) High-dose non-clozapine AAP therapy versus standard-dose clozapine

Eight RCTs \(^{10,25,27-38}\) compared high-dose non-clozapine AAP therapy with standard-dose clozapine therapy.

In pooled analyses, there were no statistically significant differences in efficacy between groups except for Global Assessment of Functioning (GAF) scores, which were improved with standard-dose CLZ compared with high-dose AAPs. One trial \(^{39}\) reported significantly improved BPRS scores in the standard-dose clozapine arm compared with high-dose risperidone, whereas there was no significant difference between high-dose olanzapine and standard-dose clozapine in the second trial. \(^{29}\) Regarding harms, there were no statistically significant differences between groups for most outcomes. High-dose non-clozapine AAPs was associated with fewer cases of parkinsonism (two RCTs \(^{29,35}\)), as well as fewer withdrawals due to adverse events (six RCTs \(^{25,29,32,35,36,39}\)). Patients on high-dose non-CLZ AAPs had a higher incidence of extrapyramidal symptoms (two RCTs \(^{36,39}\) and higher prolactin levels (two RCTs \(^{29,36}\) compared with standard-dose CLZ. There was no overlap between studies reporting total extrapyramidal symptoms \(^{29,35}\) and those reporting parkinsonism, \(^{29,35}\) which may explain the apparent discrepancy in the direction of effects for these outcomes.

d) High-dose non-clozapine AAP therapy versus standard-dose non-clozapine antipsychotic drugs

Two RCTs \(^{40,41}\) compared high-dose non-clozapine AAP therapy with standard-dose non-clozapine antipsychotic drugs.

There were no statistically significant differences between groups in efficacy or harms outcomes. Data for PANSS-total and PANSS-positive from the two included studies \(^{40,41}\) were not pooled due to a high degree of heterogeneity. For PANSS-total, a trial \(^{40}\) comparing high-dose risperidone with standard-dose haloperidol found significantly greater improvement with
high-dose risperidone, while a trial comparing high-dose quetiapine with standard-dose quetiapine did not find a significant difference. Similarly, PANSS-positive was significantly improved when high-dose risperidone was compared with standard-dose haloperidol, but not when high-dose quetiapine was compared with standard dose.

Limitations

Limitations of this systematic review include lack of and low quality of available evidence. Of the 30 included RCTs, 27 were rated as being of “poor” methodological quality. The trials were of short duration and had inadequate study power, particularly for safety outcomes.

It was difficult to compare across trials because of differences in dosing and because the RCTs included patients with various treatment histories — often, dosing levels and treatment history were not reported. There was also heterogeneity in reported outcomes (e.g., different definitions for inadequate control) and lack of data on many clinically important outcomes. In particular, there was insufficient evidence available for mortality, hospitalizations, relapse rates, suicidality, health-related quality of life, level of function, and long-term adverse effects of combination or high-dose antipsychotic use. PANSS and CGI were the primary efficacy outcomes reported in the majority of included RCTs; however, the relationship between the change in PANSS score and long-term clinical outcomes has not been well-established.

Conclusions

The systematic review showed no clinically significant improvements in efficacy with combination or high-dose AAP treatment strategies when compared with standard-dose monotherapy. The evidence regarding harms was inconclusive, but there were signals for increased harm with high dose and combination strategies in some comparisons. Despite the heterogeneity in trial populations, studies were consistent in reporting that combination and high-dose strategies were not more efficacious than standard dose monotherapy; therefore, the results of this review are largely applicable to patients in Canada with schizophrenia.

Longer-term studies of sufficient methodological quality and sample size are required to determine with more certainty the clinical value, if any, of combination or high-dose treatment strategies. Considering that clozapine serves as the standard of care for treatment-resistant patients, further comparative trials of this drug with high dose and combination therapies may be of particular value in guiding optimal treatment strategies for patients with schizophrenia.

References


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CADTH Technology Overviews is produced by:
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Production of CADTH Technology Overviews is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan, and Yukon.

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Cite as: Canadian Agency for Drugs and Technologies in Health. CADTH Technology Overviews, 2012; 2(3).

ISSN: 1481-4501 (online)