TITLE: Combination Atypical Antipsychotics in Adolescents or Adults with Bipolar Disorder with Psychotic Features: A Review of Clinical and Cost-Effectiveness and Guidelines

DATE: 06 September 2016

CONTEXT AND POLICY ISSUES

Bipolar disorder is a mental condition characterized by episodic mood swings between euphoric or irritable mania and hopeless depression which can affect social activities, functioning, and relationships.\(^1\) Episodes are typically followed by symptom-free periods referred to as euthymia.\(^2\) According to a survey conducted in 2002, one percent (1%) of Canadians 15 years and older demonstrated symptoms satisfying the criteria for bipolar disorder in the previous 12 months.\(^2\) Multiple types of bipolar disorders exist such as bipolar I, bipolar II and are defined in the Diagnostic and Statistical Manual (5th edition; DSM-V) from the American Psychiatric Association.\(^3\)

Symptoms associated with mania can include increased creativity and productivity; however, mania can also lead to immediate hospitalization or involuntary committal under the Mental Health Act. Symptoms associated with depression can lead to increased rates of suicide and suicide ideation.\(^1\) Bipolar disorder with psychotic features refers to manic or depressive episodes including psychotic symptoms such as delusions or hallucinations. Psychotic features manifest in over 50% of manic episodes and are more common in the latter than in depressive episodes.\(^4\)

Pharmacological treatment usually depends on the type of bipolar disorder (manic or depressive); however, the most common treatments include lithium and valproic acid.\(^5\) Antipsychotic medications are also used to treat bipolar disorder and can be classified as typical (first generation) or atypical (second generation).\(^6\) First generation antipsychotics mitigate bipolar disorder symptoms by antagonizing dopamine D\(_2\) receptors, while second generation antipsychotics have an affinity for serotonin 5-hydroxytryptamine receptors and adrenergic receptors in addition to being D\(_2\) receptor antagonists.\(^6\)

Atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone can be prescribed as monotherapy or in combination with mood stabilizers and...
antidepressants, as well as other treatment options.\textsuperscript{5} Although combinations of atypical antipsychotics have been used for the treatment of other disorders, such as schizophrenia, the effectiveness of combination therapy in bipolar disorder is unclear.\textsuperscript{7-9} This Rapid Response report aims to review the clinical and cost-effectiveness of combination atypical antipsychotics in adolescents or adults with bipolar disorder with psychotic features. Guidelines associated with the use of combination atypical antipsychotics in adolescents or adults with bipolar disorder with psychotic features will also be examined.

**RESEARCH QUESTIONS**

1. What is the clinical effectiveness of combination atypical antipsychotics in adolescent or adult patients with bipolar disorder with psychotic features?

2. What is the cost-effectiveness of combination atypical antipsychotics in adolescent or adult patients with bipolar disorder with psychotic features?

3. What are the evidence-based guidelines associated with the use of combination atypical antipsychotics in adolescent or adult patients with bipolar disorder with psychotic features?

**KEY FINDINGS**

No relevant literature was identified pertaining to the clinical or cost effectiveness of combination treatment of any atypical antipsychotics in adolescents and adults suffering from bipolar disorder with psychotic features. Similarly, no evidence-based guidelines were identified from the literature search.

**METHODS**

**Literature Search Methods**

A limited literature search was conducted on key resources including Medline, PsychInfo, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, guidelines, economic studies, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and August 4, 2016.

**Selection Criteria and Methods**

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adolescents and adults with bipolar disorder with psychotic features</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Combination of any atypical antipsychotics (using either high or regular dosing regimens)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Other drug combinations, atypical antipsychotics monotherapy, placebo alone or in combination with an atypical antipsychotic, no comparator</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical effectiveness, safety, cost-effectiveness and guidelines</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessment, systematic reviews, meta-analyses, randomized controlled trials, non-randomized trials, economic evaluations and guidelines</td>
</tr>
</tbody>
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Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 874 citations were identified in the literature search. Following screening of titles and abstracts, 848 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. No relevant reports were identified in the grey literature. Of these potentially relevant articles, all 26 publications were excluded because they did not meet the inclusion criteria. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Findings

No relevant literature on the clinical or cost effectiveness of combination treatment of any atypical antipsychotics in adolescents and adults suffering from bipolar disorder with psychotic features was identified. Similarly, no evidence-based guidelines were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No relevant clinical evidence or guidelines of combination treatment of any atypical antipsychotics in adolescents and adults suffering from bipolar disorder with psychotic features were identified. However, NICE guidance on the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care may provide some insight on atypical antipsychotic combination treatments. Based on evidence related to schizophrenia, the guideline suggests not to initiate regular combined antipsychotic medication, except for short periods of time (e.g. when changing medication). Although the NICE guideline does not recommend the combination of atypical antipsychotics for treatment of bipolar disorder, it should be noted that the recommendation is made on the basis that antipsychotics will have the same metabolic effects on people with bipolar disorder as they do on people with schizophrenia and based on the general bipolar population (i.e. not necessarily patients suffering from bipolar disorder with psychotic features).
REFERENCES


APPENDIX 1: Selection of Included Studies

874 citations identified from electronic literature search and screened

848 citations excluded

26 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

26 potentially relevant reports

26 reports excluded:
- irrelevant population (5)
- irrelevant intervention (20)
- other (review articles, editorials)(1)

0 reports included in review