TITLE: Combination Therapy for Attention Deficit Hyperactivity Disorder: A Review of the Clinical Effectiveness

DATE: 23 February 2016

CONTEXT AND POLICY ISSUES

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 5% to 12% of children with about 60% to 65% of children with ADHD continuing to exhibit the syndrome in adulthood.\textsuperscript{1,2} According to the Canadian ADHD Resource Alliance (CADDRA), the prevalence of ADHD in adults is estimated to be 4.4%, with less than 12% of patients able to obtain services even at the primary care level.\textsuperscript{3}

Persistent patterns of inattention, hyperactivity, and impulsivity are the core symptoms that characterize ADHD. These symptoms, along with aggressive behavior and poor concentration, may result in academic and social dysfunction making ADHD patients more likely to be offenders of the law compared to the general population. Although most ADHD patients do not commit crimes, individuals with ADHD are twice as likely to commit crime, and commit three times as many offences as those without the disorder.\textsuperscript{4} Impairments in educational and occupational performance, as well as deficits in interpersonal relationships and behavior reduce the chances of individuals with ADHD to find and keep employment.\textsuperscript{2,5}

Dopaminergic and noradrenergic deficits in the frontal cortex or regions projecting into that area have been implicated in the inattentiveness and/or hyperactivity associated with ADHD. At present, psychostimulants, which relieve symptoms by increasing intra-synaptic dopamine, norepinephrine and serotonin, are the first-line treatment and the mainstay of ADHD treatment.\textsuperscript{6} Atomoxetine, a non-stimulant drug which inhibits norepinephrine transport, has also been approved for ADHD treatment as first-line pharmacotherapy in many countries.\textsuperscript{2,3} Stimulant drugs approved to treat ADHD in Canada are amphetamine-based psychostimulants (Dexedrine, Adderall, and Vyvanse) and methylphenidate-based psychostimulants (methylphenidate, Biphentin and Concerta). Strattera (atomoxetine) and Intuniv (guanfacine XR) are the two non-stimulant ADHD medications currently approved for use in Canada. Other agents that have been used off-label for ADHD treatment include tricyclic antidepressants, bupropion, selective serotonin reuptake inhibitors, buspirone, and atypical antipsychotic drugs.\textsuperscript{3,6}
ADHD medication improves symptoms of ADHD and ameliorates associated conduct problems in children and adults. Among patients receiving ADHD medication, a significant reduction in criminality rate has been demonstrated during periods when patients were taking medication compared to periods when they did not, suggesting an inverse correlation between ADHD treatment and crime committed by ADHD patients.⁷

ADHD medications are available as immediate-release or extended-release formulations. Immediate-release medications are short-acting with durations of action in the range 3 to 6 hours.² Therefore, effective management of ADHD symptoms with immediate-release medications requires multiple dosing (three to four times) each day. Frequency of dosing is inversely correlated with adherence to treatment, with once-daily (fewer) dosing regimens shown to improve treatment adherence rates.⁵ Therefore, despite their well-documented efficacy, adherence with immediate-release medication can be particularly challenging for ADHD patients who may be unable to take their medication on time or at all, due to forgetfulness, disorganization and poor time management associated with their condition. Since extended-release medications are long-acting and may be given once daily in most cases, they help to resolve the problem of inadequate adherence due to frequent dosing requirement. However, extended-release medications tend to have slower rate of onset of effect than immediate-release medications.⁷ It has been suggested that in some patients, extended-release medication may be augmented with immediate release medication to assist with control at the beginning of the day, or to prevent an unsettling loss of effect later in the day.⁸

The aim of this review is to summarize evidence of the clinical effectiveness of combination treatment with long-acting and short-acting stimulant medications to inform decisions around combination use of these drugs for ADHD in adults.

RESEARCH QUESTION

What is the clinical effectiveness of combination treatment with a long-acting and a short-acting stimulant for adult patients with ADHD?

KEY FINDINGS

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination treatment with long-acting ADHD drugs (including atomoxetine) and a short-acting stimulant for adult patients with ADHD.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Ovid Medline, Ovid Embase, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and January 27, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.
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>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
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<td>Adults (18 or over) with ADHD</td>
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<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Combination treatment with a long-acting stimulant (e.g. Vyvanse, Adderall XR, Concerta) or non-stimulant (e.g. atomoxetine) and a short-acting stimulant (e.g. Ritalin, Dexedrine)</td>
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<tr>
<td><strong>Comparator</strong></td>
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<tr>
<td>Placebo</td>
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<td>Long-acting stimulant alone</td>
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<td>Short-acting stimulant alone</td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td>Clinical effectiveness (e.g. symptom reduction, calming/focusing), safety, harms (including abuse potential)</td>
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<tr>
<td><strong>Study Designs</strong></td>
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<tr>
<td>HTA/Systematic Reviews/Meta-Analyses; Non-Randomized Studies; Randomized Controlled Trials</td>
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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 January 2006.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 190 citations were identified in the literature search. Following screening of titles and abstracts, 173 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. None of these 18 potentially relevant articles met the inclusion criteria for this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Findings

What is the clinical effectiveness of combination treatment with a long-acting and a short-acting stimulant for adult patients with ADHD?

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination treatment with a long-acting ADHD drugs (including atomoxetine) and a short-acting stimulant for adult patients with ADHD.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination treatment with long-acting ADHD drugs and a short-acting stimulant for adult patients with ADHD.

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REFERENCES


APPENDIX 1: Selection of Included Studies

190 citations identified from electronic literature search and screened

173 citations excluded

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

1 potentially relevant report retrieved from other sources (grey literature, hand search)

18 potentially relevant reports

18 reports excluded:
- irrelevant intervention (10)
- other (review articles, editorials) (8)

No reports met the inclusion criteria for this review