



**TITLE:** High Dose Stimulants for Attention Deficit Hyperactivity Disorder: Clinical Effectiveness, Safety, and Guidelines

**DATE:** 29 January 2015

## RESEARCH QUESTIONS

1. What is the effectiveness and safety of high dose stimulants in children and adolescents (six to 18 years) with attention deficit hyperactivity disorder (ADHD)?
2. What is the comparative effectiveness and safety of high dose stimulants in adults (>18 years) with ADHD?
3. What are the evidence-based guidelines regarding the use of high dose stimulants in patients with ADHD?

## KEY FINDINGS

One systematic review, three randomized-controlled trials, and four non-randomized studies were identified regarding high dose stimulants for attention deficit hyperactivity disorder.

## METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, 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, 2010 and January 26, 2015. Internet links were provided, where available.

## SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

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**Table 1: Selection Criteria**

<b>Population</b>	Children and adolescents (six to 18 years) and adults (>18 years) with ADHD, with or without co-morbidities in out-patient and in-patient (e.g., mental health facilities) settings.
<b>Intervention</b>	High dose of stimulants i.e., above the recommended dose.  Drugs of interest: All short, intermediate, and/or long acting stimulants (e.g., methylphenidate, amphetamine, dextro-amphetamine, lisdexamfetamine)
<b>Comparator</b>	Standard of practice – Stimulants prescribed <ul style="list-style-type: none"> <li>• within the recommended maximum dose and/or</li> <li>• in combination with non-stimulants</li> </ul> Placebo
<b>Outcomes</b>	Efficacy outcomes, including but not limited to: changes in severity of ADHD symptoms, cognitive and adaptive skills, functional outcomes, quality of life and psychiatric morbidity, caregiver satisfaction, time to onset of effectiveness, duration of effectiveness.  Safety outcomes, including but not limited to: overall adverse events, withdrawals due to adverse events, missed dose, non-compliance, abuse potential, development of substance abuse disorder, long-term safety (e.g., cardiac safety, hepatotoxicity, growth effects, psychiatric effects, etc.).
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

**RESULTS**

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One systematic review, three randomized-controlled trials, and four non-randomized studies were identified regarding high dose stimulants for attention deficit hyperactivity disorder.

Additional references of potential interest are provided in the appendix.

**Health Technology Assessments**

No literature identified.

**Systematic Reviews and Meta-analyses**

1. Epstein T, Patsopoulos NA, Weiser M. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev.* 2014;9:CD005041.  
[PubMed: PM25230710](https://pubmed.ncbi.nlm.nih.gov/25230710/)

## Randomized Controlled Trials

### *Children and Adolescents*

2. Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2011 Apr;50(4):395-405.  
[PubMed: PM21421179](#)

### *Adults*

3. Faraone SV, Spencer TJ, Kollins SH, Glatt SJ, Goodman D. Dose response effects of lisdexamfetamine dimesylate treatment in adults with ADHD: an exploratory study. *J Atten Disord* [Internet]. 2012 Feb [cited 2015 Jan 29];16(2):118-27. Available from:  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3355536/pdf/nihms374903.pdf>  
[PubMed: PM21527575](#)
4. Biederman J, Mick E, Fried R, Wilner N, Spencer TJ, Faraone SV. Are stimulants effective in the treatment of executive function deficits? Results from a randomized double blind study of OROS-methylphenidate in adults with ADHD. *Eur Neuropsychopharmacol*. 2011 Jul;21(7):508-15.  
[PubMed: PM21303732](#)

## Non-Randomized Studies

### *Children and Adolescents*

5. Song DH, Choi S, Joung YS, Ha EH, Kim BN, Shin YJ, et al. Titrating optimal dose of Osmotic-controlled Release Oral delivery (OROS)-methylphenidate and its efficacy and safety in Korean children with ADHD: a multisite open labeled study. *Psychiatry Investig* [Internet]. 2012 Sep [cited 2015 Jan 29];9(3):257-62. Available from:  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3440475/pdf/pi-9-257.pdf>  
[PubMed: PM22993525](#)
6. Newcorn JH, Stein MA, Cooper KM. Dose-response characteristics in adolescents with attention-deficit/hyperactivity disorder treated with OROS methylphenidate in a 4-week, open-label, dose-titration study. *J Child Adolesc Psychopharmacol*. 2010 Jun;20(3):187-96.  
[PubMed: PM20578931](#)
7. Stevens JR, George RA, Fusillo S, Stern TA, Wilens TE. Plasma methylphenidate concentrations in youths treated with high-dose osmotic release oral system formulation. *J Child Adolesc Psychopharmacol*. 2010 Feb;20(1):49-54.  
[PubMed: PM20166796](#)

*Adults*

8. Adler LA, Orman C, Starr HL, Silber S, Palumbo J, Cooper K, et al. Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. *J Clin Psychopharmacol*. 2011 Feb;31(1):108-14.  
[PubMed: PM21192153](#)

**Guidelines and Recommendations**

No literature identified.

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**APPENDIX – FURTHER INFORMATION:**

**Non-Randomized Studies - Maximum Daily Dose Not Specified**

9. Luman M, Goos V, Oosterlaan J. Instrumental learning in ADHD in a context of reward: intact learning curves and performance improvement with methylphenidate. *J Abnorm Child Psychol.* 2014 Sep 12.  
[PubMed: PM25212229](#)
10. Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, Coles EK, Wymbs BT, et al. A dose-ranging study of behavioral and pharmacological treatment in social settings for children with ADHD. *J Abnorm Child Psychol.* 2014 Aug;42(6):1019-31.  
[PubMed: PM24429997](#)

**Clinical Practice Guidelines – Uncertain Methodology**

11. Canadian ADHD practice guidelines (CAP-guidelines) [Internet]. Markham (ON): Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA)]. 2011 [cited 2015 Jan 29]. Available from:  
<http://www.caddra.ca/cms4/pdfs/caddraGuidelines2011.pdf>  
*See: Supporting Document 7A, pages 7.11 – 7.16*  
*Supporting Document 7B, pages 7.17 – 7.20*