



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: Attention Deficit Hyperactivity Disorder**  
-January 2020-



**Background:**

The American Academy of Pediatrics published new Attention Deficient Hyperactivity Disorder (ADHD) guidelines in 2019, updating their guidelines from 2011. The changes are minimal and do not affect medication choice<sup>1</sup>. The current Indian Health Service National Core Formulary includes both classes of central nervous system stimulants (methylphenidate and amphetamines in both long-acting and immediate-release formulations) for pediatric patients. Current British, Canadian, and American guidelines concur that stimulant medications remain first-line<sup>2,3</sup>. Since many patients may not be candidates for stimulants, the committee focused on whether the National Core Formulary should include a non-stimulant alternative, and, if so, which one. After an extensive review of available data, the National Pharmacy and Therapeutics Committee voted to **ADD atomoxetine** to the National Core Formulary.

**Discussion:**

Quantifying candidates for non-stimulants

Candidates for non-stimulants include both those who have failed stimulants, either due to ineffectiveness or intolerance, as well as those at high risk for stimulant abuse. The [American Academy of Pediatrics \(AAP\) guidelines](#) state that 80% of patients will respond to at least one class of stimulants. After an extensive literature search, primary source data was identified and reported a 90% response to at least one stimulant. The available studies, however, were small in size, of low-quality, aged, and heterogeneous in their findings<sup>4</sup>. Sixty percent of patients responded to atomoxetine after failing methylphenidate, according to one randomized, controlled study<sup>5</sup>. No data was identified however reporting the response rate of patients taking non-stimulants who had failed previous trials of both stimulant classes.

Risk for stimulant abuse

In a frequently-cited survey of primarily adult patients at an ADHD clinic, 14% of patients admitted to misusing or abusing stimulant medications. Generalizability to our pediatric population is questionable. The clinic prescribed extended-release formulations four times as often as immediate-release. Nevertheless, short-acting stimulants were abused by more than four times as many patients. Crushing and snorting stimulant medications was the most common route of administration, followed by intravenous administration<sup>7</sup>. This survey was conducted prior to the approval of lisdexamfetamine.

Lisdexamfetamine use has been increasing across the agency, likely due to its theoretically compelling mechanism for lower abuse potential. As a prodrug requiring conversion to its active form dextroamphetamine, the euphoric effects of lisdexamfetamine reportedly cannot be appreciated by crushing, snorting or through intravenous administration. Furthermore, a trial among self-admitted stimulant abusers found no greater “liking” for lisdexamfetamine than for placebo until the amount exceeded the maximum approved dosage<sup>8</sup>. It should be noted that that stimulant abusers are unlikely to limit dosing to within FDA recommendations.

Fortunately, abuse of prescription stimulants has not increased over the past 15 years, despite a doubling of stimulant prescriptions<sup>9</sup>. Among American Indians/Alaskan Natives, misuse of stimulants over the past year was approximately 1-2% among both adolescents and young adults. The highest rate of stimulant misuse was 10%, among white 18-25 year olds<sup>10</sup>.

Choosing a non-stimulant

The committee reviewed 4 key meta-analyses comparing ADHD medications, including both stimulants and non-stimulants. Three studies were judged to be of high quality.

- Meta-analysis 1 (included adults): When rated by clinicians, teachers and/or parents, ADHD symptoms in children were not significantly different among non-stimulants. Additionally, efficacy of non-stimulants was not significantly different to methylphenidate but inferior to amphetamines.

For adults, atomoxetine was shown to be inferior to amphetamines but non-inferior to methylphenidate. There is no data for guanfacine and clonidine use in adults. There were more dropouts due to adverse events versus placebo, for amphetamines and guanfacine only<sup>11</sup>.

- Meta-analysis 2 (included open-label studies and lisdexamfetamine but not amphetamines): All options were found to be superior to placebo, except clonidine, with no individual option found to be superior to other medications. Only guanfacine had more withdrawals due to adverse effects than placebo<sup>12</sup>.
- Meta-analysis 3 (included both children and adolescents only): No significant effect size differences were reported among non-stimulants<sup>13</sup>.

Within the IHS, atomoxetine is currently purchased at nearly twice the rate as guanfacine. Regarding clonidine, unfortunately the National Pharmacy and Therapeutics Committee was unable to accurately determine important prescribing details for ADHD as clonidine has various unrelated indications, including hypertension and opioid withdrawal.

### Findings:

While only 1-2% of adolescents report abusing stimulants over the past year, the number of “at risk” patients for abuse is much higher. This “at risk” fraction, compounded by the 10-20% of patients who fail stimulants and those who object to using stimulants, add up to a substantial number of patients with ADHD who are not currently served by the available treatment options on the National Core Formulary.

The evidence for effectiveness of clonidine is equivocal. Guanfacine was the only non-stimulant with more dropouts due to adverse events than placebo. Atomoxetine is the non-stimulant with the strongest supporting evidence according to the AAP guidelines and is also indicated for adults, although treatment of ADHD in adults was not a focus of this review or briefing. For these reasons, atomoxetine was added to the National Core Formulary.

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*If you have any questions regarding this document, please contact the NPTC at [IHSNPTC1@ihs.gov](mailto:IHSNPTC1@ihs.gov). For more information about the NPTC, please visit the [NPTC website](#).*

### References:

1. Wolraich ML, Hagan JF, Allan C, et al. [Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents](#). Pediatrics. 2019; 144(4):1-27.
2. National Institute of Health and Care Excellence. Recommendations [Attention deficit hyperactivity disorder: diagnosis and management](#). [cited 2020 Jan 11].
3. Canadian Paediatric Society. [ADHD in children and youth: Part 2—Treatment](#). [cited 2020 Jan 11].
4. Arnold LE. [Methylphenidate vs. amphetamine: Comparative review](#). J Atten Disord. 2000; 1;3(4):200–11.
5. Dittmann RW, Cardo E, Nagy P, et al. [Efficacy and Safety of Lisdexamfetamine Dimesylate and Atomoxetine in the Treatment of Attention-Deficit/Hyperactivity Disorder: A Head-to-Head, Randomized, Double-Blind, Phase IIIb Study](#). CNS Drugs. 2013; 27(12):1081–92.
6. Hirota T, Schwartz S, Correll CU. [Alpha-2 Agonists for Attention-Deficit/Hyperactivity Disorder in Youth: A Systematic Review and Meta-Analysis of Monotherapy and Add-On Trials to Stimulant Therapy](#). J Am Acad Child Adolesc Psychiatry. 2014; 53(2):153–73.
7. Bright GM. [Abuse of Medications Employed for the Treatment of ADHD: Results from a large-scale community survey](#). Medscape J Med. 2008; 10(5):111.
8. Jasinski DR, Krishnan S. [Abuse liability and safety of oral lisdexamfetamine dimesylate in individuals with a history of stimulant abuse](#). J Psychopharmacol Oxf Engl. 2009; 23(4):419–27.
9. Han B, Jones CM, Blanco C, et al. [National Trends in and Correlates of Nonmedical Use of Prescription Stimulants, Nonmedical Use Frequency, and Use Disorders](#). J Clin Psychiatry. 2017; 78(9):1250–8.
10. Substance Abuse and Mental Health Services Administration. [2018 NSDUH Detailed Tables](#). CBHSQ Data [Internet].
11. Cortese S, Adamo N, Del Giovane C, et al. [Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis](#). Lancet Psychiatry. 2018; 5(9):727–38.
12. Luan R, Mu Z, Yue F, et al. [Efficacy and Tolerability of Different Interventions in Children and Adolescents with Attention Deficit Hyperactivity Disorder](#). Front Psych 2017 [cited 2020 Jan 4];8.
13. Cerrillo-Urbina AJ, Garcia-Hermoso A, Pardo-Guijarro MJ, et al. [The effects of long-acting stimulant and non-stimulant medications in children and adolescents with Attention-Deficit/Hyperactivity Disorder: A meta-analysis of randomized controlled trials](#). J Child Adolesc Psychopharmacol. 2018; 28(8):494–507.