**ADHD Pharmacologic Treatment**

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Attention-Deficit/Hyperactivity Disorder (ADHD), characterized by inattentiveness and/or restlessness and impulsivity that are inconsistent with the developmental level and impair daily function,1 is a common mental health diagnosis in children. Symptoms of ADHD that cause impairment may persist in adulthood in up to 70% of childhood cases.2

Treatment for ADHD can be pharmacologic, non-pharmacologic, or both. Medications approved by the Food and Drug Administration (FDA) comprise stimulants--amphetamines and methylphenidate, and non-stimulants--atomoxetine and extended-release clonidine and guanfacine (Table 1). Stimulants have generally been recommended as first-line pharmacologic treatment (Table 2). Since the report of positive effects of an amphetamine compound on ADHD symptoms in 1937, and the approval of methylphenidate by the FDA in 1955, a large body of evidence has been published on ADHD pharmacotherapy. This review summarizes recent evidence regarding ADHD medications approved by regulatory agencies. It does not directly address ADHD diagnosis1 or the advisability or inadvisability of using these medications.

**Medication utilization in ADHD**

A study using prescription databases3 found geographic variation in the prevalence of ADHD medication use, ranging in 2014, from 0.39% (France) to 5.56% (USA) in children and adolescents, and from 0.01% (Hong Kong) to 2.11% (USA) in adults.

There was an increase in the prevalence of medication use from 2001 to 2015, with average yearly percentage increase ranging between 2.83% (USA) and 45.11% (Canada) in children, and from 7.94% (Taiwan) to 75.88% (Japan) in adults. Except for the USA, the prevalence of ADHD medication use in these databases was substantially lower than the estimated ADHD prevalence (Figure 1).

In a systematic review,4 across the 12-month follow-up periods of various studies, the average time on treatment was 136 days in children and 230 days in adults. The highest discontinuation rate was in the age group 15-21.5 Reasons for discontinuation included side effects, perceived lack of effectiveness, dislike of taking medications, treatment deemed not needed, stigma, and issues with transition from child to adult services.4,5

**Efficacy and effectiveness**

A meta-analysis6 of double-blind randomized controlled trials (RCTs) with average duration of 7 weeks, showed that medications approved for ADHD were superior to placebo in decreasing the severity of inattentiveness, restlessness and impulsivity as rated by clinicians, with the largest effect sizes found for amphetamines, followed by methylphenidate (supplementary Appendix 1, available with the full text of this article at NEJM.org). By comparison, effect sizes for stimulants in children and adolescents were larger than those reported in short-term RCTs of psychiatric medications in a variety of disorders.7 Amphetamines were significantly more efficacious than methylphenidate and atomoxetine at the patient group level. However, in cross-over RCTs,8 approximately 41% of participants responded to both amphetamines and methylphenidate, 28% responded better to amphetamines, 16% responded better to methylphenidate, and the rest did not respond to either medications.8

Some pharmacoepidemiology studies used a within-individual design that compared the risk of an outcome during periods on and off medication within the same individual, presumably to account for confounding of drug prescription by indication. These studies have shown a significant decrease on medication of outcomes such as unintentional physical injuries, motor vehicle accidents (in males), substance use disorder, and criminal acts, as well as an improvement in academic functioning.9

Determining the long-term effects of ADHD medications has been challenging as it has not been possible to overcome bias in studies comparing treated and untreated patients. In a double-blind RCT of medication discontinuation, participants who had been treated with methylphenidate for an average of 4.5 years and who were randomized to continue medication, showed persistence of benefits on ADHD symptoms compared to those who were switched to placebo.10 However, effect sizes were smaller than those reported in short-term RCTs of methylphenidate. This may have been due to loss of effectiveness over time, suboptimal adjustment of medication, or overrepresentation in the study of participants with ADHD that was mild or resolving.

Effects of ADHD medications on measures of quality of life have correlated only moderately well with improvement in ADHD symptoms and, across RCTs (including discontinuation trials), ranged from non-significant to significant.11,12

**Side effects, acceptability, and safety**

In a meta-analysis of RCTs,6 medications approved for ADHD, except methylphenidate and atomoxetine in children and adolescents, were associated with higher number of dropouts due to adverse events than placebo. Methylphenidate, in children and adolescents, and amphetamines in adults, were the only medications with lower dropout rates, due to any cause, than placebo.

The most common adverse events during treatment and their suggested management are shown in Table 3. Short-term trials have shown statistically significant increases in heart rate or blood pressure in individuals with ADHD treated with stimulants or atomoxetine compared to placebo6 (average increase in adults of 5.7 bpm in heart rate and 2.0 mmHg in systolic blood pressure).13 Across RCTs, electrocardiographic changes considered abnormal with ADHD pharmacologic treatment have either not been observed or occurred in fewer than 2% of participants,13 however, patients with pre-existing cardiovascular conditions were likely to have been excluded from these trials. Continuous stimulant treatment for 10 years, started in childhood, did not increase the risk of hypertension over the 10-year period, but was associated with modest increases in heart rate at year 8 (supplementary Appendix 2, available with the full text of this article at NEJM.org).14 Even though small but persistent increases in blood pressure or heart rate would be of concern over a long period, a meta-analysis 15 showed no significant association between ADHD pharmacologic treatment and sudden death, stroke, myocardial infarction, and all-cause death, but the confidence intervals of the pooled estimates did not exclude modest increased risk.

Stimulants have been found to reduce growth in height in children by as much as 0.4 inches (1 cm)/year during the first three years of treatment.16 Pooled data from studies in 6-7-year-olds showed that after 2-year use of atomoxetine, height was about 1.06 inches (2.7 cm) less than expected according to baseline height percentiles.17 In one study, this growth deficit has attenuated over time. At a 16-year follow-up of patients who started stimulants in childhood, individuals with treatment on at least 50% of the days were on average 1.6 inches (4.06 cm) shorter than those with treatment on less than 50% of the days.18 The non-randomized nature of this study prevents definite interpretation of the findings. Other studies have reported that after discontinuing treatment for several months, ultimate adult height was not affected.19

A limited number of “within-individual” studies have shown that during treatment with ADHD medications, there was a decreased risk of seizures, depression, substance use disorder, suicidality (with stimulants), and mania in patients who were on concurrent mood stabilizers for their psychiatric disorder, and no increased risk of suicidality (with non-stimulants) or psychosis.9

In observational studies using designs aimed at reducing confounding, risk differences in pregnancy-related and offspring outcomes between mothers exposed to ADHD medications in pregnancy and reference groups ranged from 0.01% for major malformations to 3.90% for caesarean delivery, which might have been accounted for by ADHD medications or by remaining confounding.20

**Neurobiological effects of ADHD medications**

The current understanding of the brain molecular targets of ADHD medications (Table 1) does not directly inform the choice of medication in clinical practice but these mechanisms are useful in understanding the effects of the medications. Across randomized trials, the most consistent effect of acute administration of stimulants is enhancement during neuropsychological tasks of the activity of the right inferior frontal cortex and insula, which are together involved in attention control and inhibition.21 Methylphenidate also temporarily normalizes the pattern of activation of other brain networks, such as the default network, which is usually deactivated during tasks requiring attention but remains abnormally activated in people with ADHD.22

Regarding longer-term effects, compared to medication-naïve individuals, those with ADHD treated for more than 6 months have shown activation in the right caudate during attention tasks, typically reduced in these patients, that was closer to a normal level of activation.23 Average smaller cortical dimensions, at the patient group level, in children with ADHD compared to controls were not accounted for by stimulant treatment.24

**Non-medical use of ADHD medications**

In a review of the literature, use of ADHD medications without a prescription, or in a way other than prescribed, did not improve academic or work performance in individuals without ADHD.25 In this same review, up to 58.7% of college students reported non-medical use of stimulants at least once in their life and about 2% of U.S. adults acknowledged at least one episode of non-medical stimulant use in the previous year.25 Enhancement of academic or work performance was the most frequent motivation for non-medical stimulant use, followed by recreational use (“getting high”).25 Self-medication of undiagnosed ADHD may be another explanation, as individuals who engaged in stimulant non-medical use reported more symptoms of ADHD than those who did not; but overreporting of ADHD symptoms is possible. In large (>10,000 participants) studies, non-medical stimulant use was associated with symptoms that were life-threatening or produced significant disability in up to 0.4% of users, and the risk of death was increased with nasal or intravenous administration of stimulants.25

**Conclusions**

Medications used to treat ADHD are effective in reducing inattentiveness, restlessness and impulsivity, as well as some of the negative outcomes of ADHD, in the short-term and may be effective over longer periods.7 Adverse events during treatment can usually be managed but safety is a concern for some patients, especially those with pre-existing cardiovascular abnormalities. The selection of the most appropriate medication for each patient is currently on a trial-and-error basis and our understanding of the neurobiology of ADHD has not informed yet the choice of medication. In the future, incorporating biomarkers and clinical predictors of response and adverse effects, might allow clinicians to tailor treatment to the needs of patients. Advanced pharmaco-epidemiological approaches may provide a more precise estimate of the long-term effects of ADHD medications. Advances in genetics focused on genes encoding or being the target of medications could lead to compounds with novel mechanisms of actions.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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**FIGURE 1 LEGEND**

**Figure 1. Annual prevalence of medication use across countries a against meta-analytic estimate b of the prevalence of ADHD (thick red line, with dotted lines representing the corresponding 95% confidence interval bounds) in children/adolescents (3-18 years).**

**Footnote:**

**a** Recreated with data from 3; **b** Predicted average prevalence estimate rate of ADHD based on a mixed-effects model from 26 showing that, after controlling for study methods, ADHD prevalence estimates did not significantly vary as a function of year of study or geographic location. Data relative to annual prevalence of medication use in adults with ADHD are reported in Appendix 3 and Tables S1-S4, available with the full text of this article at NEJM.org.

**Table 1. Medications approved by the Food and Drug Administration (FDA) for the treatment of ADHD.a FDA approved ageand dose range are reported in Table S5.**

|  |
| --- |
| **STIMULANTS** |
| ***Mechanism of action b*** | ***Preparation (form and, when available, approximate duration of response in hours) c*** |
| **Amphetamines** |
| Increase extracellular synaptic levels of dopamine and norepinephrine via inhibition of DAT and NET; increase vesicular dopamine release via inhibition of VMAT-2 (dexamphetamine); inhibit MAO; interact with ACH, 5-HT, opioid, and GLU | *Mixed amphetamine salts (tablet, 4-6),* racemic amphetamine sulfate (tablet, 4-6), *dextroamphetamine sulfate (tablet/solution, 4-6),* racemic amphetamine sulfate (ODT, orally disintegrating tablet, 10), methamphetamine (tablet), dextroamphetamine sulfate extended-release (capsule), mixed amphetamine salts extended-release (capsule, 12), extended release XR-OS (oral solution), extended release XR-ODT (orally disintegrating tablet, 12), lisdexamfetamine (capsule, chewable tablet, 13), extended release EROS (suspension,13), tripled bead mixed amphetamines salts extended-release (capsule, 16) |
| **Methylphenidate** |
| Increases extracellular synaptic levels of dopamine and norepinephrine via inhibition of DAT and NET and redistribution of VMAT-2; agonist activity at 5-HT1A receptor | Immediate release (tablet, 4, solution, *chewable tablet*), dexmethylphenidate (tablet, 4), extended-release (tablet, chewable tablet, 8), extended-release (long-acting) (capsule, 8), controlled delivery (capsule, 8), transdermal system (patch, 9 d), delayed-release and extended-release (capsule, 11 e), osmotic-release oral system (OROS) (tablet, 12), extended-release (ODT, orally disintegrating tablet, 12), extended-release (suspension, 12), dexmethylphenidate extended release (capsule, 12), multilayer extended-release (capsule, Aptensio XR ®, 12; Adhansia XR ®, 13-16) |
| **NON-STIMULANTS** |
| **Atomoxetine** (capsule, 24). Selectively inhibits NET; increases extracellular synaptic levels of norepinephrine and dopamine |
| **Extended-release** **clonidine** (tablet). Stimulates postsynaptic alfa-2 adrenergic receptors |
| **Extended-release** **guanfacine** (tablet, 24).Stimulates postsynaptic alfa-2A adrenergic receptors  |

***a*** *As to April 1, 2020, under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) (in italics compounds available only as ANDA, with data from corresponding NDA), retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/.* ***b****Additional details on the mechanisms of action are reported in Appendix 5;* ***c*** *Additional details on the duration of response are provided in Appendix 4;* ***d*** *Response may persist for 2-3 hours after patch removal;* **e** After delayed onset (23 h post dose). *ACH: Acetylcholine; DAT: dopamine transporter; GLU: glutamate; MAO: monoamine oxidase; NET:* norepinephrine transporter; VMAT-2: vesicular monoamine transporter 2; 5-HT: 5-hydroxytryptamine (serotonin)

**Table 2. Recommendations for ADHD treatment from a selection of recent clinical guidelines.**

|  |  |  |
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| **American Academy of Pediatrics (2019)27** | **National Institute for Health and Care Excellence (NICE), UK (2018)28** | **ADHD German Guidelines (2018)29** |
| ***Preschool children (4-6 years)***First line: Parent training in behavior management and/or behavioral classroom interventionsSecond line: Methylphenidate (off-label)***Children 6-11 years***FDA-approved medications (order suggested by evidence: 1) stimulants; 2) atomoxetine; 3) extended-release guanfacine; 4) extended-release clonidine) and parent training in behavior management and/or behavioral classroom interventions (preferably both)***Adolescents 12-18 years***FDA-approved medications. Training and/or behavioral interventions if available. Educational interventions***Adults***Not included in the guideline | ***Children < 5 years***First line: ADHD-focused group parent training programme. Medication as second line only after second specialist opinion***Children ≥ 5 years and young people***ADHD-focused support. If ADHD symptoms persist in at least one area of functioning after environmental modification: medication (order: 1) methylphenidate; 2) lisdexamfetamine (or dexamphetamine if lisdexamfetamine not tolerated); 3) atomoxetine or guanfacine). If symptoms of oppositional defiant disorder or conduct disorder: parent-training. Cognitive behavioral therapy for young people if symptoms still impairing in at least one area of functioning after pharmacological treatment***Adults*** If ADHD symptoms persist in at least one area of functioning after environmental modification: medication (order: 1) methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine not tolerated); 2) atomoxetine). Supportive psychological intervention if medication ineffective of not tolerated | ***Children < 6 years***First line: ADHD-focused group or individual parent or teacher training. Medication only after specialist advice for children > 3 years ***Children ≥ 6 years and young people***After psychoeducation:*Mild to moderate ADHD:* First line: parent-training or family-based interventions; if needed, patient- and school/workplace-based interventions. Second line: medication (order: 1) stimulants; 2) atomoxetine or guanfacine)*Moderate to severe ADHD:*First line: medication (order: 1) stimulants; 2) atomoxetine or guanfacine). Second line: parent training or family-based interventions; if needed, patient- and school/workplace-based interventions***Adults***After psychoeducation, first-line treatment: medication. Non-pharmacologic treatment if patient choice, or if medication ineffective or not tolerated |

**Table 3. Management of adverse events during treatment with ADHD medications. *a***

|  |  |
| --- | --- |
| **Adverse event** | **Suggested management strategy** |
| ***Decreased appetite******Height and weight gain deficit*** | * + - * Measure height every 6 months in children and young people. Measure weight every 3 months in children ≤ 10 years, at 3 and 6 months after starting treatment in children > 10 years and young people, and every 6 months thereafter (or more often if concerns arise), and every 6 months in adults
* If weight loss of clinical concern: take medication either with or after food, rather than before meals, take additional meals or snacks early in the morning or late in the evening when stimulant effects have worn off, obtain dietary advice, consume high-calorie foods of good nutritional value, take a planned break from treatment, or change medication
* If a child has not met the height expected for their age, consider a planned break in treatment over school holidays
* *Refer to pediatric endocrinologist/growth specialist if height and weight values are below critical thresholds (Appendix 6)*
* If weight change in adults as result of the ADHD pharmacological treatment, change medication
 |
| ***Increased blood pressure/heart rate*** | * Do not offer routine blood tests or ECG unless there is a clinical indication
* Measure heart rate and blood pressure after each dose change and every 6 months
* If sustained resting tachycardia (> 120 beats per minute), arrhythmia or systolic blood pressure >95th percentile (or a clinically significant increase) measured on 2 occasions, reduce the dose and refer to a specialist *(Figure S1)*
* If sustained orthostatic hypotension/fainting with guanfacine, reduce the dose or switch to another ADHD medication
 |
| ***Sleep disturbance*** | * *If behavioural measures (sleep hygiene) are insufficient and it is not convenient to stop medication, review the possible causes of sleep problems: 1) Treat Restless Legs Syndrome if present; 2) If rebound effect with stimulants: add small doses of short-acting stimulants in the evening; 3) If stimulant is the current treatment: consider reducing dose, alternative classes or formulations of stimulants, or atomoxetine. Consider adding melatonin*
 |
| ***Tics***  | * *Monitor tics over a 3 months period before any decision regarding ADHD treatment*
* If tics are stimulant related, reduce the stimulant dose, or consider changing to guanfacine (in children aged 5 years and over and young people only), atomoxetine, clonidine or stopping medication, *or add an antipsychotic*
 |
| ***Seizure***  | * If new seizures or worsening of existing seizures, review ADHD medication and stop any medication that might be contributing to the seizures. Cautiously reintroduce ADHD medication if it is unlikely to be the cause of the seizures
 |
| ***Psychotic symptoms*** | * *If they occur with therapeutic doses of ADHD medications, reduce the dose or discontinue the ADHD drug (Appendix 6)*
* *Once the psychotic or manic symptoms resolve, consider a re-challenge with ADHD medications*
 |

***a*** *As recommended in the National Institute for Health and Care Excellence (NICE) guidelines,*28 *supplemented by additional guidance (in italics) from the American Academy of Pediatrics* 27 *and the European ADHD Guidelines Group (EAGG)30*