

REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Pharmacologic Treatment of Attention Deficit–Hyperactivity Disorder

Samuele Cortese, M.D., Ph.D.

From the Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, and Solent NHS Trust, Southampton, and the Division of Psychiatry and Applied Psychology, Institute of Mental Health, School of Medicine, University of Nottingham, Nottingham — all in the United Kingdom; and the Department of Child and Adolescent Psychiatry, New York University Grossman School of Medicine, New York. Address reprint requests to Dr. Cortese at the Centre for Innovation in Mental Health, University of Southampton, Highfield Campus, Bldg. 44, Southampton, SO17 1BJ, United Kingdom, or at samuele.cortese@soton.ac.uk.

N Engl J Med 2020;383:1050-6.
DOI: 10.1056/NEJMra1917069

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ATTENTION DEFICIT–HYPERACTIVITY DISORDER (ADHD) IS CHARACTERIZED by hyperactivity and impulsivity, by inattention, or by a combination of hyperactivity, impulsivity, and inattention that is inconsistent with developmental level and impairs daily function.¹ The disorder is commonly diagnosed in children, and in up to 70% of childhood cases, symptoms that lead to impairment in functioning persist into adulthood.²

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

MEDICATION USE IN ADHD

A study using prescription databases⁶ showed geographic variation in the prevalence of medication use for ADHD, ranging in 2014 from 0.39% (in France) to 5.56% (in the United States) among children and adolescents and from 0.01% (in Hong Kong) to 2.11% (in the United States) among adults. The prevalence of medication use increased from 2001 to 2015, with average yearly relative percentage increases ranging from 2.83% (in the United States) to 45.11% (in Canada) among children and adolescents and from 7.94% (in Taiwan) to 75.88% (in Japan) among adults. According to the databases from which these numbers are derived, the prevalence of ADHD medication use was substantially lower than the estimated prevalence of ADHD during the same periods, except in the United States and Iceland (Fig. 1).

Across the 12-month follow-up periods of various studies in a systematic review,⁸ the average duration of treatment with stimulants was 136 days in children and 230 days in adults. The highest rates of discontinuation of medication were reported in patients who were 15 to 21 years of age,⁹ and reasons for discontinuation included side effects, perceived lack of effectiveness, dislike of taking medications, a decision that treatment was not needed, stigma, and issues with the transition from child to adult services.^{8,9}

EFFICACY AND EFFECTIVENESS

A meta-analysis¹⁰ of double-blind, randomized, controlled trials (RCTs) with an average duration of 7 weeks showed that medications approved for ADHD were

Table 1. Medications Approved by the Food and Drug Administration (FDA) for the Treatment of Attention Deficit–Hyperactivity Disorder (ADHD).*

Medication	Mechanism of Action	Preparation and Form†
Stimulants		
Amphetamines	Increase extracellular synaptic levels of dopamine and norepinephrine by inhibiting dopamine transporter and NE transporter; increase vesicular dopamine release by inhibiting VMAT-2 and release of cytosolic dopamine after reverse transport by dopamine transporter; inhibit monoamine oxidase; interact with ACH, 5-HT, opioid, and glutamate	Extended-release amphetamines: XR-OS liquid oral suspension, EROS liquid oral suspension (13 hr), orally disintegrating tablet (12 hr) Dextroamphetamine sulfate: tablet or solution (4–6 hr), extended-release capsule Lisdexamfetamine: capsule (13 hr), chewable tablet (13 hr) Methamphetamine: tablet Mixed amphetamine salts: tablet (4–6 hr), extended-release capsule (12 hr) Racemic amphetamine sulfate: tablet (4–6 hr), orally disintegrating tablet (10 hr) Triple-bead mixed amphetamine salts: extended-release capsule (16 hr)
Methylphenidate	Increases extracellular synaptic levels of dopamine and norepinephrine through inhibition of dopamine transporter and NE transporter and redistribution of VMAT-2; agonist activity at 5-HT _{1A} receptor	Dexmethylphenidate: tablet (4 hr), dexmethylphenidate extended-release capsule (12 hr) Methylphenidate: immediate-release tablet (4 hr), immediate-release solution, immediate-release chewable tablet, extended-release tablet (8 hr) or chewable tablet (8 hr), extended-release long-acting capsule (8 hr), controlled-delivery capsule (8 hr), transdermal patch (9 hr)‡, delayed-release and extended-release capsule (11 hr, after 10-to-12-hr delay in onset of action), osmotic-release oral system tablet (12 hr), extended-release orally disintegrating tablet (12 hr), extended-release suspension (12 hr), multilayer extended-release capsule [Aptensio XR [Rhodes Pharmaceuticals] [12 hr]; Adhansia XR [Purdue] [13–16 hr]]
Nonstimulants		
Atomoxetine	Selectively inhibits NE transporter; increases extracellular synaptic levels of NE and dopamine in prefrontal cortex	Capsule (24 hr)
Extended-release clonidine	Stimulates postsynaptic α_2 -adrenergic receptors	Tablet
Extended-release guanfacine	Stimulates postsynaptic α_{2A} -adrenergic receptors	Tablet (24 hr)

* Shown are medications approved for the treatment of ADHD as of April 1, 2020, under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). Mixed amphetamine salts (tablet), dextroamphetamine sulfate (tablet or solution), racemic amphetamine sulfate (tablet), immediate-release methylphenidate (chewable tablet), and methylphenidate extended-release tablet (8 hr) are available only under an ANDA (www.accessdata.fda.gov/scripts/cder/daf/). Additional details on the mechanisms of action and the response duration are provided in Sections S5 and S4, respectively, in the Supplementary Appendix, available with the full text of this article at NEJM.org. FDA-approved age and dose range are shown in Table S5 in the Supplementary Appendix. ACH denotes acetylcholine, 5-HT 5-hydroxytryptamine (serotonin), NE norepinephrine, and VMAT-2 vesicular monoamine transporter 2.

† The approximate response duration, if available, is in parentheses.

‡ The response to the transdermal patch may persist for 2 to 3 hours after patch removal.

superior to placebo in decreasing the severity of inattention, hyperactivity, and impulsivity as rated by clinicians, with the largest effect sizes found for amphetamines, followed by methylphenidate (see Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). As a point of reference, effect sizes for stimulants in children and adolescents with ADHD were larger than those reported in short-term RCTs of psychiatric medications in a variety of other disorders.¹¹ Amphetamines were significantly more efficacious than methylphenidate, atomoxetine, and guanfacine at the group

level. However, at the patient level, in crossover RCTs,¹² approximately 41% of participants had equally good responses to both amphetamines and methylphenidate, 28% had a better response to amphetamines, 16% had a better response to methylphenidate, and the rest did not have a response to either medication.¹²

Some pharmacoepidemiologic studies have used a within-person design, comparing outcomes during periods on and off medication in the same person, to account for confounding of drug prescription by indication. In periods during which patients were receiving medication,

Table 2. Recommendations for ADHD Treatment from Recent Clinical Guidelines.

Organization and Patient Age	Treatment Recommendations
American Academy of Pediatrics³	
Preschool children (4–5 yr old)	First line: parental training in behavior management, behavioral classroom interventions, or both Second line: methylphenidate (off-label)
Children 6–11 yr old	FDA-approved medications (in descending order according to strength of evidence: stimulants, atomoxetine, extended-release guanfacine, extended-release clonidine) with parental training in behavior management, behavioral classroom interventions, or preferably both; educational interventions
Adolescents 12–17 yr old	FDA-approved medications; training or behavioral interventions, if available, or both; educational interventions
Adults	Recommendations are not included in the guideline
National Institute for Health and Care Excellence, United Kingdom⁴	
Children <5 yr old	First line: ADHD-focused group training for parents Second line: medication only after second specialist opinion
Children ≥5 yr old and young people	ADHD-focused support (e.g., education and information on the causes and effects of ADHD, advice on parenting strategies, and liaison with school) If ADHD symptoms persist in at least one area of functioning after environmental modification, start medication (in descending order of preference): methylphenidate, lisdexamfetamine (or dexamphetamine if unacceptable side effects with lisdexamfetamine), atomoxetine or guanfacine For symptoms of oppositional defiant disorder or conduct disorder: parental training Cognitive behavioral therapy for young people if symptoms still impairing at least one area of functioning after pharmacologic treatment
Adults	If ADHD symptoms persist in at least one area of functioning after environmental modification: medication (in descending order of preference): methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine associated with unacceptable side effect profile), atomoxetine Supportive psychological intervention if medication is ineffective or associated with unacceptable side effects
ADHD German Guidelines⁵	
Children <6 yr old	First line: ADHD-focused group or individual training for parents or teachers Second line: medication only after specialist advice for children >3 yr old
Children ≥6 yr old and young people	
Mild-to-moderate ADHD	After psychoeducation, first line: parental training or family-based interventions; if needed, patient-, school-, and workplace-based interventions After psychoeducation, second line: medication (in descending order of preference): stimulants, atomoxetine or guanfacine
Moderate-to-severe ADHD	After psychoeducation, first line: medication (in descending order of preference): stimulants, atomoxetine or guanfacine After psychoeducation, second line: parental training or family-based interventions; if needed, patient-based and school- or workplace-based interventions
Adults	After psychoeducation, first-line: medication; nonpharmacologic treatment if patient chooses it or if medication ineffective or associated with unacceptable side effects

these studies showed a significant decrease in negative outcomes, such as unintentional physical injuries, motor vehicle accidents (among male patients), substance use disorder, and criminal acts, as well as an improvement in academic functioning.¹³

Determining the long-term effects of ADHD medications has been challenging because of the difficulty in overcoming bias and confounding in studies comparing treated and untreated pa-

tients. In a double-blind RCT of medication discontinuation in which participants who had been treated with methylphenidate for an average of 4.5 years were randomly assigned to continue or discontinue medication, continuation was associated with an ongoing benefit with respect to ADHD symptoms, as compared with discontinuation and a switch to placebo.¹⁴ However, effect sizes for the benefit were smaller than those reported in short-term RCTs of meth-

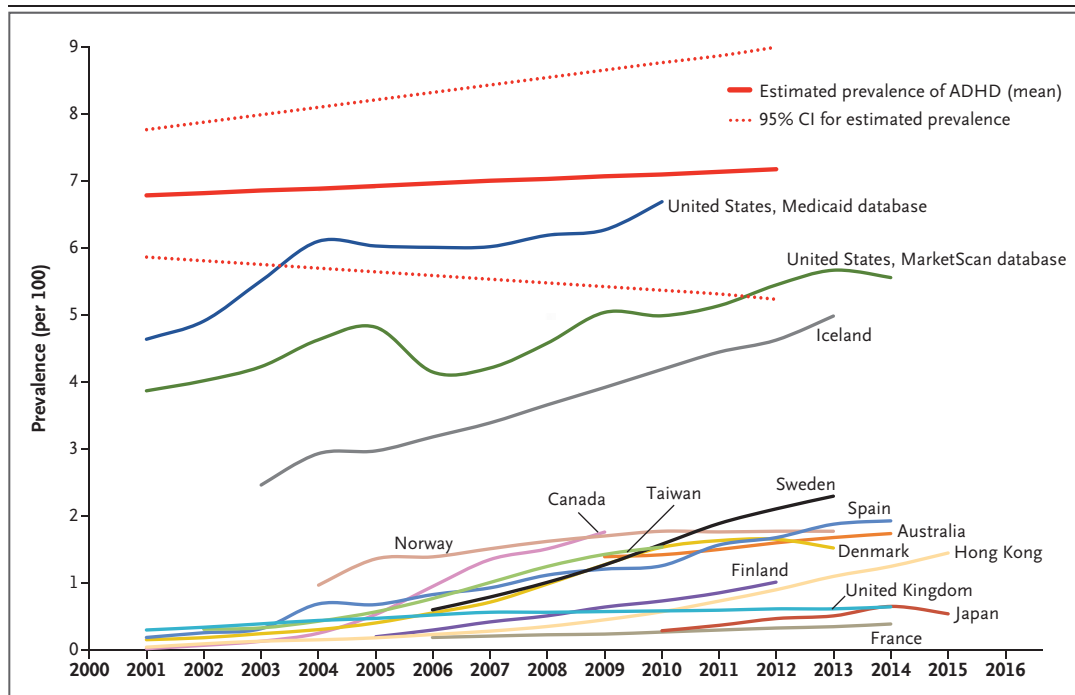


Figure 1. Annual Prevalence of Medication Use for Attention Deficit–Hyperactivity Disorder (ADHD) among Persons 3 to 18 Years of Age, According to Country.

Data on the prevalence of medication use are based on a retrospective observational study by Raman et al.⁶ The bold red line shows the estimated mean prevalence of ADHD, with the dotted red lines indicating the 95% confidence interval (CI), on the basis of a mixed-effects meta-regression model from Polanczyk et al.⁷ The model showed that, after adjustment for study methods, the prevalence estimates of ADHD did not vary significantly as a function of the year of study or geographic location. Detailed data on the annual prevalence of medication use among adults with ADHD are provided in Section S3 and Tables S1 through S4 in the Supplementary Appendix. The MarketScan database includes data on enrollees in health insurance plans in the United States, and the Medicaid database includes statistical data on Medicaid beneficiaries (persons in the United States with low incomes).

ylphenidate treatment. This may have been due to decreased effectiveness of the medication over time, inadequate adjustment of the dose, or overrepresentation in the study of participants with ADHD that was mild or resolving. The effects of ADHD medications on measures of quality of life have correlated inconsistently with abatement of ADHD symptoms; across various measures of quality of life used in RCTs (including randomized discontinuation trials), the effects of ADHD medications have ranged from nonsignificant to significant.^{15,16}

SIDE EFFECTS AND SAFETY

In a meta-analysis of RCTs,¹⁰ medications approved for the treatment of ADHD, except for methylphenidate and atomoxetine in children and adolescents, were associated with higher dropout rates due to adverse events, as compared with

placebo. Methylphenidate in children and adolescents and amphetamines in adults were the only medications associated with lower dropout rates due to any cause, as compared with placebo.

The most common adverse events during ADHD treatment and their suggested management are shown in Table 3. Short-term trials have shown significant increases in heart rate or blood pressure in persons with ADHD treated with stimulants or atomoxetine, as compared with placebo¹⁰; in a meta-analysis of RCTs of stimulants in adults, the average increase in heart rate was 5.7 beats per minute, and the average increase in systolic blood pressure was 2.0 mm Hg.¹⁸ Across RCTs, electrocardiographic changes considered to be abnormal have not been observed or have occurred in less than 2% of participants¹⁸; however, patients with preexisting cardiovascular conditions were likely to have been excluded from these trials. Stimulant

Table 3. Management of Adverse Events during Treatment with ADHD Medications.*

Adverse Event	Suggested Management Strategy
Decreased appetite, deficits in height and weight gain	<p>Measure height every 6 mo in children and young people.</p> <p>Measure weight every 3 mo in children ≤ 10 yr old; at 3 mo and 6 mo after starting treatment in children > 10 yr old and young people, and every 6 mo thereafter (or more often if concerns arise); and every 6 mo in adults.</p> <p>If weight loss is of clinical concern, recommend that medication be taken either during or after meals rather than before meals; suggest additional meals or snacks early in the morning or late in the evening, when stimulant effects have worn off; obtain dietary advice from a dietician; recommend high-calorie foods of good nutritional value; suggest a planned break from treatment; or change medication.</p> <p>If a child's height is lower than expected for age, consider a planned break in treatment during school holidays. Refer to pediatric endocrinologist or growth specialist if height and weight values are below critical thresholds (Section S6).[†]</p> <p>If weight changes in an adult as a result of ADHD pharmacologic treatment, change medication.</p>
Increased blood pressure or heart rate	<p>Do not obtain routine blood tests or electrocardiogram unless there is a clinical indication.</p> <p>Measure heart rate and blood pressure after each dose change and every 6 mo.</p> <p>If sustained resting tachycardia (> 120 beats/min), arrhythmia, or systolic pressure > 95th percentile (or a clinically significant increase) on two occasions, reduce dose and refer patient to a specialist (Fig. S1).</p> <p>If sustained orthostatic hypotension or fainting with guanfacine, reduce dose or switch to another ADHD medication.</p>
Sleep disturbance	<p>If behavioral measures (sleep hygiene) are insufficient and it is not convenient to stop medication, review the possible causes of sleep problems: treat restless legs syndrome if present; if stimulants cause a rebound effect, add small doses of short-acting stimulants in the evening; if the current treatment is a stimulant, consider a reduced dose, alternative stimulant class or formulation, or atomoxetine; consider adding melatonin.[†]</p>
Tics	<p>Monitor tics over a 3-mo period before making any decision regarding ADHD treatment.[†]</p> <p>If tics are stimulant-related, reduce the stimulant dose or consider changing to guanfacine (in children ≥ 5 yr of age and young people only), atomoxetine, or clonidine; adding an antipsychotic agent[†]; or stopping medication.</p>
Seizures	<p>If seizures are new or worsening, 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.</p>
Psychotic symptoms	<p>If symptoms occur with a therapeutic dose of ADHD medication, reduce the dose[†] or discontinue the drug (Section S6).</p> <p>Once psychotic symptoms resolve, consider rechallenge with ADHD medication.</p>

* Except as otherwise noted, recommendations are from the National Institute for Health and Care Excellence (NICE) guidelines.⁴

[†] The recommendation is from the European ADHD Guidelines Group.¹⁷

treatment that was started in childhood and continued for 10 years did not increase the risk of hypertension over the 10-year period but was associated with modest increases in the heart rate at year 8 (Section S2 in the Supplementary Appendix).¹⁹ Even though small but persistent increases in blood pressure or heart rate are of concern if sustained over a long period, a meta-analysis showed no significant association between pharmacologic treatment for ADHD and sudden death, stroke, myocardial infarction, or death from any cause, but the confidence intervals for the pooled estimates did not exclude a modest increase in risk.²⁰

Stimulant use in children with ADHD has reduced growth in height by as much as 1 cm per year during the first 3 years of treatment.²¹ Pooled data from studies in 6-to-7-year-old children showed that after treatment with atomoxetine for 2 years, height was approximately 2.7

cm less than expected according to baseline height percentiles.²² In one study, a growth deficit attenuated over time. At a 16-year follow-up of patients who had started treatment with stimulants in childhood, persons receiving treatment on at least 50% of the days were, on average, 4.1 cm shorter than those receiving treatment on less than 50% of the days,²³ but the nonrandomized nature of this study prevents a definite interpretation of the findings. Other studies have shown that several months after discontinuation of treatment, adult height was not affected.²⁴

A limited number of within-person studies have shown that while patients were being treated with ADHD medications, the risks of seizures, depression, mania (during concurrent treatment with methylphenidate and mood stabilizers), and — in persons treated with stimulants — suicidal-ity were decreased.¹³ There also was no increase

in the risk of suicidality (with nonstimulants) or of psychosis (with methylphenidate).¹³

In a review of observational studies with designs aimed at reducing confounding, risk differences in pregnancy-related and offspring outcomes between women exposed to ADHD medications during pregnancy and reference groups ranged from 0.01% for major malformations to 3.90% for cesarean delivery. The increased risks among women receiving ADHD medications may have been due to the medications or to residual confounding.²⁵

NEUROBIOLOGIC EFFECTS OF ADHD MEDICATIONS

Our current knowledge of the molecular targets of ADHD medications in the brain (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 a single dose of stimulants is enhancement during neuropsychological tasks of the activity of the right inferior frontal cortex and insula, which together are involved in attention control and inhibition.²⁶ Methylphenidate also temporarily normalizes the pattern of activation of other brain networks, such as the default network, which is usually deactivated in everyone during tasks requiring attention but is less deactivated in people with ADHD who have not received treatment.²⁷

Regarding longer-term neurobiologic effects, patients with ADHD who have received stimulants for more than 6 months may have activation in the right caudate nucleus that is generally close to normal levels during tasks requiring attention, whereas activation in this area is usually reduced in untreated persons with ADHD.²⁸ Smaller average cortical dimensions in several brain regions have been found at the group level in children with ADHD as compared with controls, but stimulant treatment did not account for the difference.²⁹

NONMEDICAL USE OF ADHD MEDICATIONS

A review of the literature showed little evidence that use of ADHD medications without a prescription or use in a way that was not prescribed improves academic or work performance in per-

sons without ADHD.³⁰ In the same review, up to 58.7% of college students in the United States reported nonmedical use of stimulants on at least one occasion, and 2.1% of adults in the United States acknowledged at least one episode of nonmedical stimulant use in the previous year.³⁰ Enhancement of academic or work performance was the most frequent motivation for nonmedical stimulant use, followed by recreational use (“getting high”). Self-medication for undiagnosed ADHD may be another explanation, since persons who engaged in nonmedical use of stimulants reported more symptoms of ADHD than those who did not engage in nonmedical stimulant use, but overreporting of ADHD symptoms in the studies included in the review is also possible. In large studies (>10,000 participants) in the review, nonmedical stimulant use was associated with symptoms that were life-threatening or that caused clinically significant disability in up to 0.4% of users. Data from poison control centers showed an increased risk of death with nasal or intravenous administration of stimulants.³⁰

CONCLUSIONS AND FUTURE DIRECTIONS

Medications used to treat ADHD are effective in reducing inattention, hyperactivity, and impulsivity in the short term and may be effective over longer periods.¹¹ Some of the negative outcomes of ADHD, such as accidents and illicit drug use, may also be reduced. Adverse events during treatment can usually be managed, but safety is a concern for some patients, especially those with preexisting cardiovascular disorders. Reasons for discontinuation of medication by patients include side effects, perceived lack of effectiveness, dislike of taking medications, and stigmatization. The selection of the most appropriate medication for each patient is currently made on a trial-and-error basis, and our understanding of the neurobiology of ADHD is not yet sufficient to inform 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 individual patients. Advanced pharmacoepidemiologic approaches may provide a more precise estimate of the long-term effects of ADHD medications. Advances in genetics focused on genes that encode or are the target of medica-

tions could lead to the development of compounds with novel mechanisms of action.

No potential conflict of interest relevant to this article was reported.

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

I thank Drs. Cristiano Fava, Ulrich Thalheimer, and Tim Wildschut for advice during the preparation of a previous version of the review.

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