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Practice Pearls for Stimulant Treatment of Attention-Deficit/Hyperactivity Disorder in Youth

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Over half of youth with attention-deficit/hyperactivity disorder (ADHD) have co-occurring psychiatric or medical conditions that present treatment challenges. Stimulants are the most effective pharmacologic treatment of ADHD for preschoolers to adults but questions about safety with co-occurring conditions frequently arise. In addition, stigma surrounding diagnosis and treatment can negatively impact care. This manuscript presents evidence-based practice pearls to guide treatment decisions for youth with ADHD and common coexisting psychiatric and medical conditions. Recommendations address specific stimulant adverse effects (i.e., anxiety, cardiac, growth, mania, psychosis) along with management strategies. Pearls were developed for the most common clinical questions, controversial topics, or therapeutic issues that may not be widely known. The goals of this manuscript are to: 1) provide a detailed resource for interprofessional teams regarding stimulant use in youth with ADHD, 2) improve therapeutic outcomes for youth with ADHD and co-occurring psychiatric and/or medical conditions through evidence-based recommendations, and 3) decrease stigma associated with stimulant use through education.

ABBREVIATIONS ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; AN, anorexia nervosa; ASD, autism spectrum disorder; BED, binge-eating disorder; BN, bulimia nervosa; d-AMP, dextroamphetamine; d-MPH, dexmethylphenidate; DSM-5-TR, Diagnostic and Statistical Manual 5th Edition Text Revision; ECG, electrocardiogram; ED, eating disorder; EEG, electroencephalogram; ER, extended-release; FDA, Food and Drug Administration; ID, intellectual disability; IR, immediate-release; LDX, lisdexamfetamine; MAS, mixed amphetamine salt; MPH, methylphenidate; MTA, Multimodal Treatment Study of Children with ADHD; NG, nasogastric; OROS, osmotic release oral system; PTBM, Parent Training in Behavior Management; R-MOAS, Retrospective Modified Overt Aggression Scale; SODAS, spheroidal oral drug absorption system; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SUD, substance use disorder; TS, Tourette syndrome; XR, extended-release.

KEYWORDS adolescent psychiatry; attention deficit hyperactivity disorder; central nervous system stimulants; child psychiatry; pediatric; psychiatrist; psychopharmacology

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) occurs in 5% to 10% of children and adolescents and can impede learning, healthy growth, and development if left untreated (Table 1).[1] Behavioral interventions are effective and should be employed, but alone are insufficient to effectively manage symptoms for most youth with ADHD.[2,3] Stimulant medications are first line treatment for ADHD in youth > 5 years old due to superior efficacy over other pharmacotherapeutic options and overall good tolerability (Table 2).[2,3] An analysis of 133 double blind, placebo-controlled trials involving approximately 11,000 youth showed a methylphenidate trial should be recommended first line among children and adolescents due to high efficacy and better tolerability than amphetamines.[2] Amphetamines, while effective, are associated with more appetite suppression, weight loss, and increased blood pressure in children and adolescents compared with methylphenidate. Of note, affect lability, moodiness, and irritability are more likely in preschoolers who receive stimulants compared with older children, warranting close monitoring and risk vs benefit assessment when initiating stimulant medication prior to age 6.[4]

Over half of individuals with ADHD have co-occurring conditions (Table 3). Anxiety, oppositional defiant, autism spectrum, substance use disorders, learning disabilities, and chronic medical conditions (e.g., diabetes, asthma) commonly occur in children and adolescents with ADHD, presenting treatment challenges.[1] The Society for Developmental and Behavioral Pediatrics has introduced the term "complex ADHD" to facilitate integrated, interprofessional assessment and treatment for patients with ADHD and coexisting conditions. Complex ADHD is defined by any of the following: age at diagnosis (before 4 years or after 12 years of age), presence of coexisting conditions, moderate to severe

Table 1. Risks and Consequences of Untreated/Undertreated ADHD[1,5,85,86]

Academic	• Impairments in school performance, academic achievement
Social	• Disruptions in peer and family relationships • Lower self-esteem • Higher rates of incarceration • Increased rates of traffic violations
Health	• Increased rates of traffic accidents • Higher rates of accidental injury • Increased rates of psychiatric hospitalization • Earlier onset and increased rate of cigarette smoking • More likely to engage in early, substance use and to develop a substance use disorder • Increased mortality

ADHD, attention-deficit/hyperactivity disorder

Table 2. AAP ADHD Treatment Guidelines[3]

Preschool	First line: PTBM, behavioral classroom interventions • If behavioral interventions ineffective after ≥3-month trial and if, moderate-severe disturbance in functioning: MPH ◦ If MPH is used, start and target small doses and use short-acting product; this age group metabolizes the medication more slowly
Elementary and Middle School	First line: medication and behavioral interventions • Behavioral interventions: PTBM, behavioral classroom interventions, educational interventions, individualized instructional support (i.e., IEP, 504 plan) • Medication: MPH considered first line, consider short- or long-acting product
High School	First line: medication and behavioral interventions • Behavioral interventions: PTBM, behavioral classroom interventions, educational interventions, individualized instructional support (i.e., IEP, 504 plan) • Medication: MPH considered first line, consider long-acting product to minimize need for afternoon doses

AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; IEP, individualized education plan; MPH, methylphenidate; PTBM, parent training in behavior management

impact of symptoms on daily functioning, diagnostic uncertainty by the primary care provider, or lower than expected response to treatment.[5]

Table 3. One-Year Prevalence of Co-Occurring Conditions in Youth With ADHD[5,10,21,24,68,87]

Oppositional defiant disorder or conduct disorder	30%–50%
Anxiety	30%–40%
Depression	20%–40%
Substance use disorder	20%–30%
Autism spectrum disorder	10%–30%
Seizure disorder	10%–20%
Eating disorder	Up to 20%
Bipolar disorder	8%–10%
Tourette syndrome	5%–10%
Disruptive mood dysregulation disorder	Undetermined

ADHD, attention-deficit/hyperactivity disorder

Pharmacists are important collaborators on the interprofessional team to ensure optimal utilization of stimulants, given their understanding of pediatric-specific risk for adverse effects, prescribing differences compared with adults, and co-occurring medical/psychiatric conditions.[2,6,7] Board Certified Psychiatric Pharmacists are specifically equipped to partner with Board Certified Pediatric Pharmacists and interprofessional teams on complex cases, including those with psychiatric comorbidities, substance use disorders, multiple medication failures, and medical complexity.[8]

When initiating, optimizing, or modifying stimulant treatment, the risks of untreated or undertreated ADHD (Table 1), unique clinical considerations that medical/psychiatric comorbidities present, and risk for adverse effects (Table 4) should be considered. This manuscript will present practice pearls regarding stimulant use in pediatric patients with ADHD and co-occurring medical and/or psychiatric conditions.

Practice Pearls

Psychiatric.

Anxiety.

Clinical Question: How Do Stimulants Impact Anxiety in Youth With ADHD?

Response. Effectively treating ADHD with a stimulant is associated with decreased anxiety for most youth. While stimulants have the potential to worsen anxiety for a minority of treated patients, treatment-emergent anxiety is more common with amphetamines than methylphenidate and it is most likely when maximum recommended daily doses are exceeded.[9] Improving ADHD symptoms likely decreases the number of anxiogenic situations they experience; children with ADHD

successfully treated with stimulants experience fewer academic problems and peer and caregiver conflict that may cause them anxiety.[9]

Supporting Evidence. Anxiety occurs in 25% to 50% of youth with ADHD and impairs functioning in social and academic settings.[5,9] Social anxiety disorder, generalized anxiety disorder, and separation anxiety are well-documented coexisting conditions in children with ADHD.[10] Clinicians may be reluctant to prescribe stimulants for ADHD in children with anxiety given "anxiety and nervousness" are listed as common stimulant adverse effects according to large drug information databases such as Micromedex, Lexicomp, and UptoDate.[11,12] Interestingly, placebo-controlled trials show most children who take stimulants for ADHD experience decreased anxiety compared with placebo, though inconsistent methods of reporting adverse effects makes it difficult to assess the relative risk.[13]

Table 4. Stimulant Adverse Effects[9,35,66,70,73,77,87–90]

Frequency	Adverse Effect	Management Strategy
Common >10%	Decreased appetite, weight loss	• Trend weight percentile using growth chart and z-scores • Give high-calorie meal when stimulant effects are low (e.g., breakfast, bedtime); offer snacks throughout the day • Consider stimulant holidays • Consider cyproheptadine, if appropriate • If concerns for disordered eating or clinically significant weight loss arise, discontinue the stimulant, and evaluate other treatment options
	Stomachache	• Administer stimulant on a full stomach
	Headache	• Divide stimulant dose • Switch to long-acting stimulant product • Administer with food
	Rebound ADHD symptoms	• Switch to a long or longer-acting stimulant product; add a short-acting stimulant dose in the afternoon
	Insomnia	• *Is insomnia related to a medication effect?* ◦ Administer dose earlier in the day; lower the last dose of the day or give it earlier ◦ Switch to a shorter-acting product • *Is insomnia related to undermanaged ADHD symptoms?* ◦ Evaluate need to further optimize stimulant treatment • Consider a sleep-promoting medication at bedtime (e.g., melatonin)
	Dry mouth, dizziness	• Encourage hydration
	Nervousness or anxiety	• Significantly more likely with AMP vs MPH products • Smaller dose, switch to long-acting product • Consider nonstimulant treatment
Uncommon 1%–10%	Decreased growth	• Monitor height and weight routinely on growth chart and trend z-scores • Reevaluate stimulant treatment if child falls from predicted growth trajectory • Consider stimulant holidays
	Irritability, jitteriness	• Reduce dose • Consider alternative medication
	Mood swings, affect lability	• Reduce dose • Consider alternative medication • Reassess diagnosis
	Tachycardia, blood pressure increase	• Reduce dose • Monitor BP/HR routinely • Change medication; MPH has lower risk compared with AMP formulations

(*Table cont. on page 218*)

Table 4. Stimulant Adverse Effects[9,35,66,70,73,77,87–90] *(cont.)*

Frequency	Adverse Effect	Management Strategy
Rare <1%	Cardiovascular event (e.g., arrythmia, myocardial infarction)	• Monitor BP/HR routinely • Discontinue stimulant • Consult cardiology
	Hallucinations	• Discontinue stimulant • Reassess diagnosis • If a stimulant is restarted, consider a MPH/d-MPH over an AMP
	Hyperkinetic movements	• Hold stimulant • Evaluate concurrent medication regimen (e.g., atypical antipsychotic) • Consider reinitiating of stimulant when movements improve • Consult neurology/psychiatry
	Mania	• Discontinue stimulant • Reassess diagnosis
	Peripheral vasculopathies (e.g., Raynaud phenomenon)	• Hold stimulant • Obtain urgent medical assistance if digital changes observed • Consider reducing dose or switching to alternative medication
	Priapism	• Both AMP and MPH products have been associated with priapism in children • Provide education to male patients and caregivers • Hold stimulant • Obtain urgent medical assistance • Consider treatment with stimulant of the alternative class once priapism is treated, evaluated, and subtypes are evaluated
	Seizure	• When seizures are well-controlled, consider initiation of methylphenidate product • If treatment-emergent seizures present, discontinue stimulant and consult neurology
	Serotonin syndrome	• It is safe to use stimulants in combination with serotonergic medications, including antidepressants (e.g., SSRIs, SNRIs) but serotonin syndrome has been reported so educate patient and caregivers on signs and symptoms of serotonin syndrome including diaphoresis, hyperreflexia, clonus, and mydriasis
	Transient, treatment-emergent tic/ worsening of underlying tic disorder	• It is safe to use a stimulant in a pediatric patient with an underlying tic disorder. Monitor for change in tic symptoms following stimulant initiation. • If concerns arise regarding a treatment-emergent tic, evaluate whether tic emergence is related to waxing and waning course of tic disorders (e.g., TS) or whether related to stimulant treatment. • Consider alpha-2 agonist (e.g., guanfacine) as an alternative treatment strategy, if a stimulant is determined to not be the ideal treatment strategy.

ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; BP, blood pressure; HR, heart rate; MPH, methylphenidate; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TS, Tourette syndrome

A meta-analysis of 23 studies involving 2959 children with ADHD demonstrated significantly decreased anxiety when taking a stimulant compared with placebo (RR, 0.86 [95% CI, 0.77–0.95], z = −2.90, p = 0.004). When evaluating stimulant-specific anxiety, methylphenidate derivatives were associated with a greater decrease in anxiety than placebo (RR, 0.85 [95% CI, 0.76–0.94], k = 17, z = −3.02, p = 0.003), whereas amphetamine

derivatives (RR, 1.02 [95% CI, 0.69–1.50], k = 6, z = −2.90, p = 0.94) were associated with a similar risk of anxiety to that of placebo.[9] Immediate-release stimulant treatment was associated with lower rates of anxiety than placebo, while anxiety in youth taking long-acting formulations was similar to placebo.[9]

The largest and longest longitudinal study of ADHD treatment in children, the Multimodal Treatment Study of Children with ADHD (MTA), showed effective treatment of ADHD with methylphenidate improved symptoms of anxiety.[14] Children with anxiety and ADHD responded better to methylphenidate and behavioral interventions compared with children without co-occurring anxiety.[9] A Cochrane review of methylphenidate adverse effects in nonrandomized studies described anxiety as a "non-serious adverse effect" for 18.4% of youth (95% CI, 11.3%–28.7%; 22 studies, 1287 participants). Non-serious adverse effect was defined as treatment-emergent anxiety that did not require discontinuation or alternative treatment.[15] Overall, stimulants can be used in pediatric patients with co-occurring anxiety disorders. When anxiety occurs, stimulant discontinuation is rarely necessary.[9,15]

Autism Spectrum Disorder (ASD).

Clinical Question: Can Stimulants Be Safely Used to Treat ADHD in Youth With ASD?

Response. Yes, stimulants can be a safe and effective treatment for ADHD in children with ASD. If functionally impairing symptoms of ADHD are present in a child with ASD, methylphenidate is the first-line recommendation with low starting (e.g., 0.3 mg/kg/day) and target doses (e.g., 0.5 mg/kg/day) and careful monitoring.[16] Youth with ASD are neurologically sensitive with higher rates of intellectual disability (ID) that may interfere with their ability to report side effects and higher prevalence of seizure disorders which could be exacerbated with stimulant treatment. Additionally, youth with ASD are also more sensitive to certain stimulant adverse effects, particularly appetite suppression and insomnia.[16]

Supporting Evidence. Approximately half of children with ASD (range, 24%–83%) exhibit functionally impairing inattention, hyperactivity, and impulsivity and meet criteria for ADHD.[17] Given high rates of ADHD symptoms in children with ASD, it is crucial to evaluate the safety of stimulants as first-line pharmacologic treatment.

Small, controlled trials show methylphenidate or dexmethylphenidate is effective and well-tolerated in youth with ASD, particularly when small doses are given with careful monitoring.[16] If methylphenidate is ineffective, amphetamine products including lisdexamfetamine may be used and are well-tolerated at small doses (less than or equal to half the maximum recommended dose for an age group).[16] Stimulants do not appear to worsen oppositional or repetitive behaviors and seem to be more effective in children without ID. Appetite suppression and insomnia are the most common stimulant adverse effects in youth with ASD, however irritability, social withdrawal, and depression have also been reported.[16]

Disruptive Behavior Disorders/Aggression.

Clinical Question: Do Stimulants Worsen Aggression in Children/Adolescents With ADHD and Disruptive Behavior Disorders?

Response. No, stimulant treatment actually improves aggression and disruptive behavior associated with oppositional defiant disorder, conduct disorder, disruptive mood dysregulation disorder and ASD when ADHD is also present.[19,20] Aggression and impulsiveness are key features of the hyperactive-impulsive and hyperactive-impulsive/inattentive combined type of ADHD.[1] Effective treatment with stimulant medication for both subtypes of ADHD improves aggression, impulse control, and inattention.[18,19]

Supporting Evidence. A randomized, controlled trial including 6- to 12-year-olds (N = 175) with ADHD and a co-occurring disruptive behavior disorder aimed to evaluate the benefit of rapid stimulant titration for impulsive aggression.[19] The Retrospective Modified Overt Aggression Scale (R-MOAS), a clinician-rated scale, was used to evaluate aggressive symptoms (i.e., verbal, self-injurious, physical aggression) among this patient population. Stimulant doses were increased weekly, to a mean stimulant dose of 42 mg/day (methylphenidate IR equivalence units) or ~1.2 mg/kg/day. Nearly 64% achieved remission of aggression symptoms (R-MOAS score <18) after an average of 75 days of stimulant treatment.[19]

Bipolar disorder, intermittent explosive disorder, and early onset psychosis are other potential causes of aggression and disruptive behavior in children and adolescents.[1,20,21] Children with these conditions without comorbid ADHD, may become more aggressive with stimulant treatment due to treatment-emergent mania, psychosis, or explosive behavior.[1,22]

Eating Disorders (ED).

Clinical Question: What Are the Risks of Using Stimulants to Manage ADHD in Pediatric Patients With an Active ED and When Can a Stimulant Be Considered in a Pediatric Patient With a History of an ED?

Response. Medical and nutritional status, as well as signs and symptoms of the ED (e.g., bingeing, purging, or restricting calories) determines whether a stimulant can be safely used for co-occurring ADHD. Stimulants should not be used if the predominant ED symptom is restricting calories, particularly in malnourished, severely underweight individuals. Stimulant treatment may be unsafe if the child's eating disorder involves bingeing and purging because associated hyponatremia and hypokalemia makes seizures or cardiac arrhythmia more likely. If an otherwise healthy child has an ED without bingeing or purging, lisdexamfetamine has been found to be safe and therapeutic. Other non-FDA approved stimulants can be beneficial for otherwise healthy youth

with binge-eating disorder (BED), but they may not be as effective as lisdexamfetamine which has been more thoroughly evaluated for this indication.

Supporting Evidence. It is estimated that ~20% of children with ADHD will develop an ED, most frequently BED, followed by bulimia nervosa (BN), and lastly anorexia nervosa (AN).[23] Research suggests that among individuals with ADHD and ED there is a shared genetic predisposition, neurobiological influence, and phenotype including difficulties in working memory, inhibitory control, and impulsivity.[23–25] ADHD symptoms typically precede the development of an ED, warranting thoughtful re-evaluation of the pharmacologic treatment plan.[26] For example, if a child is effectively treated for ADHD with a stimulant and develops an ED with associated electrolyte abnormalities from bingeing/purging, the stimulant may need to be held until the ED can be stabilized.

BED.

Lisdexamfetamine is FDA approved for the treatment of moderate to severe BED in adults, with lisdexamfetamine 50 to 70 mg daily improving global binge-eating severity, number of binge-eating episodes per day, and obsessive-compulsive and impulsive features of BED over 11 weeks of treatment.[27,28] In a long-term study which included 275 adults, risk of binge-eating relapse over 6 months was lower in participants continuing lisdexamfetamine than those randomly assigned to placebo.[29]

While lisdexamfetamine has not been systematically evaluated in children and adolescents with BED, a retrospective chart review (N = 25; 12–19 years of age) suggests some benefit in self-reported binge-eating symptoms.[30] ED treatment guidelines do not provide specific recommendations regarding the use of lisdexamfetamine in children and adolescents with BED at this time, given lack of robust data. Based on clinical practice, lisdexamfetamine may be considered for adolescents with moderate to severe BED and co-occurring ADHD, without a clinically significant cardiac history, in conjunction with other supportive ED treatment (e.g., Cognitive Behavioral Therapy).[3,31]

BN.

Case reports and a small open-label study have evaluated the role of stimulants in individuals with BN, targeting binge-eating episodes.[25,32–34] While reductions in co-occurring binge-eating episodes and ADHD symptoms have been described, safety concerns and lack of pediatric specific data limit their routine use in children and adolescents with BN.[31] ED guidelines do not provide recommendations regarding the use of stimulants in pediatric patients with BN, given lack of literature supporting their use. Cardiovascular complications associated with dehydration and electrolyte imbalances secondary to purging, including self-induced vomiting and laxative misuse, pose a significant safety concern with stimulant use among pediatric patients with BN. Additionally, orthostasis induced tachycardia and increased blood pressure have been described with stimulant use in this population.[31] Once the patient is in recovery, purging behaviors are mild/rare, labs and hydration status are stable, a stimulant can be considered targeting ongoing ADHD symptoms.

AN.

Among children and adolescents with AN, stimulants should be avoided given concern for additive appetite suppression, weight loss, exacerbation of restrictive eating, and cardiovascular risk including cardiomyopathy (e.g., hypertrophic) in a severely malnourished child.[31] Once the ED is in recovery, careful consideration to start a stimulant to target ongoing ADHD symptoms can be considered with close monitoring for changes in appetite/weight and aberrant eating behaviors such as resumption of calorie restriction.

Mania/Psychosis.

Clinical Question: Do Stimulants Exacerbate Mania or Psychosis?

Response. While an uncommon to rare occurrence, stimulants can be associated with treatment-emergent mania or psychosis. In 2007, a warning for "treatment-emergent psychotic or manic symptoms in patients with no prior history" was added to prescribing information for all stimulants by the FDA. When a patient presents with an acute onset of mania or psychosis, the stimulant should be held pending further diagnostic and medical evaluation.[35–39]

Supporting Evidence. One study aimed to evaluate risk for psychosis between different stimulant classes, through evaluation of commercial insurance claims databases that included patients 13 to 25 years of age (N = 337,919), diagnosed with ADHD, who started taking a methylphenidate or amphetamine product from January 2004 through September 2015. During a median follow-up period of 4 to 5 months, the percentage of patients who had an episode of psychosis was significantly higher in the amphetamine group than in the methylphenidate group (0.21% vs 0.10%; HR, 1.65; 95% CI, 1.31–2.09) and occurred a median of 128 days after exposure to the stimulant. Overall, new-onset psychotic symptoms were uncommon occurring in approximately 1 in 660 patients.[36] Overall, this study cannot establish causality, but offers important information regarding possible differences in risk among stimulant products for treatment-emergent psychosis.

Other studies have not demonstrated an association of stimulant treatment with psychotic symptoms.[37,38] One cohort study (Swedish Prescribed Drug Register) found an incidence rate ratio of 1.04 (95% CI, 0.8–1.34) when comparing psychotic symptoms 12 weeks post methylphenidate initiation and 12 weeks pre-treatment

initiation in adolescents/young adults (mean age, 17 years) without a history of psychosis.[38]

Childhood onset schizophrenia, bipolar disorder, or other psychiatric conditions with associated psychotic features are risk factors for stimulant-induced psychosis. Treatment-emergent psychotic symptoms resolve after discontinuation of the stimulant in 92% of patients without antipsychotic treatment.[39]

Overall, in children and adolescents with ADHD the risk for mania is low with the use of stimulants.[40–43] With co-occurring bipolar disorder and ADHD, treatment with a mood stabilizer prior to addition of a stimulant is critical. Stimulants can be safely used in pediatric patients with bipolar disorder once manic/hypomanic symptoms are effectively treated with a mood stabilizer.[44,45]

Substance Use Disorders (SUDs).

Clinical Question: Should Stimulants Be Prescribed to Pediatric Patients With Active Substance Use Disorders or a History of SUD?

Response. It depends on the severity of the SUD and patient and family preference. If the youth with a SUD is actively engaged in SUD treatment and has good support systems, it is possible to safely and effectively treat ADHD with a stimulant since it is more likely to be effective than a nonstimulant medication. In fact, the child will be better able to participate in a recovery program if their ADHD is effectively treated. A patch or other long-acting stimulant formulation with lower risk of abuse, lisdexamfetamine or serdexmethylphenidate, may be preferred.[5,46–48] Providers and caregivers should work with the child to get their assent to the treatment plan and identify a strategy for consistent supervision of medication administration.

Supporting Evidence. Dopaminergic/reward system alterations, genetics, and psychosocial factors help explain the link between ADHD and SUD.[46,47,49] When left untreated, it is estimated that up to 50% of those with ADHD will develop a SUD at some point in their lifetime.[48] Long-term follow up of the landmark MTA study (mean age, 8.5 years; N = 547) demonstrated that a childhood diagnosis of ADHD was associated with 1) more regular use of marijuana and cigarettes by young adulthood, 2) earlier substance use, and 3) faster escalation of substance use.[50]

Co-occurring ADHD predicts more severe SUD including a longer course of illness, poorer response to SUD treatment, increased likelihood of relapse, and greater social, academic, and employment challenges highlighting the importance of effective co-management.[48,51] Stimulant treatment among those with ADHD is associated with a decreased future risk for SUD[46,48,51–57] with 1 study demonstrating a 13% annual reduced risk for SUD.[53] Overall, data would suggest that early treatment initiation (before age 9) and longer duration (6 or more years) of stimulant treatment is associated with the greatest reduction in SUD risk.[54,58]

A 2023 expert consensus statement on the treatment of ADHD among adolescents and adults with co-occurring SUD states that: 1) stimulants should be used first line, 2) stimulants are generally safe to use, and 3) historic concerns that stimulants may exacerbate pre-existing substance use/disorder are unfounded.[51] Thorough screening for cardiac and seizure history is warranted.[51]

While there are some reports of lower than expected efficacy of stimulant pharmacotherapy among adolescents and adults with ADHD and comorbid SUD, it is possible that this population may require larger doses to reach a therapeutic effect.[48,59–61] Overall, tolerance effects are not clear in this population.[51] While there are generally few health risks with concurrent use of prescribed stimulants and substances, the added risk for cardiac events and seizures need to be considered for those concomitantly misusing cocaine and other potent stimulants.[51]

Diversion and nonmedical use of the stimulant needs to be considered, particularly given high rates of misuse (e.g., performance enhancement) among college-age youth. Efforts to avoid misuse are crucial and can include offering secure storage, avoiding overprescribing, educating on risks of misuse, and providing targeted training for interdisciplinary pediatric teams.[62,63] Other effective multimodal treatment strategies include psychotherapy, motivational interviewing, and harm reduction strategies.[48,50]

Tic Disorder/Tourette Syndrome.

Clinical Question: Is the Use of a Stimulant Contraindicated in a Pediatric Patient With a Tic Disorder?

Response. No, stimulants are not contraindicated for children and adolescents with tic disorders. Stimulants can be an effective treatment of ADHD in youth with pre-existing tics or Tourette syndrome (TS) without exacerbating either condition.[64,65]

Methylphenidate is the preferred stimulant when treating ADHD in youth with tic disorders because at large doses, dextroamphetamine may initially worsen tics in some children. Dose increases of both dextroamphetamine and methylphenidate may be limited due to tic exacerbation according to a Cochrane review.[65] Although stimulants have not been shown to worsen tics in most people with tic disorders, they may, nonetheless, exacerbate tics in individual cases.[65]

Supporting Evidence. The development of tics, particularly motor tics (e.g., eye blinking, nose scrunching, lip licking) has long been described as a possible adverse effect of stimulant treatment and clinicians have been advised to avoid stimulant in youth with TS or chronic tic disorder.[66] This was based on case reports from the 1970s when tics were reported in children being treated with a stimulant for ADHD.[66,67] A meta-analyses of 22 studies involving 2385 children with ADHD showed no significant difference in the occurrence of tics comparing the stimulant or placebo groups (risk ratio = 0.99; 95% CI, 0.78–1.27, z = −0.05, p = 0.962).[67] New onset or worsening tic symptoms

were commonly reported in the psychostimulant (event rate = 5.7%; 95% CI, 3.7%–8.6%) and placebo groups (event rate = 6.5%; 95% CI, 4.4%–9.5%). This study did not include youth with existing tic disorders.

A Cochrane Review found that both methylphenidate and dextroamphetamine were efficacious in treating symptoms of ADHD in youth with a chronic tic disorder. Tic symptoms improved in children treated with methylphenidate, but dose increases were limited by fears of tics worsening in 1 study. In one 3-week study, high-dose dextroamphetamine appeared to worsen tics in some children. For most youth, both tics and ADHD symptoms improved with the use of a stimulant.[65]

TS, the most common cause of motor and vocal tics, has an estimated prevalence of 0.52% and is 4 times more likely to occur in boys compared with girls.[66] Fifty percent of youth with TS experience functionally impairing ADHD and effective treatment is essential to growth and development.[68] Current standard of care for treating ADHD in children with co-occurring tics or TS includes stimulants. Tics in TS typically wax and wane in severity, so it is unclear whether a patient's tics are going to naturally increase at a given time or whether the increase is a result of a stimulant adverse effect.[64] Further, experts recommend rechallenging stimulant in youth with functionally impairing ADHD and previous reports of stimulant-associated tics. It is possible the stimulant may not worsen tics in the rechallenge.[67]

Practice Pearls

Medical.

Growth.

Clinical Question: Do Stimulants Slow Growth?

Response. Long-term studies have suggested different effects on growth, with many demonstrating no clinically significant height changes by adulthood. While data are inconsistent, pediatric guidelines still recommend routine monitoring of height using growth charts throughout stimulant treatment. For stimulant-treated youth that demonstrate notable reductions in height, alternatives to stimulant treatment should be considered including alpha-2 agonists (i.e., clonidine, guanfacine) or norepinephrine reuptake inhibitors (i.e., atomoxetine, viloxazine).

Supporting Evidence. Stimulant impact on growth may be related to changes in nutrition, lack of appetite, dopaminergic effects on growth hormone/factor, and/or decreased thyroxine secretion. The MTA study (Initial 14-month randomized clinical trial 7–10 years of age; observational long-term follow-up through age 25 years) found an overall adult height deficit of 4.7 cm when comparing those with ADHD consistently taking stimulants (n = 515) to those without ADHD not taking a stimulant (n = 258). Among those with ADHD, those taking stimulants consistently were 2.36 cm ± 1.13 cm shorter than those taking stimulants inconsistently. Inconsistent stimulant use includes youth taking "drug holidays" or not taking stimulant medication on weekends or when not in school.[69]

A naturalistic, longitudinal, controlled study (part of The ADHD Drugs Use Chronic Effects [ADDUCE] European research program) demonstrated little effect on growth among youth (mean, 9 years of age; range, 6–17) with a 24-month height velocity standard deviation score difference of −0.07 (95% CI, −0.018 to 0.04; p = 0.20) when comparing those taking (N = 756) or not taking (N = 391) methylphenidate. Interestingly, weight velocity slowed initially at 6 months in the methylphenidate group (p < 0.0001) but no differences were seen after this point. For those that had decreased weight velocity at 6 months (n = 366 methylphenidate, n = 116 no methylphenidate, n = 109 control group), no major difference was observed on height velocity. There were no differences when comparing body mass index (BMI) at any time point. When interpreting this finding, it is important to acknowledge a high loss to follow-up at 24 months (46.5%), all participants were stimulant naive, and the majority were white males.[70]

Seizure Disorders.

Clinical Question: Are Stimulants Safe and Effective to Treat ADHD in Pediatric Patients With a Seizure Disorder?

Response. Stimulant treatment for ADHD is effective in youth with seizure disorders, but may or may not be safe depending on how well-controlled a child's seizures are on antiseizure medication.[71,72] Seizures should be well-controlled on an antiseizure medication before considering a stimulant trial for ADHD because all stimulants have the potential to lower the seizure threshold and increase seizure frequency.[71] Methylphenidate is the stimulant with the most evidence for therapeutic benefit and safety in managing ADHD in children with seizure disorders.[71–74]

Supporting Evidence. ADHD is underrecognized in youth with seizure disorders.[73] Approximately 30% to 40% of youth with epilepsy have functionally impairing ADHD. Although methylphenidate is the preferred stimulant when treating ADHD in children with epilepsy, it is not without risk. A chart review of 105 youth with ADHD and epilepsy (14.8 +/− 3.4 years; range, 7–24) was conducted to assess methylphenidate's effectiveness, safety, and influence on seizures.[73] The mean duration of MPH treatment was 22 months (range, 2 weeks to 89 months) and the mean dose of MPH was 0.84 mg/kg/day. MPH was effective in controlling ADHD symptoms in both the seizure aggravation and nonaggravation groups. However, 21 (20%) patients had aggravated seizures and 32 (32.3%) had worsened electroencephalograph (EEG) findings. Patients with uncontrolled seizure or anxiety disorders at baseline were more likely to show aggravated seizures. A Cochrane review of the only randomized controlled trial of youth with ADHD and epilepsy included a US study of OROS-MPH vs placebo in 33 children (mean age 10.5 +/− 3 years) with titration

over 3 to 7 weeks. The children receiving OROS-MPH had a larger proportion of participants receiving "much improved" or "very much improved" scores for ADHD symptoms on the Clinical Global Impressions for ADHD-Improvement tool (33 participants, 1 study; low-certainty evidence). OROS-MPH also had a larger proportion of people withdrawing from treatment (RR, 2.80; 95% CI, 1.14–6.89; 33 participants, 1 study; moderate-certainty evidence). In children with a dual-diagnosis of epilepsy and ADHD, there is some evidence that use of the stimulant drug OROS-MPH is not associated with significant worsening of epilepsy, but larger doses of it may be associated with increased daily risk of seizures; the evidence is of low-certainty.[74]

Antiseizure medications vary significantly in their potential to worsen symptoms of ADHD. Phenobarbital, phenytoin, valproate, topiramate, zonisamide, perampanel, and ethosuximide may induce negative behavioral effects in children with seizure disorders and ADHD while lacosamide, carbamazepine and lamotrigine may improve symptoms of ADHD. The evidence is mixed for levetiracetam.[72] Notably, valproate has level A evidence documenting worsening attention in youth with ADHD.[71,72] Medication selection goals should aim to strike a balance between selecting an effective antiseizure medication with low risk of worsening ADHD symptoms, when possible.

Cardiac.

Clinical Question: What Are the Cardiovascular Effects and Cardiac Risks of Stimulants?

Response. Stimulants should be avoided or used with great caution in pediatric patients with known structural cardiac abnormalities. Routine screening of all children and adolescents prior to initiating a stimulant is recommended by The American Heart Association (AHA), American Academy of Pediatrics, and American Academy of Child and Adolescent Psychiatry, including a medical evaluation, family history, and physical examination.[75] Specifically, all patients should be screened for exercise intolerance, a history of syncope/fainting, arrhythmia, structural heart defects, and congenital/acquired cardiac disease. Family history of arrhythmia, early sudden death (<40 years), family history of premature cardiovascular disease (<30 years), or myocardial infarction must all be considered prior to initiation of stimulant treatment.[75] A baseline electrocardiogram (ECG) and cardiology consultation should be considered in youth with any of the aforementioned personal or family risk factors.

Supporting Evidence. Stimulants are positively chronotropic, inotropic, and increase peripheral vascular resistance as they block the reuptake of dopamine and norepinephrine, stimulate presynaptic release of dopamine, and inhibit monoamine oxidase.[76] Therefore, they can increase heart rate (~4–5 bpm), cardiac contractility, and blood pressure (~5 mm Hg). Outside of small increases in heart rate, apparent ECG changes are uncommon in otherwise healthy individuals.[77] Stimulants are pro-arrhythmogenic in those with underlying cardiac abnormalities, given their direct and indirect sympathomimetic effects. According to the AHA consensus statement regarding drug-induced arrhythmia, stimulants can precipitate or worsen atrial fibrillation, supraventricular tachycardia, or monomorphic ventricular tachycardia given the increase in beta-adrenergic stimulation in at risk individuals.[78] The value of repeating an ECG to predict who might develop an arrhythmia or who is at risk for associated sudden cardiac death is limited; instead more thorough cardiac evaluation should be considered in those with identified risk factors, as previously described.[75,77,79]

A recent systematic review and meta-analysis including 19 observational studies (N = 3,931,532) found no significant association between ADHD medication use and the risk of cardiovascular events among children and adolescents, young adults, and older adults.[80] Follow-up time ranged from 0.25 to 9.5 years (median, 1.5 years) and the pooled adjusted relative risk did not show a statistically significant association between ADHD medication use and any cardiovascular event among children and adolescents compared with people without ADHD (RR, 1.18; 95% CI, 0.91–1.53). There was no significant increase in overall cardiovascular events with stimulants (RR, 1.24; 95% CI, 0.84–1.83) including cardiac arrest/tachyarrhythmias (RR, 1.87; 95% CI, 0.96–3.68), cerebrovascular disease (RR, 0.96; 95% CI, 0.63–1.48), and myocardial infarction (RR, 1.06; 95% CI, 0.66–1.77). Notably, heterogeneity among studies was high warranting caution interpreting pooled risk ratios.[80]

A 2024 prospective, nested, case-control study (6–64 years of age) evaluated the long-term risk of stimulants among individuals with a CVD diagnosis (cases; n = 10,388) and those without a CVD diagnosis (controls; n = 51,672) at baseline. The study found a significantly increased risk of cardiovascular disease with longer cumulative use of ADHD medication compared with nonuse (median follow-up 4.1 years). Risk increased rapidly during the first 3 years of medication treatment, with each additional year of medication use associated with an average 4% increased risk. Larger doses (i.e., >45 mg/day methylphenidate/lisdexamfetamine, >22.5 mg/day amphetamines, >120 mg/day atomoxetine) were associated with higher risk. Specifically, greater risk of hypertension and arterial disease stood out with no significant increased risk for arrhythmia, heart failure, ischemic heart disease, thromboembolic disease, and cerebrovascular disease.[81]

Practical Considerations.

When to Continue or Hold a Stimulant.

In many clinical scenarios, stimulants should be held during inpatient medical admissions. Medical complexity, lack of need for sustained attention/focus, and no risk for withdrawal generally lead to a therapeutic decision to hold the stimulant during the inpatient medical admission.

When making this decision, consider asking the patient and their caregiver 1) whether they take stimulant holidays on weekends, summer holidays, or other breaks from school, 2) what symptoms the stimulant is most helpful for (e.g., hyperactive/impulsive vs inattentive), and 3) changes in symptoms that are noticed when the stimulant is missed. Answers to these questions further inform the decision to hold stimulant. For example, a child undergoing surgery does not need to focus attention for schoolwork and the stimulant may counteract sedation needed for the surgical procedure.

A common misconception is that holding a stimulant during an inpatient admission will lead to stimulant discontinuation effects. Stimulants have no risk for

Table 5. Stimulant Dose Conversion[88,89]

Product Base	Treatment Plan	Recommendation	
Mixed amphetamine salts	Adderall IR (Teva Pharmaceuticals; Horsham, PA) ➔ Adderall XR (Takeda Pharmaceuticals; Lexington, MA)	• Same total daily dose of Adderall XR, taken once daily (i.e., 5 mg BID IR ➔ 10 mg daily)	
	Adderall XR ➔ Adzenys XR-ODT (Neos Therapeutics; Grand Prairie, TX)	Adderall XR 5 mg	Adzenys XR 3.1 mg
		Adderall XR 10 mg	Adzenys XR 6.3 mg
		Adderall XR 15 mg	Adzenys XR 9.4 mg
		Adderall XR 20 mg	Adzenys XR 12.5 mg
		Adderall XR 25 mg	Adzenys XR 15.7 mg
		Adderall XR 30 mg	Adzenys XR 18.8 mg
	All AMP products ➔ Adzenys XR-ODT	• Discontinue previous treatment and titrate Adzenys XR using titration schedule in package insert • Do not substitute other amphetamine products on a mg:mg basis	
	All AMP products ➔ Adzenys ER (Neos Therapeutics; Grand Prairie, TX)	• Do not substitute on a mg:mg basis due to differences in PK profiles	
	All AMP products ➔ Dyanavel XR (Tris Pharma, Inc; Monmouth Junction, NJ)	• Discontinue previous treatment and titrate Dyanavel XR using titration schedule in package insert • Do not substitute other AMP products on a mg:mg basis	
	All AMP products ➔ Evekeo (Arbor Pharmaceuticals, LLC; Atlanta, GA)	• No direct conversion, discontinue previous treatment and titrate Evekeo using titration schedule	
	All AMP products ➔ Mydayis (Shire LLC; Lexington, MA)	• Do not substitute on a mg:mg basis due to differences in PK profiles	
	All AMP products ➔ LDX*	10 mg AMP XR	~30 mg LDX
		20 mg AMP XR	~50 mg LDX
		30 mg AMP XR	~70 mg LDX
Dextroamphetamine	Dexedrine IR (Catalent Pharma Solutions; Winchester, KY) ➔ SR	• Same total daily dose Dexedrine SR, taken once daily	
	All D-AMP products ➔ LDX	• Discontinue previous stimulant product, and titrate as outlined in package insert	
	All D-AMP products ➔ Xelstrym (Noven Pharmaceuticals, Inc; Miami, FL)	• Do not substitute for other D-AMP products on a mg:mg bases because of different AMP base compositions and differing PK profiles • Start at 4.5 mg/9 hr and titrate to response; adjust dosing in renal impairment	

(*Table cont. on page 225*)

Table 5. Stimulant Dose Conversion[88,89] *(cont.)*

Product Base	Treatment Plan	Recommendation
Methylphenidates	MPH IR ➔ MPH LA	• Same total daily dose of MPH LA, taken once daily (i.e., 5 mg BID IR ➔ 10 mg daily)
	MPH SR ➔ MPH LA	• Direct conversion on a mg per mg basis (i.e., 20 mg IR ➔ 20 mg LA)
	MPH IR ➔ Concerta (Janssen Pharmaceuticals, Inc; Titusville, NJ)	MPH IR 5 mg BID or TID — Concerta 18 mg daily MPH IR 10 mg BID or TID — Concerta 36 mg daily MPH IR 15 mg BID or TID — Concerta 54 mg daily MPH IR 20 mg BID or TID — Concerta 72 mg daily
	All MPH products ➔ Daytrana patch (Noven Pharmaceuticals, Inc; Miami, FL)	• Follow normal titration schedule; cannot convert on a mg:mg basis ◦ Week 1: 10 mg; Week 2: 15 mg; Week 3: 20 mg; Week 4: 30 mg
	All MPH products ➔ QuilliChew XR (Tris Pharma, Inc; Monmouth Junction, NJ)	• Discontinue previous treatment and titrate QuilliChew XR using titration schedule in package insert • Do not substitute other MPH products on a mg:mg basis
	All MPH products ➔ Quillivant XR (Tris Pharma, Inc; Monmouth Junction, NJ)	• No direct conversion available, given differences in PK profiles • Follow normal titration schedule; cannot convert on a mg:mg basis
	Metadate CD (Lannett Company, Inc; Philadelphia, PA) ➔ Metadate ER (Lannett Company, Inc; Philadelphia, PA)	• No direct conversion available, given differences in PK profiles • CD: faster onset of action, reaches peak more quickly, IR(30)/XR(70) beads • ER: wax matrix, with less reliable absorption
	All MPH products ➔ Cotempla XR ODT (Neos Therapeutics Brands, LLC; Grand Prairie, TX)	• No direct conversion available, given differences in PK profiles • Follow normal titration schedule; cannot convert on a mg:mg basis
	All MPH products ➔ Jornay PM (Ironshore Pharmaceuticals Inc; Cherry Hill, NJ)	• Do not substitute Jornay PM for other MPH products on a mg:mg basis • Other MPH products have different PK profiles from Jornay PM and may have different MPH base composition
Dexmethylphenidate	MPH IR ➔ D-MPH IR	• Half the current total daily dose of MPH IR (i.e., 5 mg BID ➔ 2.5 mg BID)
	MPH IR ➔ D-MPH XR	• Half of the current total daily dose of MPH (i.e., 5 mg BID ➔ 5 mg daily)
	D-MPH IR ➔ D-MPH XR	• Same total daily dose of D-MPH XR given once daily (i.e., 5 mg BID IR ➔ 10 mg daily)
	All MPH products ➔ Azstarys (Corium, Inc; Grand Rapids, MI)	• To avoid substitution errors and overdosage, do not substitute for other MPH products on a mg:mg basis

AMP, amphetamine; D-AMP, dextroamphetamine; D-MPH, dexmethylphenidate; ER, extended-release; IR, immediate-release; LA, long acting; LDX, lisdexamfetamine; MPH, methylphenidate; ODT, orally disintegrating tablet; PK, pharmacokinetics; SR, sustained release

* Estimated equivalents from phase II, double-blind, placebo-controlled cross-over study.[91]
All other information obtained from package inserts.[90]

discontinuation effects, given their pharmacokinetic properties (e.g., naturally taper off in a 24-hour period).[82] Based on clinical experience, it is reasonable to hold stimulants during an inpatient medical admission unless there is a clear clinical need for the stimulant during the admission.

For psychiatric hospital admissions, the treatment team may opt to hold the stimulant to allow for ADHD diagnostic reassessment or it may be beneficial to observe the child with stimulant on board to assess the effectiveness of a given formulation and dose.

Conversions and Therapeutic Substitutions. As described in the previous section, stimulants may be held in many clinical scenarios though conversion and therapeutic substitution of stimulants may be

Table 6. Stimulant Product Information[87,90]

Stimulant Base	Brand Name	Formulation	Duration of Action (hr)	Comments
Mixed amphetamine salts	Adderall	Tablet	Short (4–6)	• 3:1 *d* to *l* AMP. Can be crushed.
	*Evekeo	Tablet	Short (4–6)	• 1:1 *d* to *l* AMP. Sulfate base. No information available re: crushing.
	*Evekeo ODT	ODT-Tablet	Short (4–6)	• 1:1 *d* to *l* AMP. Sulfate base. Allow to dissolve on the tongue without chewing or crushing.
	*Dyanavel XR	Oral Suspension	Long (8–10)	• 3:1 *d* to *l* AMP. Sulfate base. • Contains 2.5 mg/mL of MAS. • Ensure adapter is secure and is never removed. • Shake suspension before each dose. • Bubble gum flavor.
	*Dyanavel XR	Tablet	Long (8–10)	• 3:1 *d* to *l* AMP. Sulfate base. • May be chewed or swallowed whole. • 5 mg tab is scored and can be cut into equal 2.5-mg halves.
	Adderall XR	Capsule	Long (8–12)	• 50% IR; 50% ER beads. • Can be opened and sprinkled onto applesauce. Consume entire contents immediately. Do not chew or crush beads.
	*Adzenys XR-ODT	ODT-Tablet	Long (10–12)	• 3:1 *d* to *l* AMP; 50% IR, 50% ER. • Orange/citrus flavor.
	*Mydayis	Capsule	Very Long (12–16)	• 3:1 *d* to *l* AMP. • IR beads and 2 types of ER beads; one ER bead releases at pH 5.5, other ER bead releases at pH of 7.0. • Not approved for youth <13 yr. • May be opened and contents sprinkled. Do not chew beads.
Dextroamphetamine	Dexedrine	Tablet	Short (4–6)	• IR only. Can be crushed.
	Dexedrine Spansule	Capsule	Intermediate (6–8)	• 50% IR; 50% ER. Cannot be crushed; may be opened and sprinkled on applesauce.
	*Xelstrym	Patch	Long (9–12)	• 12-hr effect when worn for 9 hr. • Applied to clean, dry area on hip, upper arm, chest, upper back, or flank. Remove after 9 hr. • Skin irritation or discoloration possible.
	Vyvanse (Takeda Pharmaceuticals; Lexington, MA)	Capsule	Long (10–13)	• Prodrug- cleaved to *d* – AMP in gut. • Delayed onset (~1–1.5 hr) • May be opened and mixed with yogurt, water, or OJ. If opened and mixed with beverage, a thin film containing inactive ingredients may remain in the container following consumption.
	*Vyvanse Chewable (Takeda Pharmaceuticals; Lexington, MA)	Chewable Tablet	Long (10–13)	• Prodrug cleaved to *d* – AMP in gut. • Delayed onset (~1–1.5 hr). • Chew thoroughly before swallowing. • Strawberry flavor.

(*Table cont. on page 227*)

Table 6. Stimulant Product Information[87,90] *(cont.)*

Stimulant Base	Brand Name	Formulation	Duration of Action (hr)	Comments
Methylphenidate	Ritalin	Tablet	Short (3–5)	• IR tablet; Can be crushed.
	Methylin (SpecGx LLC; Webster Groves, MO)	Chewable Tablet	Short (3–5)	• IR only. Chew thoroughly before swallowing. • Contains aspartame. • Grape flavor.
	Methylin (SpecGx LLC; Webster Groves, MO)	Oral Solution	Short (3–5)	• Contains aspartame. • Grape flavor.
	Ritalin SR	Tablet	Intermediate (3–8)	• Do not crush.
	Metadate ER	Tablet	Intermediate (3–8)	• Do not crush.
	Methylin ER	Tablet	Intermediate (3–8)	• Do not crush.
	Ritalin LA	Capsule	Long (8–10)	• 50% IR; 50% ER beads; SODAS technology. • May be opened and contents sprinkled. Do not chew beads.
	Metadate CD	Capsule	Long (8–10)	• 30% IR; 70% ER beads. • May be opened and contents sprinkled. Do not chew beads.
	*Cotempla XR	ODT-Tablet	Long (8–10)	• 25% IR; 75% ER. • 8.6 mg equivalent to 10 mg ER MPH. • Do not push tablet through foil; peel foil back gently. • Allow to dissolve on tongue; do not crush or chew. • Onset may be delayed up to 1 hr. • Grape flavor.
	*Quillichew	Chewable Tablet	Long (8–10)	• 30% IR; 70% ER. • Contains phenylalanine (caution in PKU). • Onset may be delayed up to 1 hr. • Cherry flavor.
	*Quillivant XR	Oral Suspension	Long (10–12)	• 20% IR; 80% ER—shake before each dose. • Onset may be delayed up to 1 hr. • Banana flavor.
	*Aptensio XR	Capsule	Long (10–12)	• 40% IR; 60% ER beads. • May be opened and contents sprinkled. Do not chew beads. • Onset may be delayed up to 1 hr.
	*Jornay PM	Capsule	Long (10–12)	• First DR/ER MPH formulation; Utilizes the Delexis delivery system. • Administer at 8pm (adjust between 6:30–9:30pm based on response). • May be opened and sprinkled on food (e.g., applesauce).
	Concerta	Tablet	Long (8–12)	• Cannot be crushed. • Ghost tablet in stool. • Generics manufactured by Actavis are bioequivalent to brand name Concerta (OROS; AB rating). Generics: Mallinckrodt, Kremers are not equivalent to the brand name and do not have the same OROS delivery mechanism. (BX equivalence rating).
	Relexxii (Vertical Pharmaceuticals, LLC; Alpharetta, GA)	Tablet	Long (8–12)	• Cannot be crushed. • Ghost tablet in stool. • OROS delivery mechanism.
	*Daytrana	Patch	Long (10–12)	• Apply 2 hr before effects are desired. • Delayed onset may necessitate MPH IR dose in AM. • Remove after 9 hr of use. • Absorption continues for 2–3 hr after patch is removed. • Skin irritation or discoloration (leukoderma) possible.

(*Table cont. on page 228*)

Table 6. Stimulant Product Information[87,90] *(cont.)*

Stimulant Base	Brand Name	Formulation	Duration of Action (hr)	Comments
Dexmethylphenidate	Focalin (Novartis; East Hanover, NJ)	Tablet	Short (3–5)	• Can be crushed.
	Focalin XR (Novartis; East Hanover, NJ)	Capsule	Long (8–12)	• 50% IR beads and 50% enteric coated delayed release beads • May be opened and contents sprinkled. Do not chew, crush or divide capsules.
	*Azstarys	Capsule	Longer (12–16)	• 30% IR dexmethylphenidate; 70% serdexmethylphenidate prodrug; uses Ligand Activated Technology. • Capsules may be opened and sprinkled onto 2 tablespoons of applesauce or into 2 ounces of water; should be consumed within 10 min.

AMP, amphetamine; DR, delayed release; ER, extended-release; IR, immediate-release; MAS, mixed amphetamine salt; MPH, methylphenidate; ODT, orally disintegrating tablet; OROS, osmotic release oral system; PKU, phenylketonuria; SODAS, spheroidal oral drug absorption system

* Brand name only.

necessary, given formulary limitations. Among children and adolescents who would benefit from ongoing stimulant treatment during their inpatient admission, Table 5 may be used to guide therapeutic substitutions.

Onset of action, duration, intermediate or long-acting component, and stimulant formulation are among the most important clinical considerations for substituting stimulant products (Table 6). Pharmacist collaboration with this decision is recommended to ensure an optimal transition.

Alternative Administration. For those pediatric patients who may benefit from stimulant treatment, but cannot swallow whole tablets or capsules, administration can be challenging. Table 6 provides information regarding the ability to crush tablets, open and sprinkle capsules, and other alternative routes of administration. While immediate-release preparations can be crushed and enterally administered, there is little evidence that describes administration of extended-release products via these routes.

Extended-release stimulant capsules (e.g., Ritalin LA, Adderall XR) are filled with beads that comprise the pharmacokinetic integrity of the long-acting formulation. Variable ratios of immediate-, extended-, and/or delayed-release beads undergo pH-dependent absorption to ensure time-released stimulant exposure. In clinical trials, opening capsules and sprinkling the beads on food (e.g., applesauce; pH of 3–3.5) has been consistently evaluated. The Institute for Safe Medication Practices (ISMP) reports that contents of long-acting capsules that contain a mix of IR/XR beads may be administered via feeding tube "as long as they are not crushed, and an adequate amount of fluid is used to wash the full dose down the tube."[83] Lisdexamfetamine capsules contain a powder which can be mixed with yogurt, water, or orange juice.[84] While not specifically evaluated, the powder can likely be administered via an enteral route with an adequate fluid flush to ensure tube clearance based on clinical experience.

Conclusions

The benefits of effectively treating ADHD outweigh the risks. Stimulant practice pearls and comparison tables can help interprofessional teams individualize treatment of ADHD for children and adolescents. Further, these can be used as a resource to thoughtfully convert between stimulants and further educate providers, patients, and caregivers on the benefits and potential risks of stimulant treatment for children and adolescents with ADHD.

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