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Individualization of attention-deficit/hyperactivity disorder treatment: pharmacotherapy considerations by age and co-occurring conditions

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that manifests in childhood and can persist into adolescence and adulthood. Impairments associated with ADHD can impact quality of life, social interactions, and increase the risk of morbidity and mortality; however, for many patients, effective treatment can lessen these effects. Pharmacotherapy with stimulants or nonstimulants is recommended in conjunction with psychosocial therapy for most patients. Determining the optimal pharmacotherapy can be complex, and the clinician needs to consider many factors such as the patient's age, comorbidities, and lifestyle. Furthermore, the needs of the patient with ADHD will change over time, with specific challenges to consider at each stage of life. A variety of Food and Drug Administration (FDA)-approved stimulant and nonstimulant formulations are available with different modes of delivery and durations of effect. This armamentarium of ADHD medications can be used to individualize ADHD treatment for each patient's needs. This article combines current information from the literature and the first-hand experience of the authors to provide guidance on ADHD treatment options for patients of different ages and for some of the more common comorbidities.

Introduction

Clinicians often struggle with managing a multitude of issues that arise in patients with attention-deficit/hyperactivity disorder (ADHD) including increased anxiety, stress, depression, and sleep problems; difficulty swallowing and unwillingness to eat; as well as issues with medicating (eg, self-medicating, not medicating, or over-medicating). ADHD often presents not in a vacuum, but instead as part of a complex spectrum of emotional, physical, and sociologic conditions. As physicians, we see these complicated cases daily. For example, we may attend to a child with autism and ADHD whose cognitive abilities are improved with medication but has difficulty swallowing a pill; a teenager with ADHD and depression who feels that his medicine helps but causes unwanted mood-related side effects; a mother who presents to her primary care physician feeling overwhelmed and anxious but forgets to mention that her son was recently diagnosed with ADHD and that she has always struggled with similar symptoms; and a dad who drinks and smokes to try to self-medicate his symptoms.

Further complicating the issue of treatment are the natural change of ADHD symptoms over time, the different manifestations of symptoms based on the environmental context, and evolving comorbidities. Children with ADHD typically present with a constellation of inattentive and hyperactive/impulsive symptoms within the context of external structures such as preschool, school, parental involvement, or other caretaking figures.[1,2] Adolescents transition into a period of increasing cognitive demands with longer duration of daily activities, increased self-autonomy, and decreased external structure, which requires an ability to modulate and self-regulate behaviors and activities.[3] During early adulthood, there are increased demands for self-modulation of symptoms combined with a more independent lifestyle and the need to form positive interpersonal relationships.[3] Coexisting oppositional defiant disorder and conduct disorder are highly prevalent in children with ADHD,[4–6] while coexisting conditions are more diverse in adults.[7,8]

For patients with ADHD, inattentive and/or hyperactive/impulsive behaviors impair activities of daily living including social interactions, relationships, and school, as well as occupational and financial performances.[6] The presence of comorbid conditions exacerbates underlying functional impairments due to ADHD and tends to worsen long-term functional impairments.[9,10] Treatment plans for ADHD need to be individualized to the patient at different stages of life to alleviate the impairment caused by the changing ADHD presentation, life situations, and comorbidities that may introduce additional challenges. A combination of interventions—or

multimodal approach—is recommended for most patients to improve the core symptoms of ADHD and overall quality of life, and includes psychosocial and pharmacological options.[7,11,12]

Given the unique situation for each patient and the shifting ADHD presentation over time, clinicians need to be knowledgeable about all available treatment options. In the United States, there are more than 30 approved medications that are mainly comprised of stimulant formulations providing different delivery mechanisms and durations of effect (Tables 1–3). Many clinicians learn of the basic ADHD medication formulations during training, but they rarely touch on the wider array of delivery systems until after training is complete. This review incorporates peer-reviewed studies and the expert experience of the authors to discuss treatment considerations and pharmacological options for patients with ADHD at each stage of life and for those with common co-occurring conditions.

Treatment Reduces the Risk of Morbidity and Mortality and Increases the Quality of Life of Individuals with ADHD

ADHD is a common neurodevelopmental disorder that begins in childhood and will persist into adulthood for many patients.[6,41] It is associated with significant morbidity,[42,43] lower quality of life,[44,45] and increased mortality[46] in all age groups compared with the non-ADHD population. In a large study of the Danish national population, the mortality rate increased by 86% in preschoolers, 58% in children, and 325% in adults over those without ADHD.[46] Furthermore, the risk of death increases in adults with ADHD and a co-occurring psychiatric disorder vs those without another psychiatric disorder (hazard ratio of ~5).[47] On the whole, people with ADHD will experience poorer long-term functional outcomes compared with those who do not have ADHD.[48] ADHD in childhood contributes to worse academic performance, lower rates of high school graduation, and lack of higher degrees.[49–51] Occupational outcomes are also negatively affected by ADHD, with higher rates of unemployment, frequent job switching, and overall financial problems.[49–51] ADHD also affects a person's social life, causing higher rates of divorce and separation, as well as issues with interpersonal relationships.[49–51] Impulsive risk-seeking behaviors exhibited by individuals with ADHD contribute to a greater likelihood of teenage pregnancy,[50] criminal behavior,[52–54] and substance abuse.[55,56]

Treatment can lower these risks, sometimes to levels similar to control populations. Pharmacotherapy has been shown to improve executive function, reduce risk-seeking behavior, and decrease rates of criminality in individuals with ADHD.[53,54,57–59] ADHD treatment has also been shown to decrease trauma rates with dramatic reduction in motor vehicle trauma,[42,60] and it can decrease the risk of substance use-related disorders.[59,61] A 2012 meta-analysis of long-term outcomes of ADHD treatment found 50% to 100% improvement in driving, obesity, self-esteem, social functioning, academics, drug use/addiction, antisocial behaviors, and use of services for treated vs untreated patients.[48] Moreover, treatment with stimulants in childhood provides protective effects against risks for disruptive mood, anxiety, and addictive disorders, academic failure, and car accidents.[62] Biederman et al found that one in every three patients with ADHD treated with stimulants were prevented from repeating a grade or developing certain comorbid disorders, and one in four were protected against developing major depressive disorder or having a car accident.[62] It is critical to treat ADHD early and effectively to minimize harm and increase a patient's quality of life.[42,44,63]

It is also important to note that pharmacotherapy is just one component of an ADHD treatment plan. For instance, in preschool-aged children with ADHD, the recommended first line of treatment is behavioral therapy and methylphenidate should be prescribed only if the behavioral interventions do not provide sufficient improvement and moderate-to-severe disturbances continue to affect the child's function.[64] Similarly, clinicians should help create long-term comprehensive plans for patients with ADHD that focus on identifying and addressing individualized and specific behavioral, academic, and/or social target goals.[64] In the comprehensive Mental Health Multimodal Treatment Study of Children with ADHD, the combination of behavioral therapy and medication was superior to medication alone for treatment of oppositional/aggressive symptoms in individuals with ADHD.[65] Treatment success may be greatly improved by clinicians encouraging patients to build environmental support systems, and to incorporate behavioral therapy as well as pharmacotherapy into their treatment plan.

Pharmacotherapy for ADHD

Medications approved to treat ADHD include stimulants (amphetamine and methylphenidate; Tables 1 and 2) and nonstimulants (atomoxetine, guanfacine, and clonidine; Table 3). Stimulants are the first-line pharmacological treatment for both children and adults because they show greater efficacy, while currently available nonstimulants are often used when a patient is unresponsive to or cannot tolerate stimulants.[7,11,12,85,86] Importantly, interpatient response to each medication class is variable, and the response to one class does not predict response to another.[87] If a patient has a suboptimal response to one class of ADHD stimulant, then a trial with another medication class should be initiated to optimize patient outcomes. In our practice, we also find that a patient may respond poorly to one stimulant delivery system, while another delivery mechanism of the same medication class may illicit a better response in regard to symptom reduction, smoothness or duration of effect, or tolerability.

Various medication delivery technologies have been developed to address individual patient needs (Tables 1 and 2). These technologies can provide a nonoral route of administration—as with the methylphenidate transdermal patch (Daytrana)[79]—or extend the release of the drug over the course of the day, allowing for once-daily dosing.[88] Extended-release technologies include capsules containing immediate-release beads and beads with a pH-dependent coating for drug release upon entry into different sections of the intestinal tract (eg, Adderall XR,[19] Adhansia XR,[82] Aptensio XR,[89] and MyDayis[24]); a methylphenidate osmotic release capsule (Concerta)[78]; an amphetamine prodrug, lisdexamfetamine dimesylate (eg, Vyvanse),[26] where a biological enzymatic reaction is required to release active amphetamine[26,90]; and ion-exchange microparticles containing immediate-release and extended-release medication (eg, Adzenys XR-ODT,[22] Cotempla XR-ODT,[91] and Dyanavel XR[23]).

Duration and onset of effect for the various medications should be considered for individualization. Short-acting formulations last for 3 to 6 hours and require multiple dosing per day. Conversely, a single dose of a long-acting formulation provides relief of ADHD symptoms from 8 to 16 hours, depending on the delivery system. Long-acting ADHD medications are associated with better adherence than short-acting medications[92] and may reduce medication-related social stigma.[11] Onset of effect should also be considered. For the patient with early morning issues, a short acting stimulant can be prescribed for immediate relief followed by a long-acting

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Table 1. FDA-Approved Amphetamine Formulations for ADHD.

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Amphetamine								
Short 	Amphetamine mixed salts	Adderall	Children ≥3	1–3	1.5 h	4-6 h	Elimination half-life 9.77-11 h for the D-isomer and 11.5-13.8 h for the L-isomer	13–15
Intermediate  	Racemic amphetamine sulfate	Evekeo	Children ≥3 (tablet) Children 6-17 (ODT)	1–2	45 min	9.25 h	Elimination half-life 10.0-11.7 h	16–18
Long 	Amphetamine mixed salts	Adderall XR	Children ≥6, adults	1	1.5 h	10.5–12 h	May be sprinkled on applesauce	19, 20
Long 	Amphetamine	Adzenys ER	Children ≥6, adults	1	1.5 h[a]	10–12 h[a]	Do not add to food or other liquids	21
Long 	Amphetamine	Adzenys XR-ODT	Children ≥6, adults	1	1.5 h[a]	10–12 h[a]	Allow tablet to disintegrate in saliva before swallowing	22
Long 	Amphetamine	Dyanavel XR	Children ≥6	1	1 h	12 h		23
Long 	Amphetamine mixed salts	Mydayis	Children ≥13, adults	1	2 h	14 h	May be sprinkled in applesauce	24, 25
Long, prodrug  	Lisdexamfetamine dimesylate	Vyvanse	Children ≥6, adults	1	1.5–2 h	12–14 h	Capsule: may be sprinkled in water, orange juice, or yogurt Chewable tablet: chew thoroughly before swallowing	26, 27

Table 1. *Continued.*

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Dextroamphetamine								
Short 	Dextroamphetamine sulfate	Dexedrine	Children 3-16	1–2	NA	4–6 h		14, 28
Short 	Dextroamphetamine sulfate	Zenzedi	Children 3-16	1–3	NA	4–6 h		29
Short 	Dextroamphetamine sulfate	ProCentra	Children 3-16	1–3	NA	4–6 h		30
Intermediate 	Dextroamphetamine sulfate	Dexedrine Spansule	Children 6-16	1–2	NA	6–10 h	Plasma half-life of approximately 12 h	14, 28
Methamphetamine								
Short 	Methamphetamine HCL	Desoxyn	Children ≥6	1–2	NA	NA	Not readily available	31

Note:  , tablet;  , capsule;  , liquid;  , chewable tablet;  , orally disintegrating tablet.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available; ODT, orally disintegrating tablet.
[a]Adzenys XR-ODT and Adzenys ER are bioequivalent to extended-release mixed amphetamine salts (ie, Adderall XR),[32, 33] but have not been tested independently in a classroom study.

Table 2. FDA-Approved Methylphenidate Formulations for ADHD.

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Methylphenidate[a]								
Short 	Methylphenidate HCL	Ritalin	Children ≥6, adults	2–3	1–2 h	4 h		66, 67
Short  	Methylphenidate HCL	Methylin	Children ≥6, adults	2-3	1 h[b]	4 h[b]	Chewable tablet: take with 8 oz of water 30-45 min before meals Oral solution: take 30-45 min before meals Last dose before 6 PM	68, 69
Intermediate 	Methylphenidate HCL	Methylin ER	Children ≥6, adults	1	NA	NA		70
Intermediate 	Methylphenidate HCL	Ritalin-SR	Children ≥6, adults	1	1.5 h	8 h	Take after meals for maximum duration of effect	66, 71
Intermediate 	Methylphenidate HCL	Metadate ER	Children ≥6, adults	1	NA	8 h		72
Intermediate 	Methylphenidate HCL	Metadate CD	Children 6-15	1	1.5 h	8-9 h	May be sprinkled on applesauce	73, 74
Long 	Methylphenidate HCL	QuilliChew ER	Children ≥6, adults	1	45 min	8 h		75, 76
Long 	Methylphenidate HCL	Ritalin LA	Children 6-12	1	30 min–1 h	12 h	May be sprinkled on applesauce	71, 74, 77
Long 	Methylphenidate HCL	Concerta	Children ≥6, adults	1	1–2 h	10–12 h		74, 78

Table 2. *Continued.*

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Long	Methylphenidate HCL	Quillivant XR	Children ≥6, adults	1	45 min	12 h	Shake bottle vigorously for 10 s before dispensing	76, 204
Long	Methylphenidate HCL	Aptensio XR	Children ≥6, adults	1	1 h	12 h	May be sprinkled on applesauce	76, 89
Long	Methylphenidate	Cotempla XR-ODT	Children ≥6	1	1 h	12 h	No crushing or chewing Allow to disintegrate in saliva before swallowing	76, 91
Long	Methylphenidate	Daytrana	Children ≥6	1	2 h	12 h	Wear for ≤9 h	74, 79
Long	Methylphenidate HCL	Jornay PM	Children ≥6, adults	1	8-10 h	12+ h	Take in the evening between 6:30 and 9:30 PM to provide early morning symptom control May be sprinkled on applesauce	80, 81
Long	Methylphenidate HCL	Adhansia XR	Children ≥6, adults	1	1 h	13-16 h	May be sprinkled on applesauce or yogurt and consumed within 10 min	82
Dexmethylphenidate								
Short	Dexmethylphenidate HCL	Focalin	Children ≥6	2	NA	6 h	At least 4 h between doses	71, 83
Long	Dexmethylphenidate HCL	Focalin XR	Children ≥6, adults	1	30 min	12 h	May be sprinkled on applesauce	74, 84

Note: , tablet; , capsule; , liquid; , chewable tablet; , orally disintegrating tablet; , transdermal patch.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available; ODT, orally disintegrating tablet.

[a]AAP recommends utilizing methylphenidate as a first choice for preschool aged children.[12]

[b]Methylin is bioequivalent to Ritalin,[69] but it has not been tested independently in a classroom study.

Table 3. FDA-Approved Nonstimulant Medications for ADHD

Formulation and Delivery Mechanism	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect[a]	Duration of Effect	Comments	References
Norepinephrine transporter reuptake inhibitor								
Long 	Atomoxetine	Strattera	Children ≥6, adults	1-2	3-4 wk	NA[b]	Dosed by body weight	34, 35
$Alpha_2$-adrenergic receptor agonist								
Long 	Clonidine HCL	Kapvay	Children ≥6	2	2 wk	NA	An antihypertensive agent May be prescribed in addition to a stimulant Discontinuation must be gradual	36, 37
$Alpha_{2A}$-adrenergic receptor agonist								
Long 	Guanfacine	Intuniv	Children ≥6	1	3 wk	Up to 24 h per dose	An antihypertensive agent Dosed by body weight May be prescribed in addition to a stimulant	38, 39

Note:  , tablet;  , capsule.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available.
[a]Time to onset of the full effect of nonstimulant medications is extended compared to stimulant medications due to long titration periods.[34, 36, 38]
[b]The duration of effect of atomoxetine has not been formally measured as in studies of stimulant medications. Evidence from clinical studies suggests that once-daily dosing of atomoxetine is associated with efficacy into the evening.[40]

formulation. Alternatively, the recently approved Jornay PM is taken at bedtime with the onset of effect delayed for 8 to 10 hours to allow the drug to be delivered in the early morning.[80] Nonstimulants can be taken once or twice daily, but often require several weeks to show a maximum treatment effect.[34,36,38]

Difficulty swallowing is another consideration when choosing an ADHD medication. While this is generally considered a problem for young children,[93] it can also occur for adolescents and adults.[94,95] Many tablets and capsules cannot be crushed or chewed, although the bioavailability of some capsules has been systematically studied when sprinkled into specific kinds of food and drink (Tables 1 and 2). Clinicians should determine whether this is an issue for individual patients so they can advise on pill swallowing techniques and aids[96,97] or prescribe a liquid, chewable, orally disintegrating tablet, or transdermal formulation (Tables 1 and 2). Nonstimulants are currently not available in alternative delivery forms and they must be swallowed whole (Table 3).

ADHD medications are associated with a range of adverse effects, although most are mild and temporary.[7] Patients on stimulants may frequently present with decreased appetite, sleeping issues, abdominal pain, or nausea/vomiting while on stimulant therapy.[98,99] For adults, increased heart rate and blood pressure may be more common with stimulant treatment.[100] Common atomoxetine-associated adverse effects include gastrointestinal symptoms, anorexia, fatigue, and weight loss.[101] Clonidine and guanfacine are both associated with sedation, somnolence, and fatigue and may decrease blood pressure in rare cases.[102,103] While serious cardiac complications are uncommon occurrences with both stimulants and nonstimulants,[104,105] these medications should be prescribed with caution in patients with known cardiac defects. Stimulant pharmacotherapy also slows the growth of children with ADHD (height and weight)[106,107]; however, ADHD treatment was not associated with differences in final adult height in a longitudinal study.[108]

Patient engagement with ADHD pharmacotherapy is another important issue. Patient engagement and adherence to stimulant medication is often low, likely due to many factors including the complexity of renewing a schedule II medication, poor tolerability to stimulants, as well as misinformation, biases, or uncertainty about the use of stimulants to treat ADHD.[109] In a recent study, stimulant prescription renewal was significantly increased when a novel text messaging intervention platform was implemented vs treatment as usual.[109] As the world becomes more digitized, innovative technological solutions for traditional compliance or engagement challenges should be used to support individuals with ADHD to easily access and fill prescriptions for their medications.

Prescribing ADHD Medication by Age

The challenges, considerations, and recommended treatments for each age group are described below and summarized in Figure 1.

Preschool

In 2016, 2.1% of U.S. children aged 2 to 5 years were diagnosed with ADHD[110] and the U.S. Food and Drug Administration (FDA) is now requiring new ADHD medications to conduct preschool studies.[111] Dramatic hyperactivity/impulsivity is the overt presentation in this group.[1] However, these behaviors can be caused by other factors, which is why a comprehensive examination for ADHD is needed before beginning treatment.[12] The American Academy of Pediatrics (AAP) suggests that ADHD can be accurately diagnosed in children beginning at 4 years of age,[12] although children as young as 2 years have been diagnosed.[110] Preschoolers with subthreshold ADHD should also be monitored closely since

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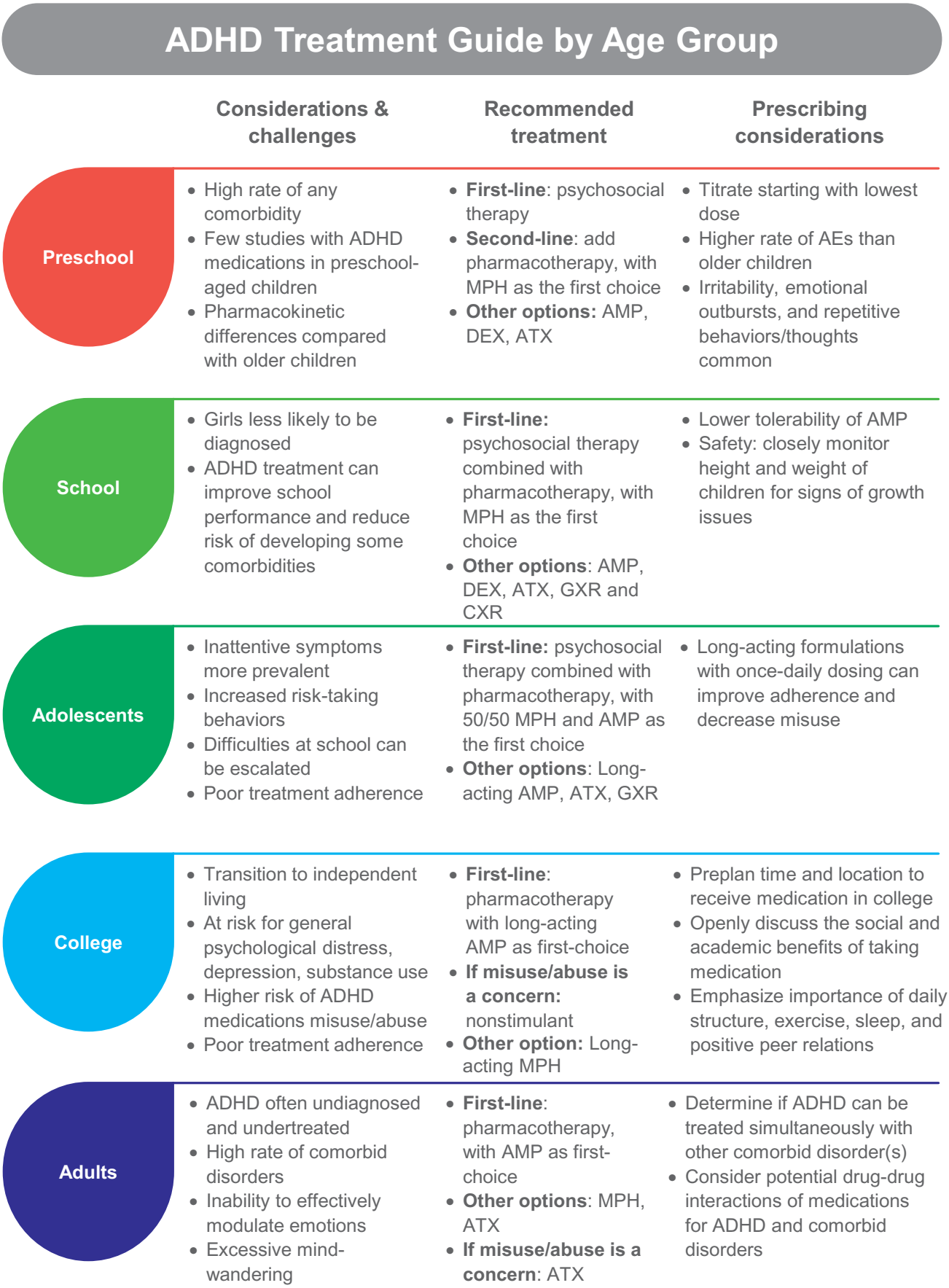

Figure 1. ADHD treatment guide by age group. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AE, adverse event; AMP, amphetamine; ATX, atomoxetine; DEX, dextroamphetamine; GXR, guanfacine extended release; MPH, methylphenidate.

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up to one-third are likely to progress to a full diagnosis of ADHD or other mental health problems.[112]

The recommended first-line treatment for children under the age of 6 is psychosocial intervention, which can include parent training, behavioral therapy, or cognitive training.[7,11,12] Psychosocial treatments improve ADHD symptoms for this group, with an effect size of 0.75 in favor of intervention.[113] Adding pharmacotherapy to the treatment plan is recommended when very young patients with moderate-to-severe ADHD do not improve with psychosocial therapies alone.[7,11,12] Accordingly, in 2016, preschool-aged U.S. children with ADHD were most commonly receiving behavioral treatment (45.8%) or no treatment (36.0%) more often than treatment with medication alone (4.5%) or medication combined with behavioral therapy (13.7%).[110]

There are five FDA-approved medications for ADHD in children 3 to 5 years of age and all are short-acting amphetamine formulations (Table 1). They include a liquid and tablet form of dextroamphetamine, a tablet for mixed amphetamine salts, and a tablet and chewable form of racemic amphetamine sulfate. While methylphenidate has not been approved for use in this age group, the AAP suggests prescribing a methylphenidate as the first-choice pharmacotherapy because there are more robust clinical studies of methylphenidate than amphetamine in preschool children.[12] Short-acting methylphenidate administered three times a day improved ADHD symptoms and impairment in preschoolers in Preschool ADHD Treatment Study (PATS).[114] A recent study demonstrated the safety and efficacy of an extended-release methylphenidate formulation (Aptensio XR) for preschoolers with ADHD.[115] In case reports, the methylphenidate transdermal system provided improvement in ADHD symptoms for preschoolers.[116] Atomoxetine reduced ADHD symptoms by at least 30% for 75% of preschoolers in a small open-label study (mean daily dose of 1.59 mg/kg).[117]

Special prescribing considerations for preschool-aged children include pharmacokinetic (PK) differences, number of comorbidities, and a higher rate of adverse effects when compared with school-aged children. Differences in drug metabolism, elimination, and gastrointestinal function between preschoolers and older children or adults may affect drug PK,[118] and few PK studies of ADHD medications in preschool-aged children are available. In PATS, preschool children metabolized short-acting methylphenidate at a slower rate, which increased overall drug exposure as compared with older children.[119] Clinicians experienced with prescribing stimulant therapy to preschool-aged children recommend that while long-acting medications help with both preschool and home activities, there are occasions when a short-acting medication may be appropriate. For example, to cover only a half-day of preschool or to test for adverse effects of a medication before transitioning to a long-acting formulation. Nonetheless, as a general rule for this group, titration should be initiated at a low dose with small increments over an extended period of time.

Comorbid disorders are common in preschool-aged children. About 70% of participants in PATS[120] and 93% of those in a large Spanish study[121] had at least one co-occurring disorder, and 57.6% of children in the Spanish study had three or more disorders in addition to ADHD. Importantly, the number of co-occurring disorders in PATS participants inversely affected the efficacy of methylphenidate treatment (effect size decreased with increasing number of comorbidities).[122] Oppositional defiant disorder occurs in about one-half of preschoolers with ADHD[120,121]; behavioral strategies may lessen parent–child conflict, potentially contributing to a more effective treatment of ADHD symptomatology. Other frequent comorbid disorders include communication-related issues, anxiety, tics, and obsessive–compulsive problems.[120,121] General prescribing recommendations for some common comorbid disorders are discussed in the next section.

Clinicians should be aware that stimulants may produce a somewhat different adverse event profile in preschoolers than older children. Decreased appetite, delay of sleep onset, headaches, and stomachaches were the top adverse effects related to methylphenidate for school-aged children,[123] whereas preschool children taking methylphenidate experienced irritability, emotional outbursts, and repetitive behaviors/thoughts in addition to decreased appetite and sleep issues.[124] Additionally, there is a higher rate of methylphenidate discontinuation due to adverse events for preschoolers than older children.[124] With atomoxetine, frequent adverse effects related to treatment were gastrointestinal issues, sleep disturbance, irritability, defiance, agitation, and crying/whining.[117]

School-aged children

The estimated prevalence of ADHD in children and adolescents ranges from 3% to 10.2%, with the highest rates in North America/the United States.[125–127] Most children are diagnosed with ADHD after entry into school,[128] with boys diagnosed at a higher rate than girls.[110] The difference in diagnosis by gender is likely driven by the referrer's perceptions that the level of ADHD symptoms (ie, frequent lack of overt hyperactivity) may cause less impairment for girls, although studies of nonreferred samples find that ADHD severity, associated comorbidities, and impairment are similar between genders.[129–131] Frequent school age comorbidities include learning disabilities and oppositional defiant disorder, with anxiety, conduct disorder, autism spectrum disorder (ASD), and tic disorders being somewhat common.[7] Without intervention, children are more likely to struggle academically, be held back a grade, and are at higher risk for developing comorbid depression, oppositional defiant disorder, and/or conduct disorder.[132]

Pharmacotherapy should be considered as first-line treatment in conjunction with psychosocial therapy for school-aged children, with stimulants preferred over nonstimulants when possible.[7,11,12] A recent network meta-analysis found that while both types of stimulants are effective at reducing ADHD symptoms, amphetamine was superior to methylphenidate, atomoxetine, and modafinil for symptom improvement in children.[133] However, due to lower tolerability of amphetamine in this age group, methylphenidate was recommended as the first-choice medication for ADHD. Regarding safety, there are data suggesting that stimulant medication may affect long-term growth (height and weight) of children[106,108]; thus, clinicians should closely monitor height and weight. Recent studies show that weight recovery treatments (eg, calorie supplementation, drug holidays, and monthly weight monitoring) may facilitate increased weight gain.[134]

In a systematic review and meta-analysis comparing long- vs short-acting methylphenidate in children (average age 8.25-11.3 years) using both parent and teacher reports on inattention and hyperactivity, no significant differences were found in efficacy and behavior at home or in school between the two methylphenidate formulations.[135] Additionally, the rate of injuries in children with ADHD was not significantly different in those taking long-acting or short-/medium-acting methylphenidate formulations.[136] For clinicians considering which duration of action of a medication is appropriate for a school-aged patient, adverse effects and individual needs at different times of day may be of higher importance than how the duration impacts school performance.

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Adolescents

According to data from the Centers for Disease Control, about 14% of U.S. teens will have had an ADHD diagnosis at some point.[110] During adolescence, symptoms of hyperactivity/impulsivity begin to wane while inattentive symptoms usually persist.[137] Risk-taking behaviors increase in this age group,[138] which can lead to high rates of injuries,[139] teenage pregnancy,[140] and driving accidents.[141] In our practice, we find that difficulties at school are often exacerbated by increased cognitive demands, decreased external structure, and longer days. Adolescents may not adhere to or may discontinue their medication[110,142] even though it helps prevent risky behaviors and increases academic performance.[60,139,143,144] In adolescence, we may also begin to see patients diverting (swapping with or selling to peers) or misusing their short-acting stimulants. Engaging the adolescent patient and parents in shared decision making about ADHD treatment and monitoring for signs of diversion and misuse can help improve medication adherence and enhance outcomes.[145] Educating parents about the importance of their active involvement in the management and delivery of medications to their child, ongoing communication between parent and child with respect to treatment effectiveness, and side effects or concerns are key elements to successful therapy. The adolescent's opinion should also be considered when making medication recommendations.[145]

Stimulants are the recommended first-line treatment for adolescents, with psychosocial therapy also recommended to create a multimodal plan.[11,12] Strategies that involve organization skills, time management, and planning are fundamental, especially at this stage of development. Methylphenidate is the first-choice medication based on combined efficacy and safety information,[133] although long-acting amphetamines, atomoxetine, and guanfacine are also effective.[146] Use of long-acting formulations with once-daily dosing improves adherence and they are less likely to be misused or diverted.[92,147,148]

College-aged young adults

The challenge of adjusting to independent living with more responsibilities is particularly difficult for people with ADHD. College students with ADHD experience higher rates of depression, substance use, and general psychological distress.[149–151] Misuse of ADHD medications is nearly five times more likely among college students with ADHD than without.[152] ADHD symptoms continue to affect academic performance and contribute to higher levels of stress in college students with ADHD as compared with unaffected students.[149] Stimulants can help to reduce symptoms of ADHD in this age group[153]; however, clinicians should monitor for misuse and abuse of ADHD medications as well as for problems with illicit substances. If the patient has a higher risk for misuse/diversion, a nonstimulant may be prescribed.

The transition from pediatric to adult healthcare is another critical feature of this time; many students will display poor treatment adherence. Several models of transitional care are available and can increase the rate of continued treatment in the college-age population.[86,154] In our experience, preplanning with high school seniors on where and how they will receive their ADHD medication (ie, sent to their college pharmacy, mailed from their parents, prescribed by their student health system) is beneficial. Daily use of ADHD treatment is improved with once-daily medications and when there is an honest and open dialogue about where treatment makes a difference in their lives. The importance of daily structure, exercise, sleep, and positive peer relations should all be discussed as important areas for successfully coping with ADHD in the college years.

Adults

Prevalence of adult ADHD is estimated at 2.8% globally[155] and 4.4% in the United States.[8] However, adult ADHD is underdiagnosed because it is often mistaken for other disorders and its symptoms may abate with age or be masked through the development of coping mechanisms.[156,157] Comorbidity is the rule rather than the exception for adult ADHD; greater than 50% of patients will have one comorbid disorder and about one in seven will have three or more co-occurring disorders.[155] Furthermore, adults with ADHD may have sleep problems, an inability to effectively modulate emotions, and excessive mind-wandering.[158] ADHD is undertreated in adults—with only 11% receiving ADHD treatment in the past 12 months, according to a U.S. survey.[8]

Pharmacotherapy is the recommended first-line treatment for ADHD.[11,86] Based on a network analysis evaluating both efficacy and safety of multiple ADHD medications, amphetamine-based medication is recommended over methylphenidate as the first-choice stimulant for adults.[133] Regarding safety, CNS stimulant medications are associated with stroke, myocardial infarction and sudden death, increased blood pressure (2-4 mmHg), and increased heart rate (3-6 bpm).[22] Therefore, patients should be routinely evaluated during treatment if they develop chest pain upon exertion, syncope, or arrhythmias.[22]

Atomoxetine has also shown efficacy in adults; however, due to the lower effect size, it is considered an option for patients at risk for substance use disorder (SUD) or who cannot tolerate stimulant formulations.[7,11,86] Guanfacine and clonidine are not approved for use in adults, and few trials in this age group have been performed. A double-blind, placebo controlled study comparing guanfacine to dextroamphetamine for the treatment of ADHD in adults found guanfacine and dextroamphetamine reduced ADHD symptoms on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Adult Behavior Checklist for Adults to a similar extent vs placebo ($P < .05$) and guanfacine was well tolerated.[159] In our experience, guanfacine use in an adult may be useful if the patient responded to this treatment in childhood.

Prescribing ADHD Medication for Patients with Common Co-Occurring Disorders

Treatment becomes more complicated when patients present with ADHD and comorbid conditions. Clinicians must determine if ADHD can be treated simultaneously with the other disorder(s), and if not, the most severe disorder should be treated first. Although not reviewed in-depth here, potential drug-drug interactions of medications for ADHD and comorbid disorders are a critical consideration (eg, the interaction of atomoxetine—a potent 2D6 inhibitor—with paroxetine—a 2D6 substrate—where the addition of paroxetine led to increased plasma atomoxetine concentrations, and increased standing and orthostatic heart rate compared with monotherapy).[160] Figure 2 presents an overview of the challenges, considerations, and prescribing recommendations.

Substance use disorder

SUD is a serious condition that emerges as a coexisting disorder in ADHD adolescents with rates increasing into adulthood.[8,161] ADHD is a risk factor for use disorder of several substances including alcohol, marijuana, psychoactive substances, and nicotine.[162] Patients with ADHD are likely to develop SUD earlier than their peers, and experience a faster transition to a higher severity of

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ADHD Treatment Guide by Comorbid Condition

Substance use disorder

Substance use disorder (SUD)

Considerations & challenges

- Risk of abuse or diversion of stimulant ADHD medication is a concern
- Treatment can reduce ADHD symptoms without exacerbating SUD

People with ADHD are 5x more likely to develop SUD

Prescribing recommendations

- Avoid short-acting stimulants
- Use long-acting formulations that minimize "rush and rebound"
- Some alternative formulations may be less likely to be abused: Concerta (OROS-MPH), Vyvanse (LDX, a prodrug of dexamphetamine), Cotempla (MPH XR-ODT), ATX

Neurological disorders

Autism spectrum disorder (ASD)

Considerations & challenges

- Swallowing issues are common
- Sensitive to adverse effects from ADHD treatment

~75% of children with ASD are also diagnosed with ADHD

Prescribing recommendations

- Low and slow titration of ADHD medication to monitor adverse effects
- Liquid formulations allow for the smallest dose increments
- To address swallowing issues, prescribe liquid, orally disintegrating tablet, or sprinkle formulations
- Any class of ADHD medication can be beneficial, and response varies for each patient

Epilepsy

Considerations & challenges

- Limited guidance on the treatment of ADHD in these patients

~1/3 of children with active epilepsy have ADHD

Prescribing recommendations

- MPH is the first-choice ADHD treatment, as it did not significant increase the frequency or severity of seizures
- ATX can also be used, but less is known about safety in epileptic patients

Tic disorders

Considerations & challenges

- Reduced the patient's quality of life

5%–15% of children with ADHD also have a tic disorder

Prescribing recommendations

- Stimulants can be effective, but monitoring for worsening of tics is necessary
- ATX can be considered if stimulants exacerbate tics
- GXR and clonidine are often effective at treating ADHD, and may improve tics

Figure 2. ADHD treatment guide by comorbid condition. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; ASD, autism spectrum disorder; ATX, atomoxetine; GXR, guanfacine extended release; LDX, lisdexamfetamine dimesylate; MDD, major depressive disorder; MPH, methylphenidate; OROS, osmotic controlled release oral delivery system; OTD, orally disintegrating tablet; SUD, substance use disorder.

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Psychiatric disorders

Anxiety

Considerations & challenges

- Anxiety exacerbates ADHD-related impairment

Comorbid with ADHD in ~15% of children and ~47% of adults

Prescribing recommendations

- Stimulants can be effective, especially when ADHD symptoms contribute to anxiety
- Long-acting, smooth-release formulations are preferred vs those with distinct phases of drug release
- Titrate slowly, and monitor anxiety as well as ADHD symptoms
- First-choice: MPH
- Other options: AMP, ATX, GXR (children only)

Bipolar disorder

Considerations & challenges

- This combination of disorders worsens and complicates each

Comorbid with ADHD in 19% of adults, also co-occurs in children

Prescribing recommendations

- Based on recent studies in children, treat bipolar disorder and ADHD concurrently
- Monitor for any worsening of bipolar symptoms

Depression

Considerations & challenges

- Incidence increases with age

MDD occurs in 19% of adults with ADHD

Prescribing recommendations

- Severe or suicidal cases: Treating depression takes precedent over ADHD treatment
- Mild cases: Treat ADHD and depression concurrently
- Taking both a stimulant and a serotonin reuptake inhibitor is well-tolerated, and may address both ADHD and depressive symptoms
- ATX is also effective for treating ADHD

Insomnia

Considerations & challenges

- Sleep issues are common in patients with ADHD, independent of medication
- Insomnia and sleep issues may improve or worsen with ADHD medication
- Insomnia can occur when initiating an ADHD medication, but may subside over time

55%–80% of adults, >80% of children with ≥1 sleep issue

Prescribing recommendations

- Monitor how the patient responds to different long-acting formulations: Does release at end of day induce or help insomnia?
- With stimulants, adjust dose or try different delivery formulation to address insomnia
- ATX is less likely to cause insomnia
- GXR or clonidine have a sedative effect: use alone or with a stimulant
- Melatonin supplement may help address sleep issues

Figure 2. *(Continued)*

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addiction.[163] Individuals whose ADHD persists from childhood into the young adult years may be five times more likely to develop SUD, whereas those with remittent ADHD are similar to the healthy population.[164] The presence of additional co-occurring disorders often occurs in patients with ADHD and SUD.[161]

Past concerns that stimulant treatment in childhood facilitates the later development of SUDs were dispelled by two meta-analyses. Schoenfelder et al revealed that treatment of childhood ADHD with stimulants was associated with lower rates of future smoking compared with no treatment.[165] Humphreys et al evaluated 15 longitudinal studies and found no differences in the risk for developing alcohol, cocaine, marijuana, or nonspecific drug use disorders at later ages between stimulant-treated and untreated children with ADHD.[166]

Many clinicians may be wary of prescribing stimulant medication to an ADHD patient with SUD, as there is a well-known higher risk for misuse and diversion.[167] However, treating ADHD should not be avoided outright given the effect ADHD can have on quality of life as discussed in the beginning of this review. Treatment can reduce ADHD symptoms without negative effects on SUD, and there have not been any specific safety issues with medication in this group.[168] We recommend avoiding short-acting stimulants and to prescribe long-acting formulations that minimize "rush and rebound."

In patients with ADHD and a specific stimulant SUD (such as amphetamine, methamphetamine, or cocaine), there may be a role for stimulants to moderate the SUD similar to the use of buprenorphine or methadone to improve opioid use disorder. One study examined D-amphetamine in managing methamphetamine use disorders and found a decrease, although not statistically significant, in self-administration of methamphetamine during D-amphetamine maintenance therapy.[169] Further research is necessary to determine whether changes in stimulant dosage or route of administration are beneficial for treatment of amphetamine or methamphetamine SUDs in patients with ADHD.

Some delivery technologies further minimize the abuse potential of long-acting stimulants. The osmotic-release oral capsule of Concerta is less likely to be abused[168] and the nondeformable shell minimizes the potential to grind or snort the medication. The prodrug delivery technology of lisdexamfetamine (Vyvanse) has been shown to have less likability than short-acting amphetamine when taken orally[170] or intravenously.[171] We are aware of one study assessing the impact of concomitant administration of alcohol on the PKs of a stimulant medication in vivo. The amphetamine extended-release orally disintegrating tablet (Adzenys XR-ODT) was studied in conjunction with concomitant alcohol concentrations of up to 40% in healthy adult volunteers. There was no change in the extent of absorption for D- or L-amphetamine and no dose-dumping of the extended release portion of the formulation.[172] Atomoxetine also displays little abuse potential.[173,174] Appropriate consideration of ADHD treatment in individuals with comorbid SUD may improve overall outcomes.

Psychiatric disorders: anxiety, bipolar disorder, depression, and insomnia

Anxiety

Comorbid anxiety disorders occur in about 15% of children and 47% of adults with ADHD,[4,8] and they cause greater ADHD-related impairment.[175] Stimulants may be useful in treating ADHD in children and adults with co-occurring anxiety,[175,176] especially in cases where the ADHD symptoms contribute to anxiety and emotional distress. Although individual responses differ, we find that methylphenidate is less likely than amphetamine to induce anxiety; smooth-release formulations (ie, where both the peak and offset are smooth, such that medication will gradually absorb into the system, rest at peak levels, and gradually decline) also often induce less anxiety. We recommend choosing a stimulant with a smooth-release profile, and to titrate slowly starting with a low dose. Atomoxetine has also been shown to effectively treat ADHD in patients with co-occurring anxiety disorders.[177] Guanfacine does not exacerbate anxiety in children[178] and may be considered if other options are ineffective.

Bipolar disorder

Bipolar disorder is a frequently encountered comorbid condition with ADHD, which may be easily missed. In the National Comorbidity Study, 19% of adults with ADHD had comorbid bipolar disorder.[8] In children with bipolar disorder, coexisting ADHD is fairly common but rates have been highly variable with as few as 4% and as many as 94% in different studies.[179] The combination of the two disorders worsens and complicates each.[179]

Historically, it was recommended to treat bipolar symptoms before treating ADHD; however, recent studies indicate that simultaneous treatment can be effective, and possibly beneficial. In a study of adults with bipolar disorder, the risk of a manic episode was increased with methylphenidate treatment alone, whereas manic episode risk was reduced when methylphenidate was taken with a mood stabilizer (aripiprazole, lithium, olanzapine, quetiapine, or valproate).[180] In two recent large, double-blind studies of medication for bipolar disorder (one of asenapine, one of lurasidone) in children and adolescents, stimulant use did not alter the effectiveness of the bipolar medication in the subgroup of patients with comorbid ADHD.[181,182]

Depression

Major depressive disorder prevalence increases with age,[183] ultimately affecting about 19% of adults with ADHD.[8] Additionally, young people with ADHD may experience depression more often when confronted with life stress than people without ADHD.[184] With mild or moderate cases of depression, treatment of ADHD should be pursued, as it can reduce the long-term risk for depressive episodes.[185] A large study in Taiwan found lower rates of antidepressant resistance when individuals with ADHD and depression received combined treatment with antidepressants and psychostimulants vs treatment with antidepressant alone.[186] However, treatment of depression should take precedent over ADHD when it is the most disabling condition such as in major depressive disorder or suicidal cases.[7]

Administration of both a stimulant and serotonin reuptake inhibitor for depression is well-tolerated.[187] Atomoxetine monotherapy was also effective and well-tolerated in an open-label study of adolescents with ADHD and major depressive disorder; although, it was only effective for ADHD symptoms.[188] Caution must be taken when prescribing amphetamine with certain medications, as there is an increased risk of serotonin syndrome when combined with buspirone, fentanyl, lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, St. John's Wort, triptans, tricyclic antidepressants, tramadol, and tryptophan.[22]

Insomnia

Insomnia is common in individuals with ADHD before ever receiving treatment and can be either worsened or improved with

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ADHD medication. One study found >80% of unmedicated children with ADHD had at least one sleep problem including involuntary movement, difficulty falling asleep or rising, sleepwalking, snoring, bed-wetting, or nightmares.[189] Insomnia occurs in 55% to 80% of adults with ADHD, with the combined ADHD subgroup showing higher rates of insomnia than the inattentive subgroup.[190]

Initial insomnia is a frequent side effect when starting an ADHD medication, although patients may experience an improvement in sleep quality with appropriate treatment over time.[191–194] In our experience, a medication with too long of a duration may exacerbate insomnia for some individuals, while, for others, a formulation with a small amount of medication released in the early evening may help to calm the brain, decrease restlessness, and improve sleep quality.[194] If insomnia is an issue with a stimulant medication, the clinician should adjust the dose or try an alternative delivery formulation. Atomoxetine is less likely to cause insomnia and other sleep issues, and can be considered as a second-choice option.[195,196] Guanfacine and clonidine induce sedation, and may be used alone or in combination with stimulants.[197–199] Prescribing a treatment such as melatonin to specifically address sleep issues may be needed in certain individuals.[200]

Neurological conditions: autism, epilepsy, and tics

Autism spectrum disorders

ASD is characterized by persistent deficits in social communication and interactions in many settings and the presence of repetitive, restricted behavior, interests, or activities.[6] Diagnosis of co-occurring ADHD and ASD was recently endorsed in DSM-V.[6] ADHD and ASD co-occur at all stages of life,[201] with around 75% of children and adolescents with ASD having comorbid ADHD.[202,203] Similar to ADHD, the symptoms and presentation of ASD change with age.[201] These patients are often extremely sensitive to side effects from ADHD medication; treatment-emergent agitation, increase in stereotypies, or worsening of anxiety can be frequent concerns.

To find the optimal dose, we recommend starting with a low dose and titrating slowly. Liquid formulations of methylphenidate (eg, Qullivant XR,[204] Methylin[68]) or amphetamine (eg, Dyanavel XR, ProCentra,[30] Adzenys ER[21]) can be titrated in very minor amounts and may aid slow titration. Swallowing issues are frequently encountered in this population and liquid, orally disintegrating, or sprinkled formulations may be beneficial. The British Association for Psychopharmacology recommends methylphenidate as the first-choice pharmacotherapy, atomoxetine as the second choice, and guanfacine and clonidine as third-line options.[205] In our clinical experience, all classes of ADHD medication can prove beneficial in patients with ASD/ADHD and the response varies dramatically between each patient.

Epilepsy

Approximately one-third of children with active epilepsy have comorbid ADHD.[206] Evidence-based recommendations on treatment of ADHD in epilepsy are limited. The Task Force on Comorbidities of the International League Against Epilepsy Pediatric Commission recommends methylphenidate as the first-choice treatment because there is a 65% to 83% improvement in ADHD symptoms without significantly increasing the frequency or severity of seizures.[207] Atomoxetine has also shown efficacy in treating ADHD in this population, but there is limited evidence regarding safety.[207]

Tic disorders

About 5% to 15% of children with ADHD also have a tic disorder.[208,209] These patients experience poorer quality of life than those with ADHD alone.[208,209] Overall ADHD medications can be effective in these patients when used with appropriate care and consideration.[210] With stimulant pharmacotherapy, monitor for possible worsening of tics.[19] Atomoxetine is unlikely to worsen tics, and can be considered if stimulants cause tic exacerbation.[210] Guanfacine and clonidine are often effective at treating ADHD with coexisting tic disorder and may improve comorbid tics.[210]

Conclusions and Future Directions

Evolving ADHD symptomology and comorbid disorders contribute to the complexity of a treatment plan for patients with ADHD over their lifetimes. Despite this, it is necessary to find the most effective treatment for the individual with ADHD to be able to improve many aspects of his or her life. Notwithstanding the many treatment challenges for patients with ADHD, clinicians have numerous options for FDA-approved ADHD pharmacotherapy allowing individualized medication to meet specific patient needs. Understanding the key challenges of ADHD treatment for different age groups and for patients with various co-occurring disorders is necessary to achieve successful treatment results. Further research is needed to develop better treatment strategies for individuals diagnosed with ADHD and comorbid neurological disorders such as epilepsy, insomnia, and tic disorders. Although not discussed in this review, the association of ADHD with certain inherited neurological diseases such as Fragile X syndrome, Prader–Willi syndrome, Williams syndrome, and Velo-cardio-facial syndrome is becoming evident.[211,212] Accordingly, further research into the treatment of ADHD comorbid with these inherited disorders would be valuable.

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