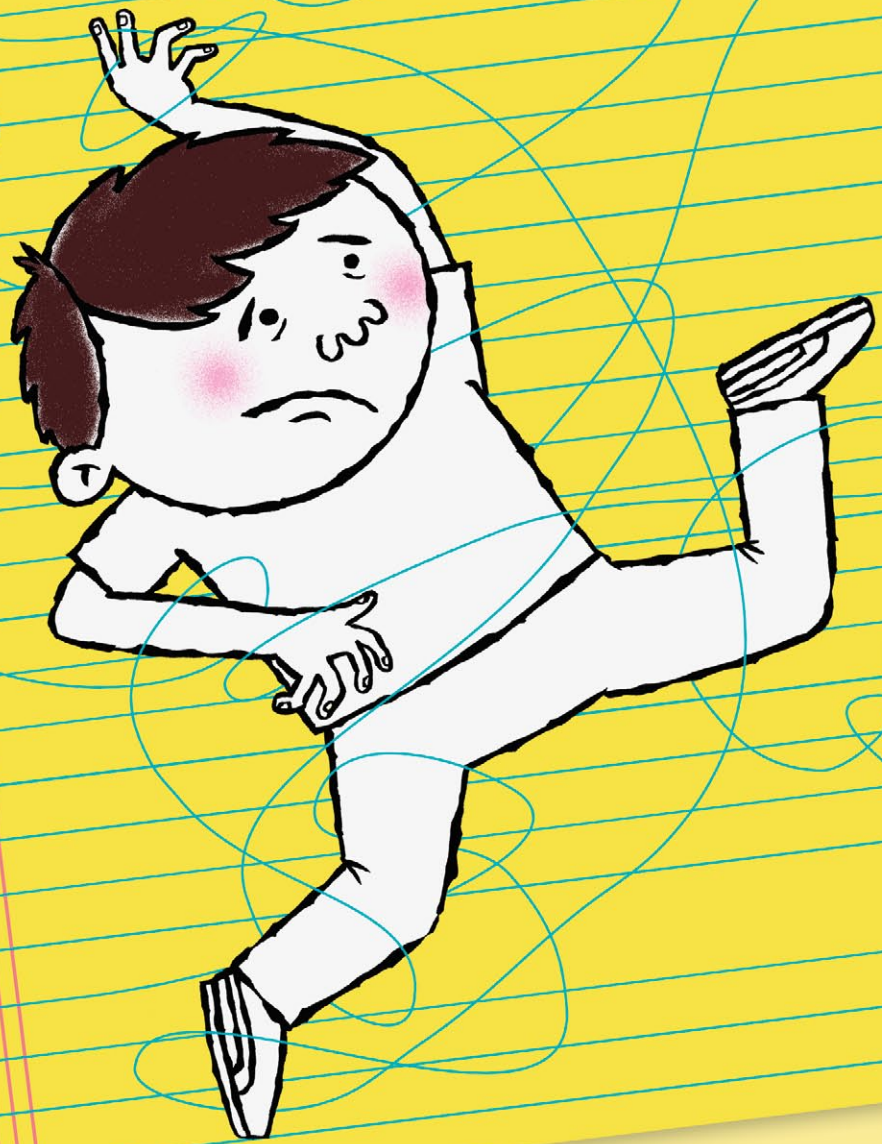
Expanding medication options for PEDIATRIC ADHD



Psychostimulant and non-stimulant agents address the symptoms of ADHD, substantial evidence shows

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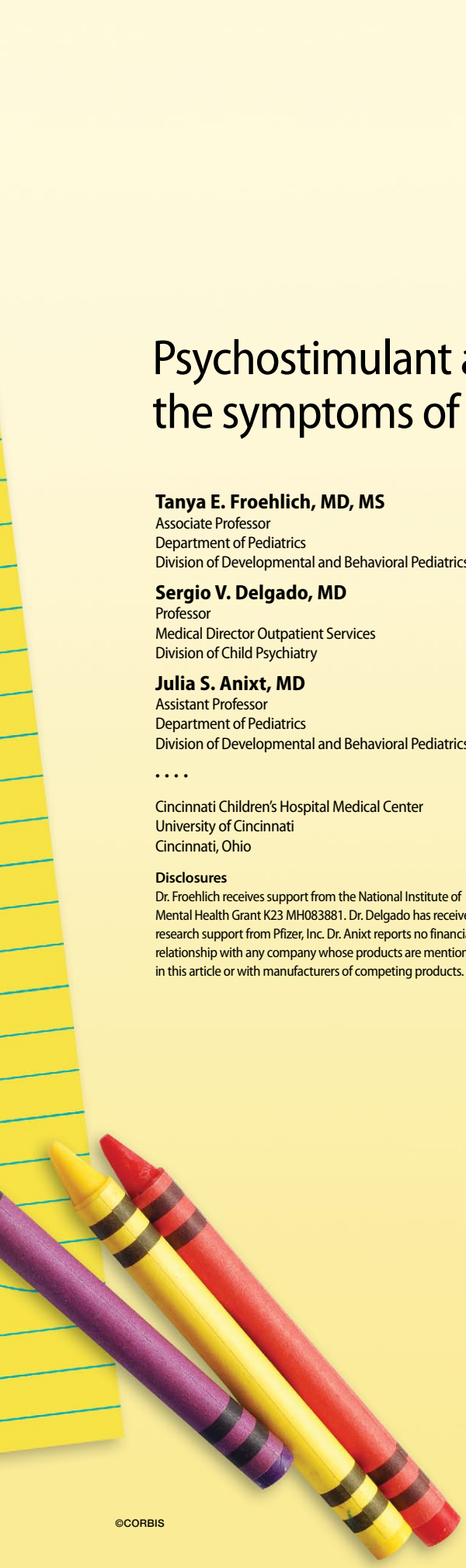

Molly, age 9, is diagnosed with attention-deficit/hyperactivity disorder (ADHD) by her psychiatrist, who prescribes a long-acting methylphenidate formulation at 1 mg/kg. She tolerates the medication without side effects and shows significant improvement in her academic performance and on-task behavior in school. Molly takes methylphenidate before school at 7:00 AM; this dose usually wears off at approximately 3:30 PM.

Molly and her parents are pleased with her response to methylphenidate, but report that she has difficulty getting ready for school because of distractibility. In the evenings Molly has trouble staying seated to do homework and often interrupts and argues with family members, but cannot tolerate afternoon dosing of immediate-release methylphenidate because of insomnia.

ADHD, the most common childhood neurobehavioral disorder, is characterized by difficulties with attention, impulse control, and modulating activity level. The pathophysiology of ADHD is thought to involve dysregulation of brain dopamine and norepinephrine systems.[1] Managing ADHD includes pharmacotherapeutic and nonpharmacotherapeutic—ie, behavioral and psychoeducational—interventions.[2,3]

In this article, we provide an overview of the efficacy, side effects, and dosing for the 3 classes of ADHD medication—psychostimulants, atomoxetine, and α_2 adrenergic agonists—including guidance on medication choice and combination treatment. We also discuss the effects of psychostimulants on tics, cardiovascular concerns, and substance abuse potential.

Psychostimulants

Methylphenidates and amphetamines are first-line agents for ADHD. Their primary mechanism of action involves blocking dopamine transporters, with additional effects including blockade of norepinephrine transporters, dampening action of monoamine oxidase (which slows dopamine and norepinephrine degradation), and enhanced release of dopamine into the synaptic space.[1]

Efficacy and response rates are similar for methylphenidate and amphetamine medications, although as many as 25% of patients may respond

Clinical Point

Improvements in noncompliance, aggression, social interactions, and academic productivity have been observed with psychostimulants

Table 1

Titrating and discontinuing ADHD medications

Class	Dosing and titration strategy	Medication holidays[a] and discontinuation
Psychostimulants (Methylphenidates, amphetamines)	No variables have been identified that reliably predict medication efficacy or optimal dose; effective dosage is not based on age or weight Start at a low dose, titrate upward every 3 to 7 days until symptom remission, unacceptable side effects develop, or maximum dose is reached Because preparations in 1 psychostimulant class may not produce identical clinical responses in individual patients, when a patient has inadequate response to 1 stimulant, clinicians may try another drug in the same class, or to try a preparation from the alternative class Several psychostimulants or dosages might need to be tried before finding one that works for a patient	"Holidays" are an option because stimulants are effective on the day given, whether or not they are given on the preceding days Can discontinue without weaning
Norepinephrine reuptake inhibitor	Weight-based for children <70 kg For patients >70 kg, there is a standard starting and maximum dose Initial effects in 1 or 2 weeks, but maximal response may not be achieved for 4 to 6 weeks	Must be administered consistently to be effective (not amenable to holidays) Can discontinue without weaning
α_2 Adrenergic agonists	Effective dosage is not based on age or weight Start at lowest dosage, titrate to next dosage after 1 week on each dosage until symptoms remit, unacceptable side effects develop, or maximum dosage is reached Initial effects may be seen in 1 to 2 weeks, but maximal response might not be achieved for 4 to 6 weeks	Must be administered consistently to be effective (not amenable to holidays) Wean dose gradually (by 0.1 mg for clonidine ER and 1 mg for guanfacine ER every 3 to 7 days) to prevent rebound hypertension on discontinuation

[a]breaks from medication

Source: References 2,7-9

to only 1 agent.[1] More than 90% of patients will have a positive response to one of the psychostimulants.[1] The beneficial effects of psychostimulants on inattention, hyperactivity, and impulsivity are well documented.[2] Improvements in noncompliance, aggression, social interactions, and academic productivity also have been observed.[4,5]

Because of increased recognition of pervasive ADHD-related impairments, which can affect functioning in social, family, and extracurricular settings, practitioners have shifted to long-acting psychostimulants to reduce the need for in-school dosing, improve compliance, and obtain more after-school treatment effects. Long-acting formulations produce a slower rise and fall of psychostimulant levels in the brain, which may decrease side effects and potential for later drug abuse.[6] See ***Table 1***[2,7-9] and ***Table 2***[2,7,9] (***page 24***) for titration, dosing, and duration of action of psychostimulants.

The most common side effects of psychostimulants are appetite loss, abdominal pain, headaches, and sleep disturbances.[2] Emotional symptoms—irritability and nervousness—may be observed with psychostimulant use, but these behaviors may improve, rather than become worse, with treatment.[5] Methylphenidates and amphetamines share many of the same side effects,[2] with many studies indicating no differences between their side-effect profiles.[1] Other studies indicate that sleep and emotional

side effects may be more prominent with amphetamines than methylphenidates,[10] although response varies by individual.

There is little evidence that methylphenidate, low-dose amphetamine, or low-dose dextroamphetamine makes tics worse in most children who have them, although significant tic exacerbation has been observed with higher-dose dextroamphetamine.[11,12] In patients with comorbid ADHD and tic disorders, a trial of psychostimulants with monitoring for worsening tics is appropriate.

Changes in heart rate and blood pressure generally are not clinically significant in patients taking psychostimulants (average increases: 1 or 2 beats per minute and 1 to 4 mm Hg for systolic and diastolic blood pressures).[12] However, psychostimulants may be associated with more substantial increases in heart rate and blood pressure in a subset of individuals (5% to 15%).[12] Large studies of children and adults in the general population have not found an association between psychostimulant use and severe cardiovascular events (sudden cardiac death, myocardial infarction, stroke).[12-14] Because of reports of sudden cardiac death in children with underlying heart disease who take a psychostimulant,[15] clinicians are advised to screen patients and consider an electrocardiogram or evaluation by a cardiologist before starting a psychostimulant in a patient who has a personal or family history of specific cardiovascular risk factors (see Perrin et al[16] and Cortese et al[12] for screening questions and conditions).

Modest reductions in height (1 or 2 cm after 3 years of psychostimulant treatment) appear to be dose-dependent, and are similar across the methylphenidate and amphetamine classes. Some studies have shown reversal of growth deficits after treatment is stopped treatment and no adverse effects on final adult height.[12,17] More study is needed to clarify the effects of continuous psychostimulant treatment from childhood to adulthood on growth.

Studies have failed to show an increased risk of substance abuse in persons with ADHD who were treated with psychostimulants during childhood. Some studies document a lower rate of later substance abuse in youths who received ADHD medications, although other reports show no effect of psychostimulant treatment on subsequent substance use disorder risk.[12] Be aware that psychostimulants can be misused (eg, to get "high," for performance enhancement, to suppress appetite, etc.). Misuse of psychostimulants is most common with short-acting preparations, and generally more difficult with long-acting preparations because extracting the active ingredients for snorting is difficult.[2,12] Monitor refill requests and patient behavior for signs of misuse, and be alert for signs of illegal drug use in the patient's family.

Psychotic symptoms—including hallucinations, delusions, mania, and extreme agitation—with psychostimulant treatment are rare, occurring at a rate of 1.5%.[12]

Atomoxetine

Approved by the FDA in 2002 for ADHD, atomoxetine is effective and generally well tolerated, although it is not as effective as psychostimulants.[2] Atomoxetine is a potent norepinephrine reuptake inhibitor[18] that does not produce euphoria, does not have potential for abuse, and has not been linked to increased tic onset or severity.[19] Atomoxetine treatment is associated with a lower rate of sleep initiation difficulty compared with psychostimulants.[18] Some studies suggest that atomoxetine may have mild beneficial effects on anxiety disorders,[18] making it a reasonable choice for patients with significant anxiety or insomnia during psychostimulant treatment. ***Table 1***[2,7-9] and ***Table 3***[2,7,9] (***page 26***) include information on dosing and duration of action for atomoxetine.

Common side effects of atomoxetine include sedation and fatigue, upset stomach, nausea and vomiting, reduced appetite, headache, and irritability.[18] Inform patients that atomoxetine carries an FDA black-box warning for suicide risk; a review of 14 studies showed suicidal ideation was more common with atomoxetine than placebo, although no suicides occurred in any trials.[20]

Hepatotoxicity is rare with atomoxetine.[21] Although routine liver enzyme testing is not required, discontinue atomoxetine if jaundice develops or elevated levels of liver enzymes are noted. Other rare but potentially serious side effects include changes in heart rate

Clinical Point

Changes in heart rate and blood pressure generally are not clinically significant in patients taking psychostimulants

Clinical Point

Atomoxetine has been linked to growth delays in the first 1 or 2 years of treatment

Table 2

Dosing and duration of action for psychostimulants

Medication	Starting daily dosage	Daily maximum dosage[a]	Dosing interval
Short-acting methylphenidate (Ritalin,[b] Methylin, Methylin chewable, Methylin solution)	5 mg	60 mg	Twice or 3 times a day (every 4 hours)
Intermediate-acting methylphenidate (Metadate CD, Metadate ER, Methylin ER, Ritalin LA, Ritalin SR[b])	10 mg (for all but Ritalin SR [20 mg])	60 mg	Once daily
Extended release methylphenidate, osmotic-release oral system (Concerta[b])	18 mg	54 mg (age <13) or 72 mg (age ≥13)	Once daily
Extended release methylphenidate, oral suspension (Quillivant XR)	20 mg	60 mg	Once daily
Extended release methylphenidate, dermal (Daytrana)	10 mg	30 mg	Once daily, apply patch for up to 9 hours
Short-acting dexmethylphenidate (Focalin[b])	2.5 mg	20 mg	Twice daily
Extended-release dexmethylphenidate (Focalin XR)	5 mg	30 mg	Once daily
Short-acting mixed amphetamine salts (Adderall[b])	2.5 to 5 mg	40 mg	Once or twice daily
Extended release mixed amphetamine salts (Adderall XR)	5 mg	40 mg	Once daily
Short-acting dextroamphetamine (Dexedrine[b], DextroStat, ProCentra)	2.5 mg	40 mg	Twice or 3 times daily
Intermediate-acting dextroamphetamine (Dexedrine SR[b])	5 mg	40 mg	Once or twice daily
Lisdexamfetamine[c]	20 mg	70 mg	Once daily

[a]Some patients may require a dosage higher than the recommended dosing of a psychostimulant because of limited response. Literature and empirical evidence from child psychiatrists support having patients on a total daily dosage of stimulant above the typical maximum. Careful attention to cardiovascular considerations and other adverse effects is recommended. Flexibility and alliance with a primary care physician and the family is crucial because it permits the child psychiatrist to gather data about the tolerability and effectiveness of the chosen medication in order to make an informed clinical decision
[b]Generic form available
[c]Stimulant prodrug

Source: References 2,7,9

(≥20 beats per min) or blood pressure that occur in 5% to 10% of patients taking atomoxetine.[22] The risk of serious cardiovascular events and sudden cardiac death with atomoxetine is extremely low, but patients should be screened for a personal and family history of cardiovascular risk factors and, if any of these are present, evaluated further before starting atomoxetine. Routine heart rate and blood pressure monitoring is recommended for all patients.[12-14,16]

Last, atomoxetine has been linked to growth delays in the first 1 or 2 years of treatment, with a return to expected measurements after an average 2 or 3 years of treatment; persistent decreases in growth rate

Duration of action	Comments
3 to 5 hours	Methylin solution is available in 5 mg/5 mL and 10 mg/5 mL concentrations
3 to 8 hours	For patients who do not swallow pills, Metadate CD and Ritalin LA capsules can be opened and microbeads can be sprinkled on food
12 hours	Must be swallowed whole; opening or crushing capsule damages the osmotic pump delivery system Has less abuse liability because osmotic pump delivery system makes it difficult to extract the methylphenidate for snorting or intravenous injection
12 hours	Available in 25 mg/5 mL concentration
3 hours after patch removal (maximum 15 hours)	Greater absorption occurs when applied to the buttocks rather than the subscapular area Dosages for patch are not equivalent to dosages of oral methylphenidate preparations Has less abuse liability because intradermal delivery system makes it difficult to extract methylphenidate for snorting or intravenous injection
4 to 6 hours	1 mg dexmethylphenidate is equivalent to 2 mg oral methylphenidate
8 to 12 hours	For patients who do not swallow pills, capsules can be opened and microbeads can be sprinkled on food 1 mg dexmethylphenidate is equivalent to 2 mg oral methylphenidate
6 hours	1 mg amphetamine is equivalent to 2 mg oral methylphenidate
10 hours	For patients who do not swallow pills, capsules can be opened and microbeads can be sprinkled on food 1 mg amphetamine is equivalent to 2 mg oral methylphenidate
4 to 6 hours	For patients who do not swallow pills, ProCentra oral suspension (5 mg/5 mL) can be used 1 mg dextroamphetamine is equivalent to 2 mg oral methylphenidate
≥6 hours	For patients who do not swallow pills, capsules can be opened and microbeads can be sprinkled on food 1 mg dextroamphetamine is equivalent to 2 mg oral methylphenidate
10 to 12 hours	For patients who do not swallow pills, capsules can be opened and contents mixed with water (efficacy when mixed with other liquids has not been studied) Has less abuse liability because prodrug form makes it difficult to extract the stimulant for snorting (cleavage of lysine is necessary to convert lisdexamfetamine to the active dextroamphetamine form) Dosages are not equivalent to dextroamphetamine dosages; data on methylphenidate dosage equivalents are not available

Clinical Point

Guanfacine and clonidine are used to treat tics and oppositional/aggressive behavior comorbid with ADHD

were observed in patients who were taller or heavier than average before treatment.[23]

α_2 Adrenergic agonists

Guanfacine ER and clonidine ER, the extended release (ER) formulations of α_2 adrenergic agonists, were FDA-approved for treating ADHD in 2009 and 2010, respectively. Short-acting guanfacine and clonidine also are used for treating ADHD.[24] Their mechanism of action involves stimulation of the pre-synaptic and post-synapic α_2 adrenergic receptors, which control the release of norepinephrine and the rate of cell firing.[25] The α_2 agonists are considered a second-line treatment for

Table 3

Dosing and duration of action for non-stimulant ADHD medications

Medication	Starting daily dosage	Daily maximum dose	Dosing interval
Norepinephrine reuptake inhibitor			
Atomoxetine (Strattera)	Patients <70 kg: 0.5 mg/kg/d for 1 week, then increase to 1.2 mg/kg/d. Patients ≥70 kg: 40 mg, then increase to 100 mg/d	Patients <70 kg: 1.4 mg/kg/d. Patients ≥70 kg: 100 mg/d	Once or twice daily
α_2 Adrenergic agonist			
Guanfacine extended release (Intuniv)	1 mg	4 mg	Once daily
Clonidine extended release (Kapvay)	0.1 mg	0.4 mg	Once or twice daily

Source: References 2,7,9

Clinical Point

Clonidine, which is more sedating than guanfacine, can be used to treat comorbid ADHD and sleep disorders

Table 4

Managing ADHD and comorbid anxiety or mood disorder

Comorbidity	Treatment recommendation
Anxiety	Starting treatment with multiple separate ADHD and anxiety agents simultaneously *is not recommended*, because primary treatment of 1 disorder may ameliorate symptoms of the other. Use atomoxetine to treat both ADHD and anxiety or first treat ADHD with a stimulant, then add a selective serotonin reuptake inhibitor if anxiety does remit with stimulant treatment[8]
Depression	Starting treatment with multiple separate ADHD and depression agents simultaneously *is not recommended* because primary treatment of 1 disorder may ameliorate symptoms of the other. Rather, expert consensus advises to treat whichever disorder is most severe first, then to add an agent for the second disorder if monotherapy does not improve both disorders[8]
Bipolar disorder	Initiate pharmacotherapy for bipolar disorder (involving a mood stabilizer or atypical antipsychotic) and stabilize manic symptoms before beginning treatment with a psychostimulant[31]

ADHD: attention-deficit/hyperactivity disorder

ADHD because their efficacy and response rate for core ADHD symptoms lags behind those of psychostimulants.[25] In addition to treating core ADHD symptoms, guanfacine and clonidine are used to treat tics and oppositional/aggressive behavior comorbid with ADHD.[24,26] Clonidine, which is more sedating than guanfacine, can be used to treat comorbid ADHD and sleep disorders.[24] The α_2 agonists do not produce euphoria and do not have drug abuse potential.[2] ***Table 1***[2,7-9] (***page 22***) and ***Table 3***[2,7,9] provide guidelines for prescribing guanfacine ER and clonidine ER.

The most common adverse effect is drowsiness; other common side effects include dizziness, irritability, headache, and abdominal pain.[24] Short-term studies of α_2 agonist treatment of ADHD have shown small, non-clinically significant reductions in heart rate and blood pressure; α_2 agonist-associated bradycardia, increased QT interval, and cardiac arrhythmias have been reported,[7,24,27] as well as rebound hypertension with abrupt discontinuation.[24] Screen patients for a personal and family history of cardiovascular risk factors and, if present, evaluate further before initiating α_2 agonists.

Combining ADHD medication classes

Combination therapy with >1 ADHD medications is employed when 1 class does not provide adequate symptom coverage or produces problematic side effects.[8,24] Psychostimulants can be combined with

	Duration of action	Comments
	18 to 24 hours	Twice a day dosing (early morning and evening) may improve efficacy and decrease side effects No abuse liability
	~24 hours	No abuse liability
	12 to 24 hours	No abuse liability

low-dose atomoxetine (0.5 to 1.0 mg/kg/d) when atomoxetine does not adequately cover ADHD symptoms in school, or when psychostimulants do not adequately cover evening symptoms or patients experience problems with evening psychostimulant rebound.[8] To date, prospective data on the safety and efficacy of combining atomoxetine and psychostimulants are limited, but what evidence is available suggests improved symptom control for some, but not all, patients, and a lack of serious adverse events.[28]

Psychostimulants have been combined with α_2 agonists when children have an inadequate response to psychostimulants alone, or in cases of ADHD comorbid with aggression or tics.[24] Although early case reports raised concern about the safety of combining psychostimulants and α_2 agonists, subsequent studies suggest that clonidine and guanfacine generally are well-tolerated when co-administered with psychostimulants.[24,27,29]

CASE CONTINUED

Molly has derived substantial benefit from long-acting methylphenidate during the school day, but continues to have significant ADHD-related impairment in the mornings and evenings. Her physician tried afternoon dosing of immediate-release methylphenidate to address evening difficulties, but Molly experienced insomnia. It would be reasonable to consider adjunctive therapy with a non-stimulant medication. A medication that can provide round-the-clock ADHD symptom coverage—such as atomoxetine, guanfacine ER, or clonidine ER—could be added to her current day-time psychostimulant treatment, potentially improving her functioning at home before school and in the evenings.

Additional considerations

Combining medication and behavior therapy offers greater improvements on academic, conduct, and family satisfaction measures than either treatment alone.[2] Clinicians can choose to employ behavior therapy alone, particularly if parents feel uncomfortable with—or children have not tolerated—medication.[2,3] Evidence-based behavioral parent training and classroom management strategies (implemented by teachers) have shown the strongest and most consistent effects among nonpharmacotherapeutic interventions for ADHD.[2] Most studies comparing behavior therapy to psychostimulants have found a stronger effect on core ADHD symptoms from psychostimulants than from behavior therapy.

When a patient does not respond adequately to FDA-approved ADHD medications alone or in combination, consider bupropion, an antidepressant with indirect dopamine and noradrenergic effects. Off-label bupropion has been shown to be effective for ADHD in controlled trials of both children and adults.[30]

Clinicians often encounter children who meet criteria for ADHD *and* an anxiety or mood disorder. ***Table 4***[8,31] summarizes treatment recommendations for these patients.

Clinical considerations

- Begin treatment with a psychostimulant at a low dosage, and titrate gradually until symptoms are controlled or side effects develop.
- Keep in mind that an effective dosage of a psychostimulant is not closely correlated with age, weight, or severity of symptoms.
- Monitor refill requests and patient behavior for signs of psychostimulant misuse. Be alert for signs of illegal drug use in patient family members.
- Lisdexamfetamine, dermal methylphenidate, and osmotic release oral system

Clinical Point

Most studies have found a stronger effect on core ADHD symptoms from psychostimulants than from behavior therapy

Pediatric ADHD

Related Resources

- National Institute of Mental Health. What is attention deficit hyperactivity disorder (ADHD, ADD)?" www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml.
- National Resource Center on AD/HD. Managing medication for children and adolescents with ADHD. www.help4adhd.org/en/treatment/medication/WWK3.

Drug Brand Names

Atomoxetine • Strattera
Bupropion • Wellbutrin, Zyban
Clonidine extended release • Kapvay
Dexmethylphenidate • Focalin, Focalin XR
Dextroamphetamine • Dexedrine, Dexedrine SR, DextroStat, ProCentra
Guanfacine extended release • Intuniv
Lisdexamfetamine • Vyvanse
Methylphenidate • Ritalin, Methylin, Metadate CD, Metadate ER, Methylin ER, Ritalin LA, Ritalin SR, Concerta, Quillivant XR, Daytrana
Mixed amphetamine salts • Adderall, Adderall XR

Clinical Point

Monitor refill requests and patient behavior for signs of psychostimulant misuse; be alert for illegal drug use in family members

methylphenidate are the formulations least likely to be misused because their delivery systems make it difficult to extract the active ingredient for snorting or intravenous injection.

- Psychostimulants have not been shown to exacerbate tics in *most* children who have comorbid ADHD and a tic disorder. When a stimulant is associated with an exacerbation of tics, switching treatment to atomoxetine or α_2 agonists is reasonable.
- For patients whose use of a stimulant is limited by an adverse effect on sleep, consider atomoxetine and α_2 adrenergic agonists as alternative or adjunctive treatments.
- All 3 classes of FDA-approved ADHD medications (psychostimulants, atomoxetine, and adrenergic agonists) have been associated with adverse cardiac events in children who have underlying cardiovascular conditions. Before initiating treatment, screen patients for a personal or family history of cardiovascular risk factors, and undertake further evaluation as indicated.

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Bottom Line

In general, the evidence supports psychostimulants as initial pharmacotherapy for ADHD, with additional options including atomoxetine and α_2 agonists. When one medication class does not provide adequate coverage for ADHD symptoms, combining medication classes can be beneficial.

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