# AMPHETAMINE-D

## Therapeutics

**Brands**
- Dexedrine Spansule
- Zenzedi
- ProCentra

**Generic?** Yes

### Class and Mechanism of Action

- Neuroscience-based nomenclature: dopamine, norepinephrine reuptake inhibitor and releaser (DN-RIRe)
- Stimulant
- Increases norepinephrine and especially dopamine actions by blocking their reuptake and facilitating their release
- Enhancement of dopamine and norepinephrine actions in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive dysfunction, wakefulness, and cortical inhibitory control of striatum (i.e., theoretically "tunes" inefficient information processing in cortical–striatal pathways, improving "top-down" regulation of striatal and other subcortical drives)
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may decrease hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depressive symptoms as well as nondepression-associated fatigue and sleepiness
- Hypothetically rebalances signal-to-noise ratios of cortical neurons: enhances focus on important tasks (signal), theoretically due to norepinephrine, and reduces awareness of background activity (noise), theoretically due to dopamine

### US FDA Approved for Pediatric Use

- Attention deficit hyperactivity disorder (Zenzedi, ages 3 to 16)
- Attention deficit hyperactivity disorder (ProCentra, ages 3 to 16)
- Attention deficit hyperactivity disorder (Dexedrine Spansule, ages 6 to 16)
- Narcolepsy (Zenzedi, ages 6 and older)
- Narcolepsy (ProCentra, ages 6 and older)
- Narcolepsy (Dexedrine Spansule, ages 6 and older)

### Off-Label for Pediatric Use (i.e., clinically established uses that are not specifically studied to obtain FDA approval)

- Approved in adults
  - None
- Other off-label uses:
  - Treatment-resistant depression (rarely used for this in children)
  - Stimulants are sometimes used to augment antidepressants
  - Stimulants also sometimes used to treat amotivational or lethargic states in the elderly with dementia but rarely in children for these symptoms

### Tests

- Before treatment, assess for presence of cardiac disease (history, family history, physical exam); consider whether an electrocardiogram (ECG) is indicated
- Blood pressure should be monitored regularly, sitting and standing
- Monitor weight and height
- Current recommendations from the American Heart Association (AHA) are that it is reasonable but not mandatory to obtain an ECG prior to prescribing a stimulant to a child; the American Academy of Pediatrics (AAP) does not recommend an ECG prior to starting a stimulant for most children
- Document basic sleep patterns prior to starting a stimulant
- When necessary to rule out suspicions for sleep apnea, nocturnal movements, or daytime sleepiness that may later be difficult to distinguish from side effects of stimulants, consider (rarely) a sleep study/polysomnogram (e.g., obese adolescents)

### What to Tell Parents About Efficacy

- Stimulant treatment for ADHD is one of the best studied of all medications in children and adolescents
- While the medicine helps ADHD by reducing symptoms and improving function, there are no cures for ADHD and it is therefore necessary to keep taking the medication to sustain its therapeutic effects
- It does not work that day if the child/adolescent has not taken their medication in the morning
- For longer-acting stimulants, be careful not to give too late (i.e., after 8 am) because it can cause insomnia that night
- Does not stay in the body for a long time, so it stops working rapidly after you stop it
- Because every treatment consideration depends on a risk/benefit analysis, parents should fully understand short- and long-term risks as well as benefits compared to nontreatment of ADHD
- Although many stimulants are approved for ADHD, if using off-label, it is often a good idea to tell parents whether the medication chosen is specifically approved for the disorder being treated, or whether it is being given for "unapproved" or "off-label" reasons based on good clinical practice, expert consensus, and/or prudent extrapolation of controlled data from adults
- Best results are often obtained when medications are combined with behavioral therapy
- Stimulants wear off after a number of hours and symptoms may return. Therefore, parents may complain that the medication isn't working if their child/adolescent is using a stimulant that lasts 8 hours, because it may have worn off after the patient has come home from school (and that is when the parents are seeing the child/adolescent) in comparison to a stimulant that lasts 10–12 hours and may keep working after the child/adolescent comes home from school
- AACAP (American Academy of Child and Adolescent Psychiatry) has helpful handouts for parents

### What to Tell Children and Adolescents About Efficacy

- Be specific about the symptoms being targeted: we are trying to help you remember things better, do your best at school, follow the rules, get into less trouble (as applicable)
- It may be a good idea to give the medication a try; if it's not working very well, we can stop the medication and try something else
- You can be part of a special plan to help us figure out if the medicine is helpful for you. Would you like to do that? (For the parents and prescriber, can consider here a trial both on and then off medication, and then on again to see if the effects are clear and thus worth continuing the medication)
- The medication can work right away, but a good try can take a few months to find the right dose
- Even if it does make you feel better, it will wear off and no longer work shortly after you stop it
- This medicine does not last very long in your body, so even if it does work, it won't work if you don't take it that day
- The medication can help you decide what you want to do, like making good choices versus bad choices; the medicine does not make you do something you don't want to do
- Medications don't change who you are as a person; they give you the opportunity to be the best person you can be

### What to Tell Teachers About the Medication (If Parents Consent)

- Stimulants can be very helpful in improving the symptoms of ADHD:

namely, inattention, impulsivity, and hyperactivity
- Some students will experience side effects from the medications that you may notice in or outside the classroom; many of these side effects can be modified
- It does not work if the child/adolescent has not taken their medication that morning
- If the patient is sleepy, ask whether the medication is keeping them up at night or if they are eating enough food
- If the patient won't eat lunch or snacks, ask whether the medication is making them lose their appetite
- This medication can be misused by others who don't have ADHD for its alertness effects and its positive impact on sustaining attention, so be aware of any medication brought into the classroom
- Medically speaking, amphetamine is not a narcotic because doctors define narcotics as something that is sedating and sleep-inducing like opioids such as heroin and Oxycontin and not stimulants like amphetamine
- Amphetamine should be kept in school under lock and key or at the nurse's office or not brought to school at all because it can be diverted and misused by those who do not have ADHD. Some schools will suspend students who are caught with medications on their person or in their backpacks; most schools know the misuse or even abuse potential of stimulants

## Safety and Tolerability

### Notable Side Effects (i.e., those that are most frequent or bothersome)

- Insomnia, headache, exacerbation of tics, nervousness, irritability, overstimulation, tremor, dizziness
- Anorexia, nausea, dry mouth, constipation, diarrhea, weight loss
- Sexual dysfunction long term (impotence, libido changes) but can also improve sexual dysfunction short-term

### Life-Threatening or Dangerous Side Effects (usually rare but important if they ever occur)

- Psychotic episodes, especially with parenteral abuse
- Seizures
- Palpitations, tachycardia, hypertension
- Rare activation of hypomania, mania, or suicidal ideation (in fact, stimulants have been used successfully in the treatment of manic episodes)
- Cardiovascular adverse effects, sudden death in patients with pre-existing cardiac structural abnormalities often associated with a family history of cardiac disease

### Growth and Maturation

- May temporarily slow normal growth in children (controversial): Multimodal Treatment Study of ADHD study showed children/adolescents grew more slowly but eventually reached their expected adult height
- Controversy exists because theoretically stimulants might suppress appetite and reduce caloric intake, which could affect potential growth; also, dopaminergic actions of stimulants might suppress growth hormone secretion and affect height development. However, expected adult height is likely attained with a delay if stimulants are continued, and slowing of growth is likely reversible with withdrawal of treatment


### Weight Gain

- Patients may experience weight loss
- Weight gain is reported but not expected, rarely seen, controversial


### Sedation

- Activation much more common than sedation
- Sedation is reported but not expected, rarely seen, controversial

### What to Do About Side Effects

- Wait, wait, wait: mild side effects are common, happen early, and usually improve with time, but treatment benefits can be delayed, and often begin just as the side effects wear off
- Adjust dose
- Switch to a long-acting stimulant
- Switch to another agent
- For insomnia: avoid dosing in the midday, late afternoon, or evening
- However, insomnia is not always due to medication, but can be the result of relapse, rebound, and withdrawal effects from the daily dose, and in fact improves with additional late-day dosing of a short-acting stimulant
- Beta blockers for peripheral autonomic side effects
- Often best to try another monotherapy prior to resorting to augmentation strategies to treat side effects, with the exception of an early-evening dose of a stimulant
- Monitor side effects closely
- For persistent insomnia: consider adding melatonin, mirtazapine, or an alpha 2 agonist, but only if not responsive to an early-evening dose of a stimulant
- For loss of appetite or loss of weight:
  1. Give medication after breakfast
  2. Switch to a nonstimulant
  3. Eat a high-protein, high-carbohydrate breakfast prior to taking medication or within 10–15 minutes of ingesting medication; snack on high-protein, densely caloric foods throughout the school day and after school; eat dinner and then a second dinner or very heavy snack at bedtime
  4. Add "liquid calories" (i.e., smoothies made with whole milk or ice cream, fruit, and protein powder; Boost or Ensure shakes)
  5. Add cyproheptadine or mirtazapine

### What to Say to Parents About Side Effects

- Explain that side effects are expected in many when starting
- Tell parents many side effects of stimulants often go away in a few days to weeks, especially nausea and insomnia, but if they don't we will change the treatment
- Predict side effects in advance (you will look clever and competent to the parents, unless you scare them with too much information and cause nocebo effects, in which case you won't look so clever when the patient develops lots of side effects and stops medication; use your judgment here); a balanced but honest presentation is an art rather than a science
- Sometimes a trial off-medication and then on again can clarify what the true therapeutic effects of the medication are
- Ask parents to support the patient while side effects are occurring
- Parents should fully understand short- and long-term risks as well as benefits
- Explaining to the parents what to expect from medication treatment, and especially potential side effects, can help prevent early termination

### What to Say to Children and Adolescents About Side Effects

- When a medicine starts to work, your body can first experience this by giving you unpleasant sensations – just like if you take a cough medicine it may taste bad – these body sensations include loss of appetite and problems sleeping. So, just like with a cough medicine, the bad taste will often go away before the medicine begins to stop the cough – many medicines work like that. It's important for you to pay attention to what your body is telling you, and we'll go over some of the ways that can happen

- Even if you get a side effect it's not permanent (it won't last forever)
- Explaining to the child/adolescent what to expect from medication treatment, and especially potential side effects, can help prevent early termination

### How Drug Causes Side Effects

- Increases in norepinephrine peripherally can cause autonomic side effects, including tremor, tachycardia, hypertension, and cardiac arrhythmias
- Increases in norepinephrine and dopamine centrally can cause CNS side effects such as insomnia, agitation, psychosis (rarely)

### Warnings and Precautions

- In children and adolescents:
  - Safety and efficacy not established in children under age 3
  - Use in young children should be reserved for the expert
  - Children who are not growing or gaining weight should stop treatment, at least temporarily
  - Usual dosing has been associated with sudden death in children with structural cardiac abnormalities
  - Consider distributing brochures provided by the FDA and the drug companies
- All ages:
  - Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nonpharmacologic treatment; it is a good idea to document this in the patient's chart
  - Use with caution in patients with any degree of hypertension, hyperthyroidism, or history of drug abuse
  - May worsen motor and phonic tics (controversial because most research not only suggests this is rare but also shows that the presence of tics is not an absolute contraindication to use of stimulants)
  - May worsen symptoms of thought disorder and behavioral disturbance in psychotic patients
  - Stimulants have a high potential for abuse and must be used with caution in anyone with a current or past history of substance abuse or alcoholism or in emotionally unstable patients, but stimulants for ADHD are less likely to be abused in terms of getting "high" and more likely to be used to stay awake, especially by college students and long-distance drivers. This misuse is the most common reason for diversion of prescription stimulants
  - Youths are neither more nor less likely to develop alcohol and substance use disorders as a result of being treated with stimulant medication
  - Adolescents and/or college students may divert/sell their medication to others for use in staying awake to study at the last minute, or to abuse; longer-acting preparations are harder to abuse than shorter-acting, immediate-release stimulants
  - Particular attention should be paid to the possibility of adolescents you are seeing for the first time feigning ADHD in order to obtain stimulants for nontherapeutic use or distribution to others; the drugs should in general be prescribed sparingly with documentation of appropriate use, and if there is any doubt about the accuracy of their complaints, refer them for psychological-educational or neuropsychological testing
  - Consider limiting the number of pills dispensed when initiating treatment, especially for patients who are not well known to you, until it is clear the patient is not escalating the dose themselves or abusing or diverting
  - Not an appropriate first-line treatment for depression or for normal fatigue
  - May lower the seizure threshold; as long as seizures are well controlled, it is generally safe to use stimulants

- Emergence or worsening of activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of a mood stabilizer and/or discontinuation of D-amphetamine

### Contraindications

- If patient has extreme anxiety or agitation
- Treating ADHD comorbid with tics or Tourette syndrome is not contraindicated, but may be for the expert
- Patients with ADHD who are comorbid for motor or vocal tics of Tourette syndrome, or even with just a family history of Tourette syndrome, may experience worsening/onset of tics with stimulant treatment (controversial). Decision to use stimulants in such cases should weigh the potential benefits for ADHD against the risks of worsening tics, and may require expert referral or consultation
- Should generally not be administered with an MAOI, including within 14 days of MAOI use, except in heroic circumstances and by an expert
- If patient has arteriosclerosis, cardiovascular disease, or severe hypertension
- If patient has glaucoma
- If patient has structural cardiac abnormalities
- If there is a proven allergy to any sympathomimetic agent
- If the patient has an eating disorder other than binge-eating disorder, be very cautious

### Long-Term Use

- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Tolerance to therapeutic effects may develop in some patients
- Weight and height should be monitored during long-term treatment
- Periodic monitoring of weight, blood pressure

### Habit Forming

- Paradoxically, stimulant abuse appears to be less likely in patients with ADHD than in those who do not have ADHD
- Stimulant abuse in ADHD patients more likely if there is a pre-existing history of alcohol/drug abuse
- Tolerance to stimulants is surprisingly rare in ADHD; tolerance should not be confused with reduction of therapeutic effects over time due to growth: as youth grow larger and as BMI increases, dose usually must be increased; otherwise, the appearance of tolerance occurs when this in reality is underdosing
- Misuse may be more likely with immediate-release stimulants than with controlled-release stimulants

### Overdose

- Rarely fatal; panic, hyperreflexia, rhabdomyolysis, rapid respiration, confusion, coma, hallucination, convulsion, arrhythmia, change in blood pressure, circulatory collapse

## Dosing and Use

### Usual Dosage Range

- All ages:
  - ADHD: 5–40 mg/day
  - Narcolepsy: 5–60 mg/day

### Dosage Forms

- Zenzedi (immediate-release tablet) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg
- Dexedrine Spansule (extended-release capsule) 5 mg, 10 mg, 15 mg
- ProCentra (immediate-release oral solution) 5 mg/5 ml

### How to Dose

- In ADHD:

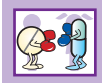
  - Ages 3–5: initial 2.5 mg/day; can increase by 2.5 mg each week; administered in divided doses (first dose on waking, additional dose(s) at intervals of 4–6 hours)
  - Ages 6 and older: initial 5 mg once or twice daily; can increase by 5 mg each week; administered in divided doses (first dose on waking, additional dose(s) at intervals of 4–6 hours)
- In narcolepsy:
  - Ages 6–12: initial 5 mg/day; can increase by 5 mg each week; administered in divided doses (all formulations; first dose on waking, additional dose(s) at intervals of 4–6 hours) or once a day (extended-release only)
  - Ages 12 and older: initial 10 mg/day; can increase by 10 mg each week; administered in divided doses (all formulations; first dose on waking, additional dose(s) at intervals of 4–6 hours) or once a day (extended-release only)

### Options for Administration

- Liquid formulation can be beneficial for patients with difficulty swallowing pills
- Extended-release capsule may have sufficient duration of action to eliminate the need for lunchtime dosing in many but not all patients

### Pharmacokinetics

- Half-life approximately 10–12 hours
- Clinical duration of action often differs from pharmacokinetic half-life and can be longer for any formulation
- Substrate for CYP450 2D6
- Taking with food may delay peak actions for 2–3 hours



### Drug Interactions

- May affect blood pressure and should be used cautiously with agents used to control blood pressure
- Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid, ascorbic acid, fruit juices, etc.) and urinary acidifying agents (ammonium chloride, sodium phosphate, etc.) lower amphetamine plasma levels, so such agents can be useful to administer after an overdose but may also lower therapeutic efficacy of amphetamines
- Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) and urinary alkalinizing agents (acetazolamide, some thiazides) increase amphetamine plasma levels and potentiate amphetamine's actions
- Desipramine and protryptiline can cause striking and sustained increases in brain concentrations of D-amphetamine and may also add to D-amphetamine's cardiovascular effects
- Theoretically, other agents with norepinephrine reuptake blocking properties, such as venlafaxine, duloxetine, atomoxetine, milnacipran, and reboxetine, could also add to amphetamine's CNS and cardiovascular effects
- Amphetamines may counteract the sedative effects of antihistamines
- Haloperidol, chlorpromazine, and lithium may inhibit stimulatory effects of amphetamines
- Theoretically, atypical antipsychotics should also inhibit stimulatory effects of amphetamines
- Theoretically, amphetamines could inhibit the antipsychotic actions of antipsychotics
- Theoretically, amphetamines could inhibit the mood-stabilizing actions of atypical antipsychotics in some patients; however, stimulants can be safely combined with atypical antipsychotics by experts
- Combinations of amphetamines with mood stabilizers (lithium, anticonvulsants, atypical antipsychotics) is generally something for experts only, when monitoring patients closely and when other options fail
- Absorption of phenobarbital, phenytoin, and ethosuximide is delayed by amphetamines

- Amphetamines inhibit adrenergic blockers and enhance adrenergic effects of norepinephrine
- Amphetamines may antagonize hypotensive effects of veratrum alkaloids and other antihypertensives
- Amphetamines increase the analgesic effects of meperidine
- Amphetamines contribute to excessive CNS stimulation if used with large doses of propoxyphene
- Amphetamines can raise plasma corticosteroid levels
- MAOIs slow metabolism of amphetamines and thus potentiate their actions, which can cause headache, hypertension, and rarely hypertensive crisis and malignant hyperthermia, sometimes with fatal results
- Use with MAOIs, including within 14 days of MAOI use, is not advised, but this can sometimes be considered by experts who monitor depressed patients closely when other treatment options for depression fail

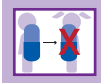
### Dosing Tips

- In children and adolescents:
  - Plasma levels are higher in lower-weight children; therefore, starting and target doses may be lower and longer intervals between dose increases may be needed (see How to Dose)
  - If losing efficacy between daily doses, it may indicate rapid metabolism and the need to increase the dose or give every 2–4 hours, or to switch to a long-acting sustained-release formulation
  - The extended-release formulation can eliminate the hassle and pragmatic difficulties of lunchtime dosing at school, including storage problems, potential diversion, and the need for a medical professional to supervise dosing away from home
  - If there are concerns about diversion or abuse, longer-acting stimulant preparations are much harder to abuse than immediate-release preparations
  - Adolescents often receive adult doses
  - Be aware that metabolism changes during puberty and entry into adolescence and becomes more like adults (i.e., slower than in children)
  - If a child on a stable dose begins to lose tolerability with more side effects upon entering adolescence, this may signal the need for a dose reduction due to changing metabolism
- Tips about drug holidays (drug holidays are controversial)
  - Drug holidays were originally done in an attempt to avoid the possibility that stimulants may blunt height
  - May be able to give drug holidays over the summer in order to reassess therapeutic utility and effects on growth and theoretically to allow catch-up from any growth suppression and assess any other side effects and the need to reinstitute stimulant treatment for the next school term. However, most studies show that parental height is what determines a patient's final height, and that most children/adolescents taking stimulants reach their expected height, just more slowly than children/adolescents not exposed to stimulants
  - May be possible to give weekend drug holidays and dose only during the school week for some ADHD patients, but there are risks as well
  - Hyperactivity and impulsivity increase the chances of accidents (i.e., broken bones and head injuries) and illicit alcohol and drug abuse
  - Studies have shown that adolescents with ADHD who drive vehicles without their stimulants are much more likely to get into motor vehicle accidents and that the severity of the accident is much greater than would be expected
  - Hyperactive and impulsive children/adolescents tend to have more

difficulties getting along with family members and friends, increasing the chances of developing low self-esteem and poor self-image
    - Social benefits can be lost over the summer if children/adolescents are taken off stimulants; social rejection by other children can lead to isolation and depression, increasing the chances of bullying, victimization, and further isolation and peer rejection
    - Inattention makes it harder for kids to learn the rules of life and pay attention to what is going on around them (e.g., noticing when a peer is not being a true friend, when someone is starting to get annoyed, when a car is coming towards you and you're in the middle of the street)
- All ages:
    - Immediate-release dextroamphetamine has a 4–6-hour duration of clinical action
    - Extended-release dextroamphetamine has up to an 8-hour duration of clinical action
    - Tablets contain tartrazine, which may cause allergic reactions, particularly in patients allergic to aspirin
    - Dexedrine Spansule is controlled-release and therefore should not be chewed but rather should only be swallowed whole
    - Avoid dosing late in the day because of the risk of insomnia
    - Off-label uses are dosed the same as for ADHD
    - Side effects are generally dose-related

### How to Switch

- From one stimulant to another or from one formulation to one with a different duration of action:
    - When switching from one stimulant to another, the first one can be abruptly stopped and the new one started the next morning
    - Side effects from abrupt discontinuation are not expected; however, some patients may experience marked fatigue and sleepiness for several days
- If urgent, can usually cross-taper from a stimulant to a nonstimulant, or vice versa, by decreasing the first medication perhaps by a quarter to half, and starting the new medication at a low dose



### How to Stop

- Taper not necessary, especially for patients who have only had short-term treatment or intermittent treatment
- However, if withdrawal symptoms develop, resume dosing the medication and then taper slowly over several days
- Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstitution of treatment
- Return of symptoms of the underlying disorder after discontinuing treatment may sometimes be confused with symptoms due to drug withdrawal
- Usually symptoms after discontinuation are return of symptoms of the underlying disorder rather than symptoms due to drug withdrawal
- Supervision during withdrawal is always recommended for any psychotropic medication
- Discontinuation of stimulants from abusive use must be especially closely supervised because severe depression may occur

### When Not to Prescribe

- When on contraindicated drugs
- When behavioral therapy and organizational skills can be sufficiently effective

## What to Expect

### Onset of Action

- Some immediate effects can be seen with first dosing
- Takes a few days to attain therapeutic benefit but may take weeks to find optimal dose

### Duration of Action

- Medication must be taken daily to maintain therapeutic effects
- Immediate-release tablet: 4–5-hour duration
- Immediate-release solution: 4–6-hour duration
- Extended-release capsule: 6–8-hour duration

### Primary Target Symptoms

- Concentration, attention span, distractibility
- Motor hyperactivity
- Impulsiveness
- Physical and mental fatigue
- Daytime sleepiness
- Depression

### What Is Considered a Positive Result?

- The goal of treatment of ADHD is reduction of symptoms of inattentiveness, motor hyperactivity, and/or impulsiveness that disrupt social, school, and/or occupational functioning
- Can also improve oppositional and disruptive behaviors associated with ADHD
- The goal of treatment is complete remission of current symptoms
- If treatment works, it most often reduces or even eliminates symptoms, but is not a cure because symptoms often recur after medicine is stopped

### How Long to Treat

- ADHD is typically a lifelong illness; if any symptoms improve, hyperactivity is more likely to improve than inattention
- Can tell parents there is some chance that your child can grow out of this in adulthood, but many adults continue to have symptoms of ADHD throughout adolescence and adulthood
- Continue treatment until all symptoms are under control or improvement is stable and then continue treatment as long as improvement persists
- Re-evaluate the need for treatment periodically; some clinicians advise to periodically taper stimulants in patients who are not severely symptomatic to observe how the patient responds, but this is not routinely done by most clinicians
- Treatment for ADHD begun in childhood may need to be continued into adolescence and adulthood if continued benefit is documented

### What If It Stops Working?

- Some patients who have an initial response may relapse even though they continue treatment, sometimes called "poop-out"
- Growth/developmental changes may contribute to apparent loss of efficacy as well as to new onset of side effects as metabolism slows and drug levels rise in transition from childhood to adolescence; dose adjustment (increase or decrease) should be considered
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying or newly evolved bipolar disorder, major depressive episodes with mixed features of mania, new onset of major depression or an anxiety disorder (GAD, OCD, PD), and require stimulant discontinuation and a switch to the clinically appropriate medication(s)