Resources Advancing Mental Health in Pediatrics

RAMP

Mental Health Care in the Pediatric Clinic

ADHD, Part 3

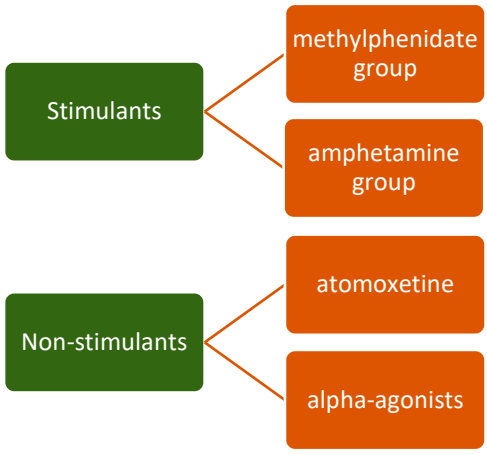
Objectives

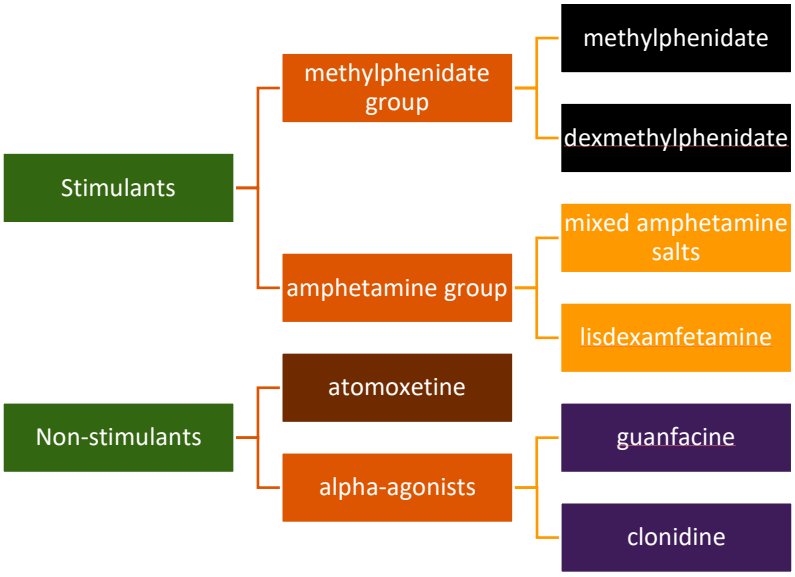
List the commonly-used non-stimulant medications for ADHD.
Describe treatment strategies for ADHD.
Recognize conditions comorbid with ADHD.

Adela

You see Adela back in 3 months after the last visit. She has been taking the methylphenidate ER 27 mg, and has good control of her inattentive symptoms. However, she hates it that she can't eat lunch. Her BMI has dropped from 19th to 17.4th percentile. She has delayed sleep onset, up to 90 minutes, even with good sleep hygiene. She is still mildly anxious in social settings.
You suggest changing to a shorter-acting stimulant to see if that helps with sleep onset, but Adela and her parents don't want to try another stimulant. They ask if there are other options.

Here is a brief reminder of the taxonomy of ADHD medications. We have stimulants and non-stimulants. Non-stimulants include 2 separate classes of medication: atomoxetine, and the alpha-agonists. Other non-stimulant medications are sometimes used, including bupropion and in the past, tricyclic antidepressants, but we will not cover those here.





Here is the same taxonomy with specific medications included. Atomoxetine is in its own group, and the alpha agonists include guanfacine and clonidine, both in their short-acting and extended release forms.

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Atomoxetine

Potent selective inhibitor of presynaptic NE transporter – increases norepinephrine at synapse

- Minimal affinity for other receptors or transporters
- Increases dopamine in prefrontal cortex but not elsewhere
- Effective once a day, despite plasma half-life of 4 hours
- Give with food, breakfast or dinner, divide BID if side effects
- Start with 0.5 mg/kg/day for 5-7 days
- Increase to initial target dose 1.2 mg/kg/day
- Maximum 1.8 mg/kg/day
- Safe to combine with stimulants, if necessary
- No QTc prolongation
- Cytochrome p450 metabolism by 2D6
- Supplied in 10, 18, 25, 40, 60, 80 and 100 mg capsules

Atomoxetine is dosed once a day, and the target dose is based on weight rather than on efficacy, as with the stimulants. You start at a little less than half the target dose and increase weekly until reaching the target dose. The slow titration is to minimize unpleasant GI side effects. Once at the target dose, it takes 3 weeks or so to achieve full efficacy.

Atomoxetine Side Effects: Common

- Decreased appetite, weight loss
- Nausea, vomiting – usually resolves with time
- Dizziness
- Tiredness, sedation
- Slight increase in pulse and BP

Less common side effects include:

- Irritability
- Manic activation (if patient has bipolar disorder comorbid with ADHD)
- Instruct parents not to open the capsules: contents can be caustic, especially to the eyes.

Not observed, or rarely observed:

- Withdrawal symptoms have not been reported
- Atomoxetine does not generally worsen tics.
- No reported deaths due to overdose with atomoxetine alone.
- Incidence of aggression or suicidal ideation not different from placebo

Atomoxetine vs Stimulants

Atomoxetine mean effect size 0.6 to 0.7
Stimulant mean effect size 0.8 to 0.9
In head-to-head trials, atomoxetine less effective than

- Mixed amphetamine salts XR
- Methylphenidate
- Methylphenidate ER

Over 40% of nonresponders to methylphenidate ER responded to atomoxetine and vice versa (Newcorn et al. 2008)

Comparing atomoxetine to stimulants as a class, we see that the mean effect size of atomoxetine is inferior to that of stimulants. However, some patients will respond better to atomoxetine than they will to a stimulant. At this point, this response difference is still not predictable for an individual patient.

Alpha agonists: guanfacine and clonidine

Alpha agonists have been used for years in children in their short-acting forms, mostly for hyperactive or disruptive behavior in younger children.
Utility has been limited by sedating effect and limited duration of action per dose (about 4 hours).
An extended release form of each medication, FDA approved for ADHD in children, was marketed:

guanfacine ER in 2009
clonidine ER in 2010

Alpha agonists: extended release guanfacine and clonidine

- Can cause sedation, somnolence and fatigue which may decrease over time.
- All can lower blood pressure. They should be tapered off to avoid rebound hypertension (guanfacine products by 1 mg and clonidine products by 0.1 mg every 3-7 days).
- Takes 2-4 weeks for full effect.
- Once effective provides 24 hour coverage.
- Tablets must be swallowed whole for sustained release.

Alpha agonists: dosing extended release guanfacine and clonidine

guanfacine ER :

1 mg daily increasing by 1 mg/week to max 0.12 mg/kg/day or 4 mg/day (6-12 years) or 7 mg/day (13-17 years)
Originally maximum dose was 4 mg day but doses up to 7 mg in adolescents are tolerated and effective.

clonidine ER

Start with 0.1 mg q bedtime, increase by 0.1 mg/week to max of 0.2 mg bid
Must be given bid for 24 hr effect.

Above is dosing information for guanfacine ER and for clonidine ER. It looks complicated, but you start with a unit dose (1 mg guanfacine ER and 0.1 mg of clonidine ER) and increase weekly until effective. The maximum dose for both medications initially was 4 unit doses per day. That means guanfacine ER 4 mg daily, and clonidine ER 0.2 mg bid. Clonidine ER has to be given bid. Recent clinical trials indicate that guanfacine ER can safely and effectively be given up to 7 mg daily in adolescents. You have to dose this with 2 pills given once daily, that is, with a 4 mg and a 3 mg pill prescribed concurrently.

Alpha agonists: short acting guanfacine and clonidine

Effective for inattention, hyperactivity, impulsivity and tics. Daytime use limited by sedative effect. Nighttime dose helps with sleep onset, may be higher than daytime doses.

guanfacine <45 kg: 0.5 mg nightly, titrate in 0.5 mg increments TID to max dose 2 mg (27-40.5 kg) or 3 mg (40.5-45 kg). >45 kg: 1 mg nightly, titrate in 0.5 mg increments TID to max dose 4 mg/day.

clonidine <45 kg: 0.05 mg nightly, titrate in 0.05 mg increments QID to max dose 0.2 mg (27-40.5 kg) or 0.3 mg (40.5-45 kg). >45 kg: 0.1 mg nightly, titrate in 0.05 mg increments QID to max dose 0.4 mg/day.

Sometimes we still use short acting alpha agonists to control ADHD symptoms. This may occur if a child cannot swallow the extended release form, or if you want to target a specific time of the day, or if insurance won't cover the extended release form. The short acting forms are generally dosed morning, noon, and after school. An evening dose does not address ADHD symptoms but may help with sleep onset.

Non-stimulants: When might they be first choice?

- Family refuses stimulants
- Pre-existing
  - Severe ADHD symptoms in the mornings
  - Insomnia
  - Low weight or picky eater
  - Anxiety
- Adolescent or college student who might share/sell stimulant

Non-stimulants: when might you use them as augmentation?

- When you have partial response to a stimulant but can't get to full symptom response.
- When you cannot get to full dosing on stimulants due to side effects
- When the child has severe early morning or evening ADHD symptoms
- When the child has comorbid tics-consider alpha-agonist
- When the child has comorbid anxiety – consider atomoxetine

Adela

Because Adela has mild anxiety, you offer atomoxetine.

Adela weighs 32 kg
Her initial target dose is: 38.4 mg
The closest dose of atomoxetine is: 40 mg
You write a prescription for
atomoxetine 10 mg 1 po daily for 5 days, then 2 daily for 5 days, then 3 daily for 5 days # 30,
and another for atomoxetine 40 mg po daily to start after the titration.

The recommended starting dose of 0.5 mg/kg/day would be 16 mg. You could either go low, at 10 mg/day or high, at 18 mg/day.
Because Adela has a sensitive stomach, you go low.

You see Adela back in 5 weeks.
She is tolerating the atomoxetine well, after a few days of upset stomach. She is pleased with her focus.
Vanderbilt rating scales:
Parent: inattention: 8 hyperactivity: 6
Teacher: inattention: 9 hyperactivity: 7

A year later, in October of 5th grade, *Adela says that it is harder for her to focus and she is missing instructions in class.*
She now weighs 39.8 kg.
The next capsule size of atomoxetine is 60 mg, which would be 1.51 mg/kg/day.
Atomoxetine's maximum recommended dose is 1.8 mg/kg/day.
You increase Adela's dose to 60 mg daily and her symptom control improves.

Let's meet another patient, Franklin, who will illustrate the role of non-stimulant augmentation of a stimulant.

Franklin

Franklin, aged 11 years, is new to your practice. He was diagnosed with ADHD in first grade and has taken essentially all of the stimulant medications with moderate benefit. He has taken methylphenidate ER, mixed amphetamine salts, and lisdexamfetamine, and he and his mother feel that the current medication, dexmethylphenidate XR 25 mg with

additional dexmethylphenidate immediate-release 10 mg at 4 pm is the best he has taken in terms of side effects and symptom control.
However, mornings and evenings are rough.
Franklin requires constant reminders to complete his daily routines and he gets irritated with what feels like nagging. He has difficulty with friendships because he is impulsive, gets into other people's space, and talks excessively about things of interest to him, without waiting to hear from others.
Vanderbilt rating scales:
Parent: inattention: 13 hyperactivity: 22
Teacher: inattention: 19 hyperactivity: 17

Here is a reminder of the **age and gender specific norms for ADHD rating scales**, totaling the first and second 9 questions on the Vanderbilt which reflect levels of inattentive and hyperactive symptoms, respectively. Eleven year-old Franklin's scores are all over the top average range.

Top, average range	**Parent**			**Teacher**		
Boys	**Total score**	**Inattention**	**Hyperactivity**	**Total score**	**Inattention**	**Hyperactivity**
5-7 year old boys	22.51	11.02	12.15	31.48	16.41	15.98
8-10 year old boys	21.99	11.98	10.78	34.27	18.82	16.48
11-13 year old boys	22.82	12.97	10.33	28.83	17.44	12.68
14-18 year old boys	18.34	11.06	8	24.78	15.52	10.46
Girls						
5-7 year old girls	17.68	8.96	9.53	25.86	13.85	12.93
8-10 year old girls	15.07	8.53	7.18	22.49	13.33	9.96
11-13 year old girls	15.33	9.73	6.36	21.01	12.73	9.23
14-18 year old girls	15.1	8.64	7.11	14	9.35	5.37

Table courtesy of John Lavigne, PhD

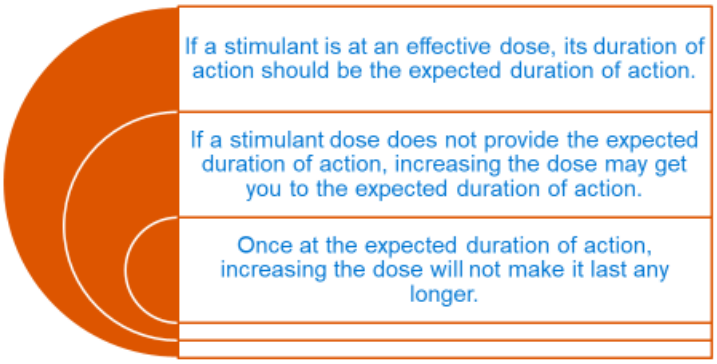
Franklin and his mother feel that the dexmethylphenidate has provided the best symptom control with least side effects of any stimulants tried, so you opt to increase the dose of dexmethylphenidate XR to 30 mg to see if you can reduce his symptoms further.

Franklin's mother calls 5 days later to say that on the increased dose of dexmethylphenidate XR 30 mg, Franklin feels tired and has headaches. His focus is no better, and the mornings and evenings are not improved. What next?

Medication	Expected duration of action
methylphenidate immediate release (IR)	4 hours
methylphenidate CD	6-8 hours
methylphenidate ER	10-12 hours
methylphenidate HCl XR oral suspension	10-12 hours
dexmethylphenidate IR	4 hours
dexmethylphenidate XR	6-8 hours
mixed amphetamine salts IR	4-6 hours
mixed amphetamine salts-extended release	10-12 hours
lisdexamfetamine	12 hours

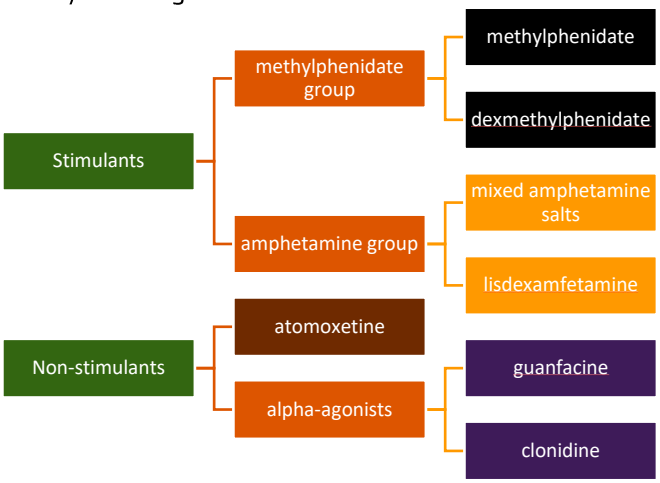
Above is a review of the expected duration of action of several commonly prescribed stimulants from both classes- the methylphenidate class and the amphetamine class. For most children, symptom coverage through the school day and into the late afternoon is sufficient. Some children, however, have marked rebound symptoms when the medication wears off in the evening, or wake up with such high levels of dysregulation that mornings are chaotic and stressful.

Stimulant dose and duration of action



Here are a few reminders regarding the relationship between stimulant dose and the duration of action. A caveat is that there are some children who won't get the expected duration of action at any dose. These patients will generally do best with a short-acting medication dosed three times daily.

Here is a review of your treatment options. You have stimulants and non-stimulants. Non-stimulants can be given alone, or they can augment a stimulant.



Franklin

Increasing the dexmethylphenidate XR did nothing to address the problematic periods of Franklin's day, and he does not tolerate the higher dose.

It's time to consider augmentation with a non-stimulant. You discuss the benefits, risks, and side effects, and recommend starting guanfacine ER with an initial target dose of 3 mg.

You drop the dexmethylphenidate XR back to 25 mg and keep the after school dose of dexmethylphenidate IR 10 mg.

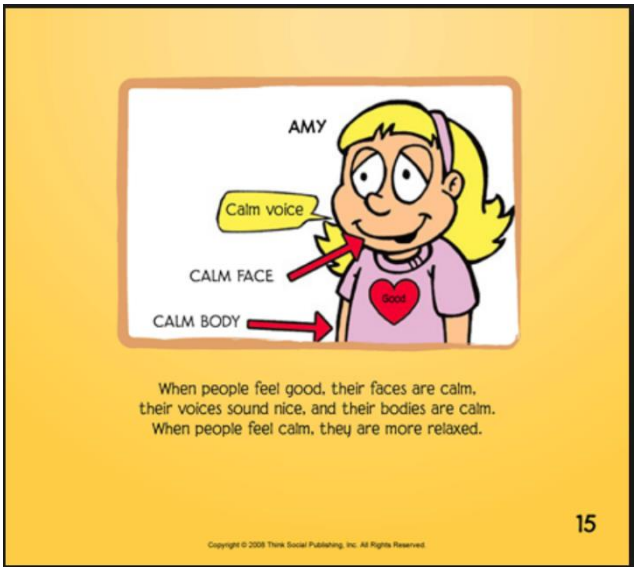
You prescribe guanfacine ER 1mg daily for a week, guanfacine ER 2 mg daily for 1 week, and then guanfacine ER 3 mg daily for a month.

The main side effect is sedation, which is why you are going up slowly.

The tablet has to be swallowed whole for the extended-release function to work.
Guanfacine ER can be taken in the morning or evening, whichever is associated with less daytime sedation.
Guanfacine ER has to be taken every day to be effective.

Franklin comes back in 4 weeks.
He is tolerating the guanfacine ER 3 mg without sedation or other side effects.
He is more focused and capable of following through on activities and instructions early and late in the day.
Vanderbilt scales:
Parent: inattention: 8 hyperactivity: 12
Teacher: inattention: 10 hyperactivity: 12

Franklin still has difficulties with social interactions and fitting in with other kids. This is related to his ADHD, but not among the core ADHD symptoms, and will not resolve fully with medication alone. You recommend social skills training for Franklin. This is a type of specific remediation for skills deficits which complement medication treatment of core ADHD treatment.



Social Skills Training
Not all children with ADHD have social skills deficits, but for some, their impulsivity and lack of attentiveness to social cues results in behaviors that are not conducive to friendship and teamwork. Social skills training explicitly teaches skills that most children learn implicitly: how to listen, how to interpret other people's body language, how to observe and respect personal space, taking turns, showing interest, and social problem solving. One commonly used format is the Social Detective curriculum, a page of which is shown here.

I've diagnosed ADHD. Parents want treatment for their child. Where do I start? How do I chose?

Overview:

- Start on a low dose of a stimulant medication
- Try as many as 3 stimulants to achieve optimal response
- Check for adherence issues if poor response
- Reassess the diagnosis if poor response
- Consider non-stimulant if poor response to stimulants
- Titrate according to response
- Monitor with parent and teacher reports

- Refer for psychiatric consult if no response

Choosing the first stimulant

- The choice is based on physician/parent preference
- Consider
    - Desired duration of action
    - Form of the medication (can the patient swallow pills?)
    - Insurance preferred medications
- There are no data to support the initial use of one short-acting stimulant versus another, or one longer-acting stimulant versus another
- Your decision: start with MPH-based, or AMP-based medication?

One approach may be to pick which medication you want to start with and start with it every time, and then have a second medication you will choose if you need to switch. This will allow you to become comfortable with those 2 medications, and then you may start to use others if you need a 3rd option, or the family or insurance has a different preference.

Choosing Short-Acting Versus Longer-Acting for titration

Short-acting is preferred by some

Especially preferred for children < 10 years

Can be regulated more precisely

Titrating with short-acting is not always possible

Decision: is there a problem with giving a dose at school?

Stigma? Impractical?

If so, consider titration with longer-acting medication

Weekend use

Weekend use of both short-acting and longer-acting medication is recommended

- Target symptoms occur outside of school
- The MTA study showed better results with TID/7days a week doses

Maintenance schedule

- Schedule monthly follow-up visits for the first 3 months.
- If ADHD is stable after 3 months and there are no comorbidities
    - Change visit schedule to up to every 3 months at physician's discretion
    - Obtain parent ratings of behavior and side effects at each visit
    - Obtain teacher reports every 3 months if the child is stable

If ratings show an increase in symptoms

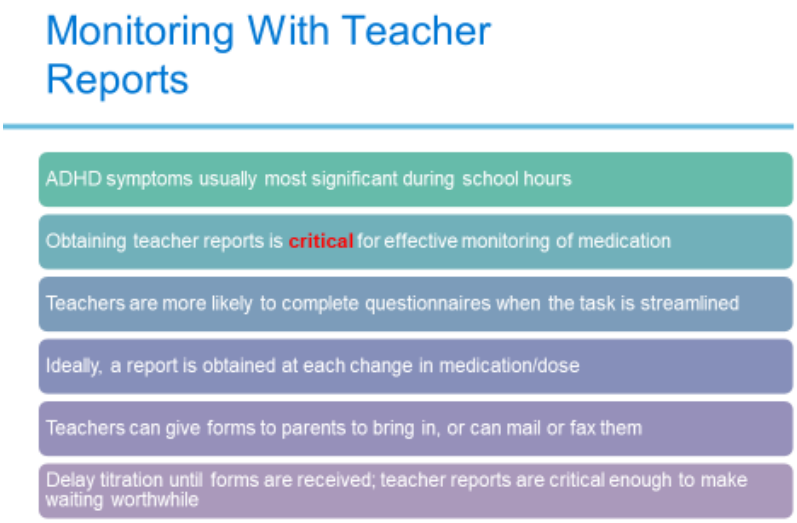
If there are clinically significant increases in scores on the parent or teacher Vanderbilt Scale:

- Assess for changes in classroom, sleep schedule, and medication
- If both ratings reflect clinically significant increases in scores, then increase dose.
- Obtain ratings 1-2 weeks after dose increase.
- If clinically significant improvement occurs (i.e., a return to level established during titration) then resume maintenance at that dose level.

- If no clinically significant improvement, then increase dose again (if below maximum allowable). If that is ineffective, switch to another stimulant (if not tried before) or non-stimulant

Choosing teachers to provide ratings

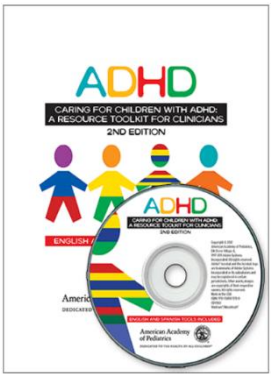
- Children differ in the number of teachers involved in their education
- Typically, more teachers are involved at higher grade levels
- Parents decide which teacher(s) to involve
    - Focus on core subjects (reading, math, social studies, science)
- If one teacher is involved, only one Vanderbilt needs to be obtained
- If more than two teachers are involved, ideally get ratings from one morning teacher and one afternoon teacher



Elements of a basic ADHD toolkit

Buy, build, or borrow a toolkit: To treat ADHD in a way that is efficient, satisfying, and cost-effective, you need a system. A basic ADHD toolkit includes the elements listed here.

1. Vanderbilt or other scale: parent and teacher versions
2. Parent education materials
    1. Diagnosis
    2. Medications/side effects
3. Template for school administration of medications
4. Template letter supporting 504 plan
5. Office policy for follow-up and medication refills
6. If not part of EHR: formularies of major insurance plans with ADHD medication preferred drugs



The toolkit shown above is available through the AAP bookstore. An older version of it is available for free download on the NICHQ website.

Let's look at one more case.

Roger

Roger is a 12 year old 6th grader who was first seen in your practice for his well child check last year. He comes in after getting several detentions at school for refusing to attempt work and talking back to teachers. He is has been increasingly withdrawn and irritable this school year. His grades have dropped from B/C level in elementary school to C/D/F. He has difficulty following the schedule, switching classes, and carrying out projects. He is somewhat less irritable at home.

You ask Roger what frustrates him at school. He says he feels like he can't keep up. He feels confused about the assignments and that makes him feel stupid. He has started refusing rather than attempt work at which he thinks he will fail.

Roger always struggled to follow instructions and do projects, but middle school is so much more complicated. He denies being bullied, or using drugs, or suicidal ideation.

ADHD and Comorbidity

ADHD is frequently accompanied by other disorders.
Two disorders in particular are important because they can be treated pharmacologically

- Anxiety
- Depression

Children with unidentified or untreated ADHD can become frustrated, demoralized, and eventually depressed.
Anxious children with unidentified or untreated ADHD may find their inability to study and learn effectively a major source of anxiety.

Roger's situation is not unusual. ADHD sometimes goes undiagnosed because symptoms are compensated for by the child's abilities or structural supports at school and/or home. These children will get by until the demands of the academic setting step up abruptly, and then they start to have difficulty. This commonly happens in 3rd grade, when the content of reading material increases in complexity, and 6th grade, when there are greater demands for organization and planning.

Treating ADHD with <u>severe</u> comorbidity

Children with severe symptoms of major depression should be treated as if the depression is primary.
These include children with psychosis, suicidal thoughts, or severe neurovegetative signs.
Children with severe anxiety will also need primary treatment for their anxiety, as well as ADHD.

Treating ADHD with <u>less severe</u> comorbidity

If less severe depression or anxiety accompanies ADHD

- Initiate a trial on stimulants as outlined, above.
- If ADHD symptoms improve and the anxiety/depression symptoms improve, continue on stimulant only.
- Assess change in ADHD symptoms as above.

- Assess change in anxiety or depression using anxiety or depression scales.
- If ADHD symptoms improve, and anxiety or depression symptoms do not, then consider starting an SSRI and/or referring to CBT

Roger

You get Vanderbilt scales from parent and 2 teachers:
Parent: inattention 18 hyperactivity 6
Math teacher: inattention 20 hyperactivity 5
English teacher: inattention 18 hyperactivity 6
PHQ9-A score: 14, no suicidal ideation
GAD-7 score: 7

Your assessment is that Roger has significant inattentive ADHD symptoms, moderate depression and mild anxiety symptoms. Much of Roger's negative thoughts and worries are around his feeling inadequate in school performance. You, Roger and his parents agree with the plan to target the ADHD symptoms first. You start lisdexamfetamine 20 mg. You write a letter recommending a 504 plan for Roger at school.

***Within 3 weeks**, you have titrated Roger up to lisdexamfetamine 40 mg, and he is very pleased.*
"I can follow what the teacher is saying, and when I sit down to do homework, I can stay with it."

Parent: inattention 5 hyperactivity 6
Math teacher: inattention 6 hyperactivity 5
English teacher: inattention 8 hyperactivity 6
PHQ9-A score: 3, no suicidal ideation
GAD-7 score: 4

In the best cases, kids like Roger feel like a light has gone on for them. They find that things that seemed impossible for them are now possible. They are simply able to do what their peers are doing, with a similar level of effort. It's a relief, and a revelation, and their mood often improves markedly.

Summary

- ADHD is common and highly treatable.
- ADHD is a clinical diagnosis, and requires data from parents and teachers.
- Stimulants are first line therapy and highly effective.
- Stimulant side effects are common and manageable.
- Non-stimulants can be used as monotherapy or as adjunctive therapy.
- Environmental modifications and behavioral management can support ADHD pharmacologic treatment.
- Academic and social skills remediation may be needed.