ADHD Medications

GENERAL PRESCRIBING TIPS

Generally, when you have a patient with ADHD symptoms, your first choice will be one of the psychostimulants, because these are usually more effective than the alternatives—atomoxetine, bupropion, clonidine, guanfacine, and viloxazine. Which psychostimulant will you choose? Here are some of the factors that will influence your decision:

1. *Long-acting vs short-acting.* Choosing between long- and short-acting stimulants is more art than science. Trial and error, combined with patient preference, will dictate the final regimen. Adults will often start with a long-acting agent so they can take a single dose in the morning and have it carry through their workday. Kids may do better with short-acting stimulants so that they will have an appetite when the medication wears off at lunch.
2. *Amphetamines vs methylphenidates.* More recent data have suggested that, based on safety and efficacy, methylphenidates are a better choice in kids and adolescents whereas amphetamine-class agents are better in adults. Generally, this is a Coke vs Pepsi decision—some people like one better than the other, and you can't predict their preference ahead of time. We recommend a methylphenidate over an amphetamine because amphetamines may have more side effects and are more likely to be abused or diverted, but our algorithm starts with an amphetamine first given the efficacy data.
3. *Stimulants vs non-stimulants.* Stimulants are more effective than non-stimulants, so they will be your first-line choice for most patients. If you have a patient with a substance use disorder, start with atomoxetine. Some special clinical circumstances seem to naturally call for other options. For example, bupropion is helpful for ADHD symptoms, as well as for depression, tobacco use, and being overweight, so it might be a great choice for patients with a combination of these problems. Alpha agonists, such as guanfacine and clonidine, are helpful for both ADHD and insomnia, another potential two-fer, though these meds tend to be used more frequently for children.
4. *Fancy formulations.* Many new formulations of amphetamines and methylphenidates have been introduced over the last few years, including the use of various drug delivery technologies, enantiomers, prodrugs, salts, and dosage forms. While they may have been marketed to increase drug company profits, some of them may have clinical utility. Examples of potentially useful advances include Quillichew ER (a chewable long-acting methylphenidate), Cotempla XR-ODT (an ODT long-acting methylphenidate), Adzenys XR-ODT (an ODT long-acting amphetamine), Dyanavel XR (a long-acting liquid amphetamine), and most intriguingly, Jornay PM (a long-acting methylphenidate you take at night that kicks in the next morning). We cover these formulations in the ADHD Medications table.
5. *Cost.* Most ADHD meds are available generically, but some reasonable choices are still branded and therefore more expensive. The most popular of these is Vyvanse, which is a long-acting amphetamine. Vyvanse appears to have a genuine advantage over many other stimulants, mainly in terms of tolerability and less potential for abuse. However, you'll have a hard time convincing insurance companies to cover the cost of Vyvanse unless you can clearly document intolerance in several other trials of stimulants. While the generic just launched, it's still more expensive than other stimulant generics.

Dose Equivalents and Switching Strategies

Most patients need to try different stimulants, or stimulant formulations, before settling on the one that works best for them. The dose equivalents are, luckily, fairly easy to remember.

1. From one amphetamine to another amphetamine
   - With the exception of Vyvanse, all amphetamines, including both Adderall IR and XR, are roughly equivalent in potency. For example, if a patient is taking Dexedrine 10 mg TID, you can switch this to Adderall 15 mg BID or Adderall XR 30 mg QD. That said, some people believe that Dexedrine, being 100% dextroamphetamine, might be more potent than Adderall, which is 75% d-amphetamine and 25% l-amphetamine (eg, 30 mg/day of Dexedrine may be closer to 40 mg/day of Adderall). In reality, the difference is likely negligible in most people.
   - Vyvanse is composed of both lysine and amphetamine, with amphetamine making up only about 30% of Vyvanse. This means that it's much less potent than straight Dexedrine. So, when switching from another amphetamine to Vyvanse, you have to at least double the dose.
2. From one methylphenidate to another methylphenidate
   - With the exception of Concerta and Focalin, all methylphenidate preparations are roughly equivalent in potency.
   - Concerta, because of its complex delivery system, delivers less methylphenidate than implied by the mg amount you prescribe. The usual conversion percentage used is 83%, meaning that the body sees 83% of Concerta

in methylphenidate equivalents. Thus, Concerta 18 mg is equivalent to methylphenidate 15 mg, 36 mg is equivalent to 30 mg, and so on.
- Focalin is the dextro-isomer of methylphenidate, which is twice as potent as methylphenidate. Thus, use about half the dose when prescribing Focalin.

3. From a methylphenidate to an amphetamine (or vice versa)
   - Methylphenidate is roughly half as potent as amphetamine, so Ritalin 10 mg = Dexedrine 5 mg, etc. Consistent with this equivalency, child psychiatrists often dose methylphenidate at 1 mg/kg, whereas they dose amphetamine at 0.5 mg/kg. Conversely, if you're switching from Dexedrine to Ritalin, you would need to increase the dose by a factor of two.

4. From an oral methylphenidate to the methylphenidate patch (Daytrana)
   - According to a clinical trial of patients switched from various versions of long-acting methylphenidate to the patch, you should dose the patch at about half the dose of the oral medication (Arnold LE et al, *Curr Med Res Opin* 2010;26(1):129–137).

See Table 2 for dose-by-dose breakdowns.

How to Switch

Once you've determined the dose equivalence, the actual switching is easy. You don't have to cross-taper; instead, have your patient take the last dose of stimulant A on day one and start stimulant B on day two. To be prudent, start the new stimulant at a somewhat lower dose than you calculate would be needed based on the equivalent dose rules of thumb. Those equivalencies are based on averages and may not apply to a given individual.

Side Effects and Class Warnings

The following apply to all stimulants:

- *Potential to cause psychosis or aggression.* This is a rare and dose-related effect; it may be more likely in patients with a predisposition for psychosis.
- *Worsening or new-onset Tourette's or tic disorders.* Stimulants may unmask tics. Of stimulants, methylphenidate is favored. The non-stimulant guanfacine is an even better alternative.
- *Seizures.* Stimulants may lower the seizure threshold, although data are contradictory; monitor patients with seizure disorders closely.
- *Growth inhibition or weight loss.* With long-term use, some growth inhibition may occur occasionally in children, but this is generally not a major problem. Monitoring growth and considering "drug holidays" may limit growth suppression.
- *Cardiovascular safety.* The FDA issued a serious class warning in 2006 with regard to cardiovascular safety. However, newer data, both in children and in adults, have been reassuring. Cardiac events occurred at virtually the same or lower rates among people who took stimulants compared to those who did not. From a practical perspective, we recommend asking about cardiac problems and consulting the child's pediatrician or cardiologist if a problem exists. Amphetamines should be avoided in patients with known or suspected cardiovascular disease.
- *Potential for misuse and abuse.* The FDA updated the class warnings for all stimulants in 2023 to include the potential for misuse, abuse, addiction, overdose, and death compared to the previous warning of a "potential for abuse and dependence." Just as before, patients should be assessed and monitored for risk of misuse.
- *No refills.* All stimulants are controlled substances (Schedule II), which means they can't be refilled or called in. Patients must be given a new prescription every month. In most states, you are allowed to give patients post-dated prescriptions for convenience.

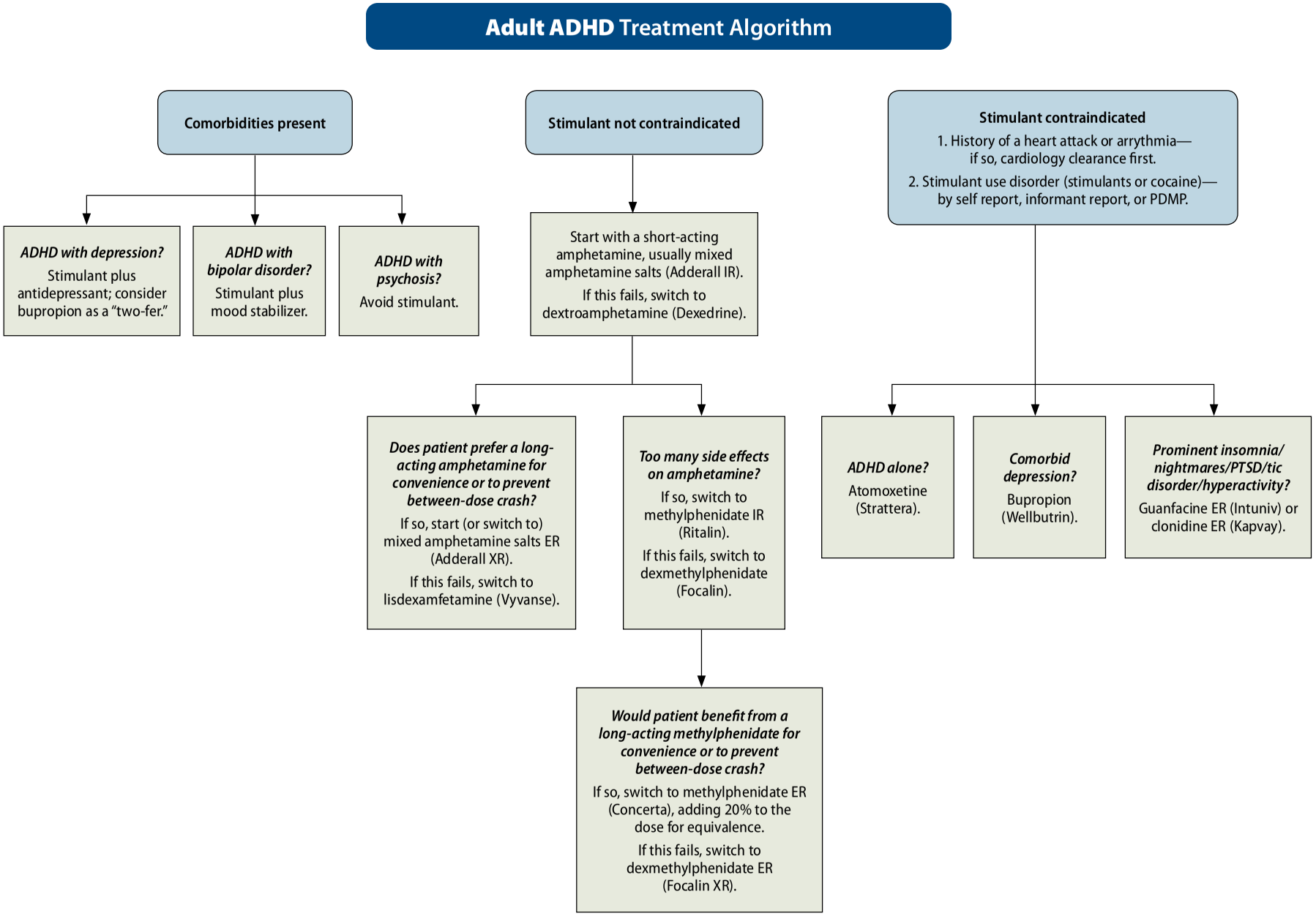
Adult ADHD Treatment Algorithm
Comorbidities present
Stimulant not contraindicated
Stimulant contraindicated
1. History of a heart attack or arrythmia—if so, cardiology clearance first.
2. Stimulant use disorder (stimulants or cocaine)—by self report, informant report, or PDMP.
ADHD with depression?
Stimulant plus antidepressant; consider bupropion as a "two-fer."
ADHD with bipolar disorder?
Stimulant plus mood stabilizer.
ADHD with psychosis?
Avoid stimulant.
Start with a short-acting amphetamine, usually mixed amphetamine salts (Adderall IR).
If this fails, switch to dextroamphetamine (Dexedrine).
Does patient prefer a long-acting amphetamine for convenience or to prevent between-dose crash?
If so, start (or switch to) mixed amphetamine salts ER (Adderall XR).
If this fails, switch to lisdexamfetamine (Vyvanse).
Too many side effects on amphetamine?
If so, switch to methylphenidate IR (Ritalin).
If this fails, switch to dexmethylphenidate (Focalin).
Would patient benefit from a long-acting methylphenidate for convenience or to prevent between-dose crash?
If so, switch to methylphenidate ER (Concerta), adding 20% to the dose for equivalence.
If this fails, switch to dexmethylphenidate ER (Focalin XR).
ADHD alone?
Atomoxetine (Strattera).
Comorbid depression?
Bupropion (Wellbutrin).
Prominent insomnia/nightmares/PTSD/tic disorder/hyperactivity?
Guanfacine ER (Intuniv) or clonidine ER (Kapvay).

Table 1: **ADHD Medications**

Brand Name (Generic Name, if different than heading) Year FDA Approved *[G] denotes generic availability*	Available Strengths (mg except where noted)	Usual Dosage Range (starting–max) (mg)	Onset of Action (minutes) / Duration of Action (hours)	Can It Be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate, CR = controlled, DR = delayed, ER = extended release)
Methylphenidates						
Short-Acting						
Focalin [G] (Dexmethylphenidate) 2001	2.5, 5, 10	2.5–10 BID	30–45 / 3–4	Yes (not scored)	6–17	Tablet; d-enantiomer of Ritalin; 2× more potent than methylphenidate
Methylin CT [G] 2003	2.5, 5, 10	2.5 BID–20 TID	30–45 / 3–4	Yes	6–17, adults	Chewable, grape-flavored tablet
Methylin oral solution [G] 2002	5 mg/5 mL, 10 mg/5 mL	2.5 BID–20 TID	30–45 / 3–4	N/A (liquid)	6–17, adults	Clear, grape-flavored liquid
Ritalin [G] 1955	5, 10, 20	2.5 BID–20 TID	30–45 / 3–4	Yes	6–17, adults	IR tablet
Intermediate-Acting						
Metadate ER [G] (Branded generic of Ritalin SR) 1999	20	10 QAM–30 BID	60–90 / 6–8	No	6–17, adults	CR tablet (less predictable because of wax matrix)
Methylin ER [G] (Branded generic of Ritalin SR) 2000	10, 20	20–60 QAM	60–90 / 4–8	No	6–17, adults	Hydrophilic polymer tablet; possibly more continuous than others in category
Ritalin SR [G] 1982	10, 20	10–60 QAM	60–90 / 4–8	No	6–17, adults	CR tablet (less predictable because of wax matrix)
Long-Acting						
Adhansia XR 2019	25, 35, 45, 55, 70, 85	25–85 QAM	45–60 / 10–16	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 20% IR beads & 80% DR beads
Aptensio XR 2015	10, 15, 20, 30, 40, 50, 60	10–60 QAM	45–60 / 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 40% IR beads & 60% DR beads
Azstarys (Serdexmethylphenidate/ dexmethylphenidate) 2021	26.1/5.2, 39.2/7.8, 52.3/10.4	39.2/7.8–52.3/10.4 QAM	30–60 / 8–13	Can be sprinkled or added to water	6–17, adults	Combination of prodrug of dexmethylphenidate (70%) and d-MPH (30%); equivalent to 20, 30, 40 mg dexmethylphenidate (Focalin); twice as potent as methylphenidate
Concerta [G] 2000	18, 27, 36, 54	18–72 QAM	45–60 / 10–12	No	6–17, adults	CR tablet with 22% IR & 78% DR

[1]Strattera dosing: Weight <70 kg, start 0.5 mg/kg, target 1.2 mg/kg, max 1.4 mg/kg; weight >70 kg, 40–100 mg

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Cotempla XR-ODT 2017	8.6, 17.3, 25.9	17.3–51.8 QAM	45–60 8–12	No (ODT)	6–17	Orally disintegrating; ER with 25% IR & 75% ER
Daytrana patch (Methylphenidate transdermal system) 2006	10, 15, 20, 30	10–30 QAM; remove after 9 hrs	120 10–12	No	6–17	CR patch; duration can be shortened by decreasing wear time; drug effects may persist for 5 hrs after removal
Focalin XR [G] (Dexmethylphenidate XR) 2005	5, 10, 15, 20, 25, 30, 35, 40	6–17 yrs: 5–30 QAM; Adults: 10–40 QAM	30 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads; mimics BID dosing; twice as potent as methylphenidate
Jornay PM 2018	20, 40, 60, 80, 100	20–100 QPM	8–10 hrs 8–12; after delay in onset	Can be sprinkled; do not crush or chew	6–17, adults	ER capsule of DR beads; taken in evening between 6:30–9:30 p.m.
Metadate CD [G] 2001	10, 20, 30, 40, 50, 60	20–60 QAM	60–90 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 30% IR beads & 70% DR beads; mimics BID dosing
Quillichew ER 2015	20, 30, 40	20–60 QAM	45–60 8–12	Yes	6–17, adults	Chewable ER for those who will not swallow pills or take liquids; 30% IR & 70% ER
Quillivant XR 2012	25 mg/5 mL	20–60 QAM	45 8–12	N/A (liquid)	6–17, adults	20% IR & 80% ER in oral solution; shake prior to use
Relexxii 2022	18, 27, 36, 45, 54, 63, 72	18–72 QAM	45–60 10–12	No	6–17, adults	Offers higher doses of 63 mg and 72 mg in one ER tablet
Ritalin LA [G] 2002	10, 20, 30, 40, 60	20–60 QAM	60–90 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads
Amphetamines						
Short-Acting						
Desoxyn [G] (Methamphetamine) 1943	5	5 QAM–10 BID	30–45 3–5	Yes (scored)	6–17	Tablet
Dexedrine, Dextrostat [G] (Dextroamphetamine) 1976	5, 10	3–5 yrs: 2.5 QAM–20 BID; 6–16 yrs: 5 QAM–20 BID	30–45 3–5	Yes	3–16	Scored tablet
Evekeo [G] Evekeo ODT (Amphetamine) 2012, 2019	5, 10 ODT: 5, 10, 15, 20	3–5 yrs: 2.5 QAM–20 BID; 6–17 yrs: 5 QAM–20 BID	30–45 3–5	Yes (scored) No (ODT)	3–17	Scored tablet or ODT; 1:1 ratio of l- and d-amphetamine

[1]Strattera dosing: Weight <70 kg, start 0.5 mg/kg, target 1.2 mg/kg, max 1.4 mg/kg; weight >70 kg, 40–100 mg

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Liquadd, ProCentra [G] (Dextroamphetamine oral solution) 2008	5 mg/5 mL	5–20 BID	30–45 / 3–5	N/A (liquid)	3–16	Bubblegum-flavored liquid
Zenzedi (Dextroamphetamine) 2013	2.5, 5, 7.5, 10, 15, 20, 30	3–5 yrs: 2.5 QD–20 BID; 6–16 yrs: 5 QAM–20 BID (same as Dexedrine dosing)	30–45 / 3–5	Yes	3–16	Tablet; 5 mg scored, 10 mg double scored, rest unscored
Intermediate-Acting						
Adderall [G] (Mixed amphetamine salts) 1960	5, 7.5, 10, 12.5, 15, 20, 30	3–5 yrs: 2.5 QAM–20 BID; 6–17 yrs: 5 QAM–20 BID; Adults: 5 QAM–20 BID	45–60 / 6–8	Can be crushed	3–17, adults	Tablet; mixed salt of l- and d-amphetamine
Long-Acting						
Adderall XR [G] (Mixed amphetamine salts) 2001	5, 10, 15, 20, 25, 30	6–12 yrs: 5–30 QAM; 13–17 yrs: 10–40 QAM; Adults: 20–60 QAM	45–60 / 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads; mixed salt of l- and d-amphetamine; mimics BID dosing
Adzenys XR-ODT (Amphetamine) 2016	ODT: 3.1, 6.3, 9.4, 12.5, 15.7, 18.8	6–12 yrs: 6.3–18.8 QAM; 13–17 yrs: 6.3–12.5 QAM; Adults: 12.5 QAM	45–60 / 8–12	N/A (ODT)	6–17, adults	50% IR & 50% ER; ER ODT; 3.1 mg is equivalent to 5 mg mixed-salts product; increasing dose preparations are equivalent to 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg respectively.
Dexedrine Spansules [G] (Dextroamphetamine) 1976	5, 10, 15	5 QAM–20 BID	30–60 / 6–8	Can be sprinkled; do not crush or chew	3–16	Capsule of 50% IR & 50% sustained-release beads
Dyanavel XR (Amphetamine) 2015	5, 10, 15, 20 Oral suspension: 2.5 mg/mL	6–17 yrs: 2.5–20 QAM	45–60 / 8–12	No (oral suspension)	6–17	ER oral suspension allowing once-daily dosing (must shake well); 2.5 mg = 4 mg mixed amphetamine salts
Mydayis (Mixed amphetamine salts) 2017	12.5, 25, 37.5, 50	13–17 yrs: 12.5–25 QAM; Adults: 12.5–50 QAM	45–60 / 10–16	Can be sprinkled; do not crush or chew	13–17, adults	pH-dependent ER capsule formulation; may have effect up to 16 hrs

[1]Strattera dosing: Weight <70 kg, start 0.5 mg/kg, target 1.2 mg/kg, max 1.4 mg/kg; weight >70 kg, 40–100 mg

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Vyvanse [G] (Lisdexamfetamine) 2007	Capsule: 10, 20, 30, 40, 50, 60, 70 Chewable: 10, 20, 30, 40, 50, 60	30–70 QAM	60–90 / 8–13	Capsules can be dissolved in water	6–17, adults	Lisdexamfetamine is prodrug of dextroamphetamine
Xelstrym (Dextroamphetamine transdermal system) 2022	4.5, 9, 13.5, 18	4.5–18 QAM; remove after 9 hrs	120 / 12	No	6–17, adults	CR patch; duration can be shortened by decreasing wear time; drug effects may persist for 5 hrs after removal
Non-Stimulants						
Intuniv [G] (Guanfacine ER) 2009	1, 2, 3, 4	1–4 QD (do not increase faster than 1 mg/wk) (adolescents 7 mg/day max)	N/A / 24	No	6–17	ER tablet; do not stop abruptly (rebound hypertension); not a 1:1 conversion from IR; do not give with high-fat meals
Kapvay [G] (Clonidine XR) 2010	0.1, 0.2	0.1 QHS; increase by 0.1 mg/day weekly and give divided BID; max 0.4 QD	N/A / 12–16	No	6–17	ER tablet; titrate gradually (orthostatic hypotension); avoid abrupt discontinuation; somnolence
Provigil [G] (Modafinil) 1998	100, 200	100–400 QAM	N/A / 18–24	Yes (200 mg tabs are scored)	Not FDA approved for ADHD	Tablet; studies have shown modafinil to be helpful for ADHD, but low incidence of serious rash; minimal data in children
Qelbree (Viloxazine ER) 2021	100, 150, 200	6–11 yrs: 100–400 QD; 12–17 yrs: 200–400 QD; Adults: 200–600 QD	N/A / 24	Can be sprinkled	6–17, adults	ER capsule; norepinephrine reuptake inhibitor
Strattera [G] (Atomoxetine) 2002	10, 18, 25, 40, 60, 80, 100	Dosage varies; see footnote 1 below	N/A / 24	No	6–17, adults	Capsule; norepinephrine reuptake inhibitor
Tenex [G] (Guanfacine IR) 1986	1, 2	1–4 QD (do not increase faster than 1 mg/wk)	N/A / 17	Can be crushed	Not FDA approved for kids or ADHD; approved only for adults 18+ for hypertension	Tablet
Wellbutrin [G] (Bupropion) 1985	75, 100	1.4–6 mg/kg/day	N/A / 6–9	Yes	Not FDA approved for ADHD	Tablet; bupropion SR & XL versions exist

[1]Strattera dosing: Weight <70 kg, start 0.5 mg/kg, target 1.2 mg/kg, max 1.4 mg/kg; weight >70 kg, 40–100 mg

Table 2: **Relative Equivalency and Conversion Guide for Stimulants**[1]

Methylphenidates	
Alternative Formulation	**Regular Methylphenidate Equivalent**
Adhansia XR 25 mg QAM	5 mg IR TID
Adhansia XR 100 mg QAM	20 mg IR TID
Aptensio XR 10 mg QAM	5 mg IR BID or 10 mg ER QAM
Concerta 18, 27, 36, 54 mg tablets	10–15, 15–20, 20–30, 30–45 mg/day, respectively; use 63 mg or 72 mg formulations for 45–60 mg/day
Cotempla XR-ODT 8.6, 17.3, 25.9 mg tablets	5 mg IR TID or 10-15 mg ER QAM
Daytrana patch 10 mg	5 mg IR BID or 10 mg ER QAM
Focalin 5 mg BID	IR 10 mg BID
Focalin XR 10 mg QAM	IR 20 mg QAM
Jornay PM 20 mg QPM	4 mg IR TID
Jornay PM 100 mg QPM	20 mg IR TID
Quillichew ER 20 mg QAM	10 mg IR BID or 20 mg ER QAM
Quillichew ER 30 mg QAM	15 mg IR BID or 30 mg ER QAM
Quillichew ER 40 mg QAM	20 mg IR BID or 40 mg ER QAM
Quillivant XR 10 mg (2 mL) QAM	5 mg IR BID or 10 mg ER QAM
Quillivant XR 20 mg (4 mL) QAM	10 mg IR BID or 20 mg ER QAM
Quillivant XR 30 mg (6 mL) QAM	15 mg IR BID or 30 mg ER QAM
Quillivant XR 40 mg (8 mL) QAM	20 mg IR BID or 40 mg ER QAM
Amphetamines	
Alternative Formulation	**Regular Mixed Amphetamine Salts Equivalent**
Adzenys XR-ODT 3.1 mg QAM	2.5 mg IR BID or 5 mg ER QAM
Adzenys XR-ODT 6.3 mg QAM	5 mg IR BID or 10 mg ER QAM
Adzenys XR-ODT 9.4 mg QAM	7.5 mg IR BID or 15 mg ER QAM
Adzenys XR-ODT 12.5 mg QAM	10 mg IR BID or 20 mg ER QAM
Adzenys XR-ODT 15.7 mg QAM	12.5 mg IR BID or 25 mg ER QAM
Adzenys XR-ODT 18.8 mg QAM	15 mg IR BID or 30 mg ER QAM
Dyanavel XR 6.25 mg (2.5 mL)	5 mg IR BID or 10 mg ER QAM
Dyanavel XR 12.5 mg (5 mL)	10 mg IR BID or 20 mg ER QAM
Dyanavel XR 18.75 mg (7.5 mL)	15 mg IR BID or 30 mg ER QAM
Mydayis 37.5 mg QAM	25 mg ER QAM plus 12.5 mg IR eight hours later
Vyvanse 30 mg QAM	5 mg IR BID or 10 mg ER QAM
Vyvanse 50 mg QAM	10 mg IR BID or 20 mg ER QAM
Vyvanse 70 mg QAM	15 mg IR BID or 30 mg ER QAM
Zelstrym patch 9 mg	5 mg IR BID or 10 mg ER QAM

IR = immediate release; ER = extended release

[1]These are approximate equivalencies provided as guidance; taper and titrate each agent based on recommended dosing when switching rather than direct substitution

AMPHETAMINE (Adzenys XR-ODT, Dyanavel XR, Evekeo) Fact Sheet [G]

Bottom Line:

Amphetamine is a 50:50 racemic mixture of dextro- and levo-amphetamine. In clinical practice, the most commonly prescribed amphetamine is Adderall (mixed amphetamine salts; see fact sheet later in this chapter). Based on meta-analyses, amphetamines are clearly the most effective option in both children and adults with ADHD. That doesn't mean they should always be the first choice, though. Methylphenidates are often better tolerated and have relatively less abuse potential. Several newer formulations of amphetamine may be helpful for patients who don't like to swallow pills—but they come with a price tag.

FDA Indications:

ADHD (Adzenys XR-ODT: adults and children ≥6; Dyanavel XR: children ≥6; Evekeo: children ≥3); **narcolepsy** (Evekeo); obesity (Evekeo).

Off-Label Uses:

Treatment-resistant depression.

Dosage Forms:

- **Tablets (Evekeo, [G]):** 5 mg, 10 mg (scored); **(Evekeo ODT):** 5 mg, 10 mg, 15 mg, 20 mg.
- **ER tablets (Dyanavel XR):** 5 mg (scored), 10 mg, 15 mg, 20 mg.
- **ER orally disintegrating tablets (Adzenys XR-ODT):** 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg.
- **ER oral suspension (Dyanavel XR):** 2.5 mg/mL.

Dosage Guidance:

- Tablets (Evekeo, [G]):
  - Children 3–5: Start 2.5 mg QAM, increase in 2.5 mg/day increments weekly.
  - Children 6–17: Start 5 mg QAM, increase in 5 mg/day increments weekly to maximum of 40 mg/day in divided doses.
  - Narcolepsy: Start 5 mg QAM (ages 6–12) or 10 mg QAM (ages >12), increase by 5 or 10 mg/day increments weekly, respectively. Maximum 60 mg/day in divided doses.
- ER ODT (Adzenys XR-ODT):
  - Start 6.3 mg QAM, increase in 3.1–6.3 mg/day increments weekly. Maximum of 18.8 mg/day (ages 6–12) or 12.5 mg/day (ages 13–17 and adults).
- ER oral suspension (Dyanavel XR):
  - Children 6–12: Start 2.5–5 mg QAM, increase in 2.5–10 mg/day increments every four to seven days. Maximum 20 mg/day.

Monitoring: ECG if history of cardiac disease.

Cost: (G): $$$; others: $$$$

Side Effects:

- Most common: Abdominal pain, decreased appetite, weight loss, insomnia, headache, nervousness.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:

- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily via CYP2D6; t ½: 11 hours.
- Avoid use with MAOIs, antacids.

Clinical Pearls:

- These racemic forms of amphetamine differ from dextroamphetamine in that the l-isomer component is more potent than the d-isomer in peripheral activity (potentially resulting in more cardiovascular effects and tics).
- A racemic mixture may be less appetite suppressing compared to dextroamphetamine.
- Divide IR (Evekeo) doses by intervals of four to six hours.
- Approximate equivalence doses of Adzenys XR-ODT and mixed amphetamine salts XR (Adderall XR) are: 3.1 mg = 5 mg, 6.3 mg = 10 mg, 9.4 mg = 15 mg, 12.5 mg = 20 mg, 15.7 mg = 25 mg, 18.8 mg = 30 mg.
- Dyanavel XR oral suspension: Shake well to get the intended extended-release effect. The approximate equivalence of 2.5 mg/mL is 4 mg of mixed amphetamine salts.

Fun Facts:

The term "amphetamine" is the contracted name of the chemical "alpha-methylphenethylamine." Its first pharmacologic use was in 1934 when pharmaceutical company Smith, Kline and French sold amphetamine under the trade name Benzedrine as a decongestant inhaler.

ATOMOXETINE (Strattera) Fact Sheet [G]

Bottom Line:
Atomoxetine is a non-stimulant ADHD treatment that carries no abuse potential, causes less insomnia and anxiety, and is unlikely to worsen tics. Unfortunately, it is generally less effective than stimulants and takes longer to work (two to four weeks).

FDA Indications:
ADHD (adults and children ≥6 years).

Off-Label Uses:
Treatment-resistant depression.

Dosage Forms:
Capsules (G): 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg.

Dosage Guidance:
- Start 40 mg QAM for three days, ↑ to 80 mg QAM; may ↑ to 100 mg/day after two to four weeks if needed (max 100 mg/day); may divide doses >40 mg/day (morning and late afternoon/early evening).
- Special dosing for children <70 kg: Start 0.5 mg/kg QAM for three days, ↑ to 1.2 mg/kg QAM; may ↑ to max 1.4 mg/kg/day or 100 mg/day (whichever is less) after two to four weeks if needed; may divide doses >0.5 mg/kg/day.

Monitoring: Baseline LFTs; follow up if signs of liver disease.

Cost: $

Side Effects:
- Most common: *Children:* Headache, abdominal pain, decreased appetite, fatigue, nausea, vomiting. *Adults:* Nausea, dry mouth, decreased appetite, insomnia, constipation, fatigue, erectile dysfunction, abdominal pain, dizziness, urinary hesitation.
- Serious but rare: Class warning for suicidal ideation in children and teens. Severe hepatic injury including increased hepatic enzymes (up to 40 times normal) and jaundice (bilirubin up to 12 times upper limit of normal). Increased blood pressure (↑ 15–20 mmHg) and heart rate (↑ 20 bpm).
- Pregnancy/breastfeeding: Limited but reassuring data in pregnancy; minimal data in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Selective norepinephrine reuptake inhibitor (NRI).
- Metabolized primarily via CYP2D6; t ½: 5 hours.
- Avoid use with MAOIs. Exercise caution with 2D6 inhibitors such as fluoxetine, paroxetine, and quinidine (increased atomoxetine serum levels); use slower titration and do not exceed 80 mg/day in presence of 2D6 inhibitors or in 2D6 poor metabolizers.

Clinical Pearls:
- QAM and BID dosing are equally effective, but BID dosing has better GI tolerability. Can also be dosed at bedtime if it causes fatigue.
- Appears to be more effective in improving attention than in controlling hyperactivity.

Fun Fact:
Atomoxetine was originally known as "tomoxetine"; however, the FDA requested that the name be changed because the similarity to "tamoxifen" could lead to dispensing errors.

CLONIDINE (Catapres, Kapvay) Fact Sheet [G]

Bottom Line:
Clonidine is an alpha-2 agonist that has no abuse potential, does not worsen tics, and does not cause insomnia. However, it's less effective than stimulants and has a delayed onset of effect (two to four weeks); it is often added to a stimulant to prevent insomnia. Clonidine may be used as a second-line option for opioid detoxification if buprenorphine or methadone are not available.

FDA Indications:
Hypertension; **ADHD** (children ages 6–17), as monotherapy or adjunctive therapy to stimulants (not approved for ADHD in adults).

Off-Label Uses:
Conduct disorder; Tourette's and motor tics; pervasive developmental disorders; migraine prophylaxis; opioid withdrawal.

Dosage Forms:
- **IR tablets (Catapres, [G]):** 0.1 mg, 0.2 mg, 0.3 mg.
- **ER tablets (Kapvay, [G]):** 0.1 mg, 0.2 mg.
- **Patch (Catapres-TTS, [G]):** 0.1 mg/day, 0.2 mg/day, 0.3 mg/day.

Dosage Guidance:
- IR: Start 0.1 mg BID, ↑ by 0.1 mg/day at weekly intervals; max 2 mg/day. For opioid withdrawal, may be dosed 0.1–0.2 mg every four to six hours as needed. Daily dosing requirement can be established by tabulating the total amount administered over the first 24 hours and dividing this amount into a TID or QID schedule. Total dose should not exceed 1.2 mg the first 24 hours and 2 mg/day beyond that.
- ER: Start 0.1 mg QHS, ↑ by 0.1 mg/day at weekly intervals; max 0.4 mg/day. May divide doses >0.2 mg/day; divided doses may be unequal with higher dose given at bedtime.

Monitoring: Blood pressure (hold doses for BP <90/60).

Cost: $

Side Effects:
- Most common: Dry mouth, somnolence, dizziness, constipation, fatigue, headache.
- Serious but rare: Hypotension, syncope, orthostasis.
- Pregnancy/breastfeeding: Limited data in pregnancy; not recommended in breastfeeding and may lower milk supply.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Centrally acting, selective alpha-2 adrenergic agonist.
- Metabolized primarily through CYP2D6; t ½: 6–20 hours.
- Avoid use with MAOIs. Caution with 2D6 inhibitors (eg, paroxetine, fluoxetine, duloxetine).

Clinical Pearls:
- Not a controlled substance.
- Clonidine tends to be more sedating than guanfacine, another alpha agonist.
- When used in detox, clonidine relieves most opioid withdrawal symptoms but is less effective than methadone or buprenorphine. Therefore, adjunctive medications are often used with clonidine to manage insomnia, muscle pain, headache, agitation, and other symptoms. Even so, detox completion rates with clonidine are typically significantly lower than those with buprenorphine or methadone.
- The patch formulation is not typically used (except for hypertension) because clonidine's effects on BP may be prolonged and continue even after patch removal.
- If patient misses two or more consecutive doses, consider repeating titration.
- Minimize side effects, especially somnolence, by administering at bedtime.
- Monitor blood pressure, especially during initial dosing titration.
- Risk of nervousness, anxiety, and possibly rebound hypertension two to four days after abrupt discontinuation. Taper dose in no more than 0.1 mg/day decrements, every three to seven days.

Fun Fact:
The Federal Bureau of Prisons' clinical guidance document, *Detoxification of Chemically Dependent Inmates,* recommends maintaining strict control over medication access to prevent diversion or misuse. It cites the example of inmates eating clonidine patches to obtain a state of euphoria.

DEXMETHYLPHENIDATE (Azstarys, Focalin, Focalin XR) Fact Sheet [G]

Bottom Line:
Dexmethylphenidate (Focalin) is the d-isomer of methylphenidate and is two times more potent than methylphenidate. Azstarys is a newly approved (and expensive) combination of Focalin and a prodrug version of Focalin—the Focalin is absorbed quickly while the prodrug is absorbed more slowly (it's the Vyvanse of methylphenidate). There's no clear advantage of Focalin over Ritalin—the main difference is that Focalin may mean fewer tablets for patients. Focalin XR only recently went generic, so it will likely remain quite expensive for a while. Azstarys may be less abusable than Focalin.

FDA Indications:
ADHD in adults (Azstarys, Focalin XR) and in children ≥6 years (Azstarys, Focalin IR and XR).

Off-Label Uses:
Narcolepsy, obesity, treatment-resistant depression.

Dosage Forms:
- **Dexmethylphenidate tablets (Focalin, [G]):** 2.5 mg, 5 mg, 10 mg.
- **Dexmethylphenidate ER capsules (Focalin XR, [G]):** 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg.
- **Serdexmethylphenidate/dexmethylphenidate ER capsules (Azstarys):** 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg.

Dosage Guidance:
- d-MPH IR: Start 2.5 mg BID, ↑ by 5–10 mg/day every seven days. Max 20 mg/day; divide IR doses by at least four hours.
- d-MPH ER: Start 10 mg QAM, ↑ by 10 mg/day every seven days. Max 40 mg/day. For children, start 5 mg QAM, ↑ by 5 mg/day every seven days. Max (children) 30 mg/day.
- Serdex-MPH/d-MPH: Start 39.2/7.8 mg QAM, ↑ to max dose of 52.3/10.4 mg after one week if indicated.

Monitoring: ECG if history of cardiac disease.

Cost: IR: $; ER: $$; Azstarys: $$$$

Side Effects:
- Most common: Decreased appetite, insomnia, anxiety, GI distress, irritability, tics, headache, tachycardia, hypertension, dry mouth.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Serdexmethylphenidate (Serdex-MPH) is a prodrug of dexmethylphenidate (d-MPH). d-MPH is metabolized primarily via de-esterification, not CYP450. d-MPH t ½: 2–4.5 hours (2–3 hours in children); d-MPH ER delivers 50% of dose immediately and 50% about five hours later. Azstarys t ½: 6–12 hours; delivers 30% d-MPH immediately and 70% as prodrug.
- Avoid use with MAOIs.

Clinical Pearls:
- d-MPH is the d-isomer of methylphenidate and is two times more potent than methylphenidate, which is why it is prescribed at about half the dose. Serdex-MPH is a prodrug, converted to d-MPH in the lower GI tract.
- Use the same total daily dose of Focalin IR as Focalin XR. The combined dose of Azstarys 26.1/5.2, 39.2/7.8, or 52.3/10.4 mg is equivalent to 20, 30, or 40 mg of Focalin, respectively.
- Focalin XR capsules contain two kinds of beads: Half are IR beads and half are enteric-coated DR beads. A single, once-daily XR capsule provides the same amount of dexmethylphenidate as two IR tablets given four hours apart.
- The ER capsules cannot be split in half. However, they can be opened and the beads sprinkled over food. The patient should then eat all that food—eating half won't work to split the dose accurately because it won't be possible to determine if the eaten portion contains more immediate-release or delayed-release beads.
- Give with food if GI side effects occur.

Fun Fact:
With two stereoactive centers, methylphenidate has four possible stereoisomers. Of the four, dexmethylphenidate is the most active biologically.

DEXTROAMPHETAMINE (Dexedrine, Dextrostat, Liquadd, ProCentra, Zenzedi) Fact Sheet [G]

Bottom Line:
Dextroamphetamine is the dextro-isomer of racemic amphetamine. It has a long history of safe use in children, and is available in short- and long-acting formulations as generics.

FDA Indications:
ADHD (children ≥3 years); **narcolepsy** (adults and children ≥6 years).

Off-Label Uses:
Obesity, treatment-resistant depression.

Dosage Forms:
- **Tablets (Dexedrine, Dextrostat, [G]):** 5 mg, 10 mg (scored).
- **Tablets (Zenzedi):** 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg (5 mg scored, 10 mg double scored; rest unscored).
- **ER capsules (Dexedrine Spansules, [G]):** 5 mg, 10 mg, 15 mg.
- **Liquid (Liquadd, ProCentra, [G]):** 5 mg/5 mL.

Dosage Guidance:
- ADHD (IR and ER):
  - Adults and children ≥6 years: Start 5 mg QAM, ↑ by 5 mg/day at weekly intervals to max 60 mg/day, though doses ≥40 mg/day are rarely more effective. Divide IR dose QD–TID.
  - Children 3–5 years: Start 2.5 mg QAM, ↑ by 2.5 mg/day weekly to max 60 mg/day, though doses >40 mg/day are rarely more effective. Divide IR dose QD–TID.
- Narcolepsy (IR and ER):
  - Start 10 mg QAM, ↑ by 10 mg/day weekly to max 60 mg/day. Divide IR dose QD–TID.

Monitoring: ECG if history of cardiac disease.

Cost: IR/ER: $ (Zenzedi: $$; ProCentra: $$$$)

Side Effects:
- Most common: Abdominal pain, anorexia, nausea, tics, insomnia, tachycardia, headache.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP2D6 (minor) and glucuronidation; t ½: 12 hours.
- Avoid use with MAOIs, antacids.

Clinical Pearls:
- Dextroamphetamine is the more potent d-isomer of amphetamine; it has potentially less peripheral effects (eg, motor tics) than a racemic mix (eg, mixed amphetamine salts like Adderall, amphetamine, or methamphetamine).
- IR tablets and oral solution: Doses can be given at intervals of four to six hours.
- Dextroamphetamine is the only stimulant, other than Adderall IR, approved for children <6 years (approved for children ≥3 years).
- The newer Zenzedi brand offers more dosing flexibility options, but it is more expensive than generic IR tablets.
- Also available as D,L racemic mixture of amphetamine as Evekeo tablets, Adzenys XR-ODT, and Dyanavel XR oral suspension (see amphetamine fact sheet).

Fun Fact:
Dexys Midnight Runners, the British band famous for its song "Come On Eileen" (1982), derived their name from Dexedrine—"Dexys" after the drug's name and "Midnight Runners" in reference to the energy it provides.

DEXTROAMPHETAMINE TRANSDERMAL (Xelstrym) Fact Sheet

Bottom Line:
Like Daytrana, Xelstrym is helpful for those who, for whatever reason, cannot use any of the wide variety of oral stimulant preparations. Otherwise, we don't recommend it due to high cost, lag time for onset of effect, and the side effect of rash, which is pretty common and unpleasant.

FDA Indications:
ADHD (adult and children ≥6 years).

Dosage Forms:
Transdermal patch: 4.5 mg, 9 mg, 13.5 mg, 18 mg/9 hour.

Dosage Guidance:
- Adults: Start 9 mg/9 hour patch QAM (for initial therapy or for patients switching from other amphetamine preparations, regardless of dose). Titrate in increments of 4.5 mg weekly up to a maximum 18 mg QAM.
- Children: Start 4.5 mg/9 hour patch QAM; titrate in weekly increments of 4.5 mg up to max 18 mg QAM.

Monitoring: ECG if history of cardiac disease.

Cost: $$$$

Side Effects:
- Most common: Decreased appetite, headache, insomnia, tic, abdominal pain, vomiting, nausea, irritability, increased BP and pulse. Application site reactions and sensitization may occur.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP2D6 (minor) and glucuronidation; t ½: 11.5 hours (6.4 hours in children).
- Avoid use with MAOIs, antacids.

Clinical Pearls:
- Apply to hip, upper arm, chest, upper back, or flank two hours before an effect is needed and remove nine hours after application (drug effects may persist for five hours after removal). Increase dose at weekly intervals by using next higher dose system. May be removed sooner if shorter duration is desired or if late-day side effects occur. Rotate application sites.
- Clinical effect usually seen in two hours and lasts approximately 12 hours.
- Exposure of application site to a heat source (eg, hair dryer, heating pad, electric blanket) may increase the rate and amount of drug absorbed.
- For localized skin reactions (redness at site), use cortisone cream (1%–2%). For more severe or systemic reactions, discontinue patch.

Fun Fact:
While Daytrana is approved for pediatric use only, Xelstrym is also approved for use in adults.

GUANFACINE (Intuniv, Tenex) Fact Sheet [G]

Bottom Line:
Guanfacine is an alpha-2 agonist that has no abuse potential, does not worsen tics, and does not cause insomnia. However, it is less effective than stimulants and has a delayed onset of effect (two to four weeks). Guanfacine ER is now available in generic and is easier to use than IR.

FDA Indications:
ADHD (children ages 6–17), as monotherapy or adjunctive therapy to stimulants (not approved for ADHD in adults).

Off-Label Uses:
Conduct disorder; Tourette's and motor tics; pervasive developmental disorders; migraine prophylaxis; opioid withdrawal.

Dosage Forms:
- **IR tablets (Tenex, [G]):** 1 mg, 2 mg.
- **ER tablets (Intuniv, [G]):** 1 mg, 2 mg, 3 mg, 4 mg.

Dosage Guidance:
- IR dosing depends on weight:
  - 27–40.5 kg (55–90 lbs): Start 0.5 mg QHS, ↑ by 0.5 mg/day at weekly intervals up to 1.5 mg/day; may ↑ to 2 mg/day after two weeks; max 2 mg/day in two to four divided doses.
  - 40.5–45 kg (90–99 lbs): Start 0.5 mg QHS, ↑ by 0.5 mg/day at weekly intervals; max 1 mg per dose, 3 mg/day.
  - >45 kg (>99 lbs): Start 1 mg QHS, ↑ by 1 mg/day at weekly intervals up to 3 mg/day; may ↑ to 4 mg/day after 2 weeks; max 1 mg per dose, 4 mg/day.
- ER: Start 1 mg QHS, ↑ by 1 mg/day at weekly intervals; max 4 mg/day. Alternative: 0.05–0.12 mg/kg QD or QHS; max 4 mg/day. Doses up to 7 mg/day ER studied as monotherapy in adolescents.

Monitoring: Blood pressure.

Cost: $

Side Effects:
- Most common: Dry mouth, somnolence, dizziness, constipation, fatigue, headache.
- Serious but rare: Hypotension, syncope, orthostasis.
- Pregnancy/breastfeeding: Not well studied.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Centrally acting, selective alpha-2 adrenergic agonist.
- Metabolized primarily through CYP3A4; t ½: 13–14 hours in children (16–18 hours in adults).
- Avoid use with MAOIs. Caution with 3A4 inhibitors (eg, clarithromycin, fluvoxamine) and inducers (eg, St. John's wort, carbamazepine).

Clinical Pearls:
- Not a controlled substance.
- Guanfacine IR and ER are not interchangeable on a mg:mg basis. When switching from one formulation to the other, taper and re-titrate.
- Guanfacine tends to be less sedating than clonidine, another alpha agonist.
- If patient misses two or more consecutive doses, consider repeating titration.
- ER tablets should not be taken with a high-fat meal due to increased medication exposure.
- Minimize side effects, especially somnolence, by administering at bedtime.
- Monitor blood pressure, especially during initial dosing titration.
- Risk of nervousness, anxiety, and possibly rebound hypertension two to four days after abrupt discontinuation. Taper dose in 1 mg/day decrements, every three to seven days.

Fun Fact:
Some prescribers have taken advantage of guanfacine's sympatholytic properties for the treatment of nightmares and dissociative symptoms in PTSD.

LISDEXAMFETAMINE (Vyvanse) Fact Sheet [G]

Bottom Line:
Vyvanse may have a gentler, "smoother" side effect profile than other amphetamines, and it probably has a lower risk of diversion or abuse. However, its high cost even in generic form means insurance companies don't like to pay for it without prior authorization.

FDA Indications:
ADHD (adults and children ≥6 years); **binge eating disorder** (BED).

Off-Label Uses:
Narcolepsy; obesity; treatment-resistant depression.

Dosage Forms:
- **Capsules:** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg.
- **Chewtabs:** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg.

Dosage Guidance:
- ADHD (adults and children ≥6 years): Start 30 mg QAM, ↑ by 10–20 mg/day at weekly intervals. Target lowest effective dose; max 70 mg/day.
- BED: Start 30 mg QAM, ↑ by 20 mg/day at weekly intervals to target 50 mg/day; max 70 mg/day.

Monitoring: ECG if history of cardiac disease.

Cost: $$$

Side Effects:
- Most common: Headache, insomnia, anorexia, abdominal pain, irritability, agitation, tics, decreased appetite, increased heart rate, jitteriness, anxiety.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through non-CYP-mediated hepatic and/or intestinal metabolism; t ½: lisdexamfetamine (inactive prodrug) <1 hour; dextroamphetamine (active metabolite) 12 hours. Dextroamphetamine metabolized by CYP2D6.
- Avoid use with MAOIs and antacids. Caution with antihypertensives (decreased efficacy of antihypertensive). Caution with 2D6 inhibitors, which may increase stimulant effects.

Clinical Pearls:
- Lisdexamfetamine is dextroamphetamine with the chemical lysine bound to it, which renders it inactive. It remains inactive until GI enzymes cleave off lysine and convert it to active dextroamphetamine. This means that drug abusers can't get high by snorting or injecting it.
- Anecdotally, Vyvanse has a more gradual onset and offset than other stimulants, and it may cause fewer side effects than other amphetamines.
- Taking with food decreases the effect slightly and delays peak levels by an hour. If patients feel it's not "kicking in" fast enough, have them take it earlier or on an empty stomach.
- Lisdexamfetamine 70 mg is equivalent to 30 mg of mixed amphetamine salts (Adderall).
- While indicated for BED, it is not approved for use as a weight loss or anti-obesity agent.

Fun Fact:
The manufacturer of Vyvanse pursued an indication as an add-on medication for depression, but disappointing results in clinical trials put an end to this effort.

METHAMPHETAMINE (Desoxyn) Fact Sheet [G]

Bottom Line:
Methamphetamine is highly addictive when used in its crystal form ("crystal meth"), because it causes an immediate and intense high when snorted or smoked. Its use is generally not recommended. Watch the television show "Breaking Bad" if you're not convinced!

FDA Indications:
ADHD (children ≥6 years); obesity (adults and adolescents ≥12 years).

Dosage Forms:
Tablets (G): 5 mg.

Dosage Guidance:
ADHD (adults and children ≥6 years): Start 5 mg QAM–BID, ↑ by 5 mg/day at weekly intervals to max 20 mg/day, divided BID.

Monitoring: ECG if history of cardiac disease.

Cost: $$$$

Side Effects:
- Most common: Anorexia, tachycardia, dizziness, insomnia, tremor, tics, restlessness, headache, constipation (decreased GI motility). Dental complications, such as poor dental hygiene, diffuse cavities, bruxism, and tooth wear, may develop with abuse.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP2D6 to active metabolite (amphetamine); t ½: 4–5 hours.
- Avoid use with MAOIs and antacids. Caution with 2D6 inhibitors, which may increase stimulant effects.

Clinical Pearls:
- High risk of abuse.
- Not widely used (DEA reports that there were only 8,000 prescriptions written in 2021). When prescribed for obesity, the recommendation is for short-term use only (ie, a few weeks) and as an adjunct to caloric restriction due to its high addiction and diversion potential.
- Methamphetamine's CNS-stimulating effect is approximately equal to or greater than that of amphetamine but less than that of dextroamphetamine; less blood pressure elevation than with amphetamine.

Fun Facts:
Methamphetamine was originally used in nasal decongestants and bronchial inhalers (the levo-isomer is still utilized for these indications, sold over the counter as Vicks VapoInhaler, Equaline, and generics).

METHYLPHENIDATE IR (Methylin, Ritalin) Fact Sheet [G]

Bottom Line:
Methylphenidate has a better side effect profile and somewhat lower abuse potential than amphetamines. However, patients often prefer the "kick" they get from Adderall.

FDA Indications:
ADHD (adults and children ≥6 years); **narcolepsy**.

Off-Label Uses:
Obesity; treatment-resistant depression.

Dosage Forms:
- **Tablets (Ritalin, [G]):** 5 mg, 10 mg, 20 mg.
- **Chewable tablets (Methylin CT, [G]):** 2.5 mg, 5 mg, 10 mg.
- **Oral solution (Methylin, [G]):** 5 mg/5 mL, 10 mg/5 mL.

Dosage Guidance:
- ADHD:
  - Adults: Start 5–10 mg BID, ↑ by 10 mg/day at weekly intervals to max 60 mg/day.
  - Children ≥6 years: Start 0.3 mg/kg BID or 2.5–5 mg BID before breakfast and lunch, increase by 0.1 mg/kg/dose or 5–10 mg/day at weekly intervals to a max of 2 mg/kg/day or 60 mg/day.
- Narcolepsy: Same dosing as ADHD.

Monitoring: ECG if history of cardiac disease.

Cost: $; chewable tabs: $$$

Side Effects:
- Most common: Insomnia, headache, nervousness, abdominal pain, nausea, vomiting, anorexia, weight loss, affect lability, tics.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Hepatic metabolism via carboxylesterase CES1A1, not CYP450 isoenzymes; t ½: 2–4 hours.
- Avoid use with MAOIs, antacids.

Clinical Pearls:
- Methylphenidate generally causes fewer side effects than amphetamine preparations—patients are less likely to report feeling "wired."
- While all stimulants may cause tics, a Cochrane review of eight randomized trials showed that methylphenidate did not worsen tics in children with ADHD and a tic disorder; in some cases it even improved tics.
- Methylin chewable tablets: Administer with at least eight ounces of water or other fluid.

Fun Fact:
Methylphenidate was synthesized by Ciba (now Novartis) chemist Leandro Panizzon. His wife, Marguerite, had low blood pressure and would take the stimulant before playing tennis. He named the substance "Ritaline" (yes, with the "e" on the end) after his wife's nickname, Rita.

METHYLPHENIDATE ER (Concerta, Ritalin SR and LA, others) Fact Sheet [G]

Bottom Line:
There are many longer-acting methylphenidate preparations. Two good options are Concerta and Ritalin LA, both of which are now available generically.

FDA Indications:
ADHD (adults and children ≥6 years); **narcolepsy**.

Off-Label Uses:
Obesity; treatment-resistant depression.

Dosage Forms (more commonly used):
- **Tablets**
  - **Ritalin SR, Metadate ER, Methylin ER, (G):** 10 mg, 20 mg.
- **Capsules**
  - **Concerta, Relexxii, (G):** 18 mg, 27 mg, 36 mg, 54 mg, 63 mg, 72 mg (22% IR/78% ER).
  - **Ritalin LA, (G):** 10 mg, 20 mg, 30 mg, 40 mg, 60 mg (50% IR/50% ER).
  - **Metadate CD, (G):** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (30% IR/70% ER).
  - **Aptensio XR:** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (40% IR/60% ER).
  - **Adhansia XR:** 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg (20% IR/80% ER).
  - **Jornay PM:** 20 mg, 40 mg, 60 mg, 80 mg, 100 mg (onset delayed 10 hours).
- **Oral solution (Quillivant XR):** 25 mg/5 mL (20% IR/80% ER).
- **Chewable tablets (Quillichew ER):** 20 mg, 30 mg (scored), 40 mg (scored) (30% IR/70% ER).
- **Orally disintegrating tablets (Cotempla XR-ODT):** 8.6 mg, 17.3 mg, 25.9 mg (25% IR/75% ER).

Dosage Guidance:
- Intermediate-acting (Ritalin SR, Metadate ER, Methylin ER):
  - Titrate to effective daily dose with IR, then switch to equivalent eight-hour SR or ER dose QAM–BID.
- Long-acting (Aptensio XR, Metadate CD, Ritalin LA, Quillivant XR, Quillichew ER):
  - Start 10–20 mg QAM, ↑ by 10–20 mg/day at weekly intervals; max 60 mg/day.
- Long-acting (Adhansia XR):
  - Start 25 mg QAM, ↑ by 10–15 mg/day at weekly intervals; max 70 mg/day (children) and 85 mg/day (adults).
- Long-acting (Cotempla XR-ODT):
  - Start 17.3 mg QAM, ↑ by 8.6–17.3 mg/day at weekly intervals; max 51.8 mg/day.
  - 8.6 mg, 17.3 mg, 25.9 mg equivalent to 10 mg, 20 mg, 30 mg of other methylphenidate formulations, respectively.
- Long-acting (Concerta, Relexxii):
  - Start 18–36 mg QAM, ↑ by 18 mg/day at weekly intervals; max 72 mg/day.
  - Children ≥6 years: Start 18 mg QAM, ↑ by 18 mg/day in weekly intervals to max 54 mg/day (ages 6–12) or 72 mg/day (age 13+).
- Jornay PM:
  - Start 20 mg daily in the evening and increase by 20 mg/day up to maximum of 100 mg/day. Adjust timing between 6:30 and 9:30 p.m.
- Narcolepsy: Start 10–20 mg ER QAM, ↑ by 10 mg/day at weekly intervals; max 60 mg/day.

Monitoring: ECG if history of cardiac disease.

Cost: $; Concerta: $$$; Aptensio XR, Cotempla XR-ODT, Jornay PM, Quillivant XR, Quillichew ER, Relexxii: $$$$

Side Effects and Mechanism, Pharmacokinetics, and Drug Interactions:
See methylphenidate IR fact sheet.

Clinical Pearls:
- **ER capsules** contain a mixture of 30% IR and 70% ER beads. **Aptensio XR** contains a mixture of 40% IR and 60% ER beads, whereas **Adhansia XR** contains 20% IR and 80% ER. **Ritalin LA** and its generic ER capsules are a combination of 50% IR and 50% DR beads. These products mimic BID dosing of IR. **Cotempla XR-ODT** delivers a mixture of 25% IR and 75% ER in an orally disintegrating extended-release formulation. **Jornay PM** is dosed in the evening; if early-morning awakening occurs, dose earlier in evening.
- **Concerta** is based on the OROS osmotic delivery system (also used for Invega). 22% of the dose is immediate (with effects in one to two hours) and 78% is delayed.

METHYLPHENIDATE TRANSDERMAL (Daytrana) Fact Sheet [G]

Bottom Line:
Daytrana is helpful for kids who, for whatever reason, cannot use any of the wide variety of oral stimulant preparations. Otherwise, we don't recommend it due to high cost, lag time for onset of effect, and the side effect of rash, which is pretty common and unpleasant.

FDA Indications:
ADHD (children ≥6 years).

Dosage Forms:
Transdermal patch (G): 10 mg, 15 mg, 20 mg, 30 mg/9 hour.

Dosage Guidance:
Start 10 mg/9 hour patch QAM (for initial therapy or for patients switching from other methylphenidate preparations, regardless of dose). Apply to hip two hours before an effect is needed and remove nine hours after application (drug effects may persist for five hours after removal). Increase dose at weekly intervals by using next higher dose system. May be removed sooner if shorter duration is desired or if late-day side effects occur. Rotate application sites. Max 30 mg QD.

Monitoring: ECG if history of cardiac disease.

Cost: $$$; Daytrana: $$$$

Side Effects:
- Most common: Headache, insomnia, irritability, decreased appetite, anorexia, nausea, tics, application site reaction (10%–40% incidence in children).
- Serious but rare: Allergic contact dermatitis/sensitization, characterized by intense local reactions (eg, edema, papules) that may spread beyond patch site; sensitization may subsequently manifest systemically with other routes of methylphenidate administration.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Hepatic metabolism via carboxylesterase CES1A1, not CYP450 isoenzymes; t ½: 3–4 hours.
- Avoid use with MAOIs, antacids.

Clinical Pearls:
- Apply patch to clean, dry area of the hip; don't apply to waistline or to areas under tight clothes, as it may rub off. Alternate sites daily (eg, opposite hip). Absorption not affected by perspiration. Remove after nine hours. If dislodged, replace with a new patch but remove within the nine-hour total wear time.
- Clinical effect usually seen in two hours and lasts approximately 12 hours.
- Exposure of application site to a heat source (eg, hair dryer, heating pad, electric blanket) may increase the amount of drug absorbed.
- For localized skin reactions (redness at site), use cortisone cream (1%–2%). For more severe or systemic reactions, discontinue patch.
- In June 2015, the FDA added a warning that Daytrana could cause chemical leukoderma, a permanent loss of skin color. These reactions are irreversible and not harmful but can be disfiguring. Instruct patients to contact their physician if they notice skin color changes or lightening of skin areas; in such cases an alternative medication should be considered.

Fun Fact:
Since 2006, Shire Pharmaceuticals has issued at least 10 recalls of Daytrana patches because users have had difficulty removing the protective cover from the patch. Recall costs have reached into the millions.

MIXED AMPHETAMINE SALTS (Adderall, Adderall XR, Mydayis) Fact Sheet [G]

Bottom Line:
Adderall contains 75% dextroamphetamine and 25% levoamphetamine. This ratio of amphetamine isomers is effective but is probably the most abused and diverted of all prescription stimulants.

FDA Indications:
ADHD (adults and children ≥3 years for IR, ≥6 years for XR, ≥13 years for Mydayis); **narcolepsy** (adults and children ≥6 years).

Off-Label Uses:
Obesity; treatment-resistant depression.

Dosage Forms:
- **Tablets (G):** 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg.
- **ER capsules (G):** 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg.
- **ER capsules (Mydayis):** 12.5 mg, 25 mg, 37.5 mg, 50 mg.

Dosage Guidance:
- ADHD:
  - Rule of thumb for both preparations: Initial dose should be 0.5 mg/kg, but shoot for a target dose of 1.0–1.2 mg/kg.
  - Adults:
    - IR: Start 5 QAM–BID, max 40 mg/day divided BID.
    - ER: Start 20 mg QAM, increase to max 60 mg/day QAM. For Mydayis, start 12.5 mg QAM, increase in increments of 12.5 mg/day weekly, to max 50 mg/day.
  - Children and adolescents:
    - IR: Start 2.5–5 mg BID, max 40 mg/day divided BID.
    - ER: Start 5–10 mg QAM, increase gradually to max 30 mg/day, or 40 mg/day QAM in adolescents. For Mydayis (adolescents ≥13 years), start 12.5 mg QAM, increase in increments of 12.5 mg/day weekly, to max 25 mg/day.
- Narcolepsy: Start 10 mg QAM, increase by 10 mg/day at weekly increments; max 60 mg/day.

Monitoring: ECG if history of cardiac disease.

Cost: IR/ER: $; Mydayis: $$$$

Side Effects:
- Most common: Insomnia, headache, decreased appetite, abdominal pain, weight loss, agitation.
- Serious but rare: See class warnings in chapter introduction.
- Pregnancy/breastfeeding: Limited data in pregnancy; likely safe in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP2D6; t ½: 9–14 hours. Duration of action: 6–8 hours (IR), 8–12 hours (XR).
- Avoid use with MAOIs, antacids. Caution with 2D6 inhibitors, which may increase stimulant effects.

Clinical Pearls:
- Each dose contains a mixture of amphetamine salts, resulting in a 75:25 ratio of dextro- and levo-isomers of amphetamine.
- When converting from IR to ER, use the same total daily dose, given QAM.
- Adderall may provide more of a "kick" than methylphenidate preparations. Roughly twice as potent (per mg) as methylphenidate.
- Mydayis is formulated with pH-dependent drug-releasing beads, with IR and DR beads that release drug at pH 5.5 and 7.0. Duration of effect may be up to 16 hours.
- Dextroamphetamine and mixed amphetamine salts are the only stimulants approved for children <6 years (approved for children ≥3 years), with the exception of Mydayis, which causes very high rates of side effects (insomnia, reduced appetite) in children <13 years and should only be used in children ≥13 years.

Fun Fact:
Was briefly pulled from the market in Canada in 2005 because of cardiac concerns.

VILOXAZINE XR (Qelbree) Fact Sheet

Bottom Line:
Like the first norepinephrine reuptake inhibitor for ADHD, atomoxetine, viloxazine has no abuse potential and is less likely than stimulants to cause insomnia, anxiety, or tics. However, it is generally less effective than stimulants and takes longer to work. It's unclear if it has any advantage, and unlike atomoxetine, there's no option for a cheaper generic.

FDA Indications:
ADHD (adults, children ≥6 years).

Off-Label Uses:
Treatment-resistant depression.

Dosage Forms:
ER capsules: 100 mg, 150 mg, 200 mg.

Dosage Guidance:
- Children 6–11: Start 100 mg QD, ↑ by 100 mg/day at weekly intervals to max 400 mg QD.
- Children 12–17: Start 200 mg QD, ↑ by 200 mg after one week to max 400 mg QD.
- Adults: Start 200 mg QD, ↑ by 200 mg/day at weekly intervals to max 600 mg QD.

Monitoring: Baseline renal function.

Cost: $$$$

Side Effects:
- Most common: Somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, irritability.
- Serious but rare: Class warning for suicidal ideation in children and teens. Mania reported. May increase pulse and BP.
- Pregnancy/breastfeeding: Not recommended due to lack of human data and concerning animal data..

Mechanism, Pharmacokinetics, and Drug Interactions:
- Selective norepinephrine reuptake inhibitor (NRI).
- Metabolized primarily via CYP2D6, UGT1A9, UGTB15; t ½: 7 hours.
- Avoid use with MAOIs. Strong 1A2 inhibitor; exercise caution with 1A2 substrates with narrow therapeutic index (eg, clozapine, duloxetine, ramelteon, tasimelteon, theophylline, tizanidine) as combination may increase side effects of substrate.

Clinical Pearls:
- ER capsules, so do not cut, crush, or chew; can open and sprinkle contents in applesauce or pudding.
- Adjust dose in severe renal impairment (eGFR <30 mL/min); max 200 mg/day.
- Data from one of four studies suggest viloxazine may work a bit faster than atomoxetine (week one vs week three), but this finding is not based on head-to-head data and it's hard to know whether it is clinically significant.

Fun Fact:
Viloxazine has been studied for various indications since the 1970s and originally received an FDA orphan drug designation for narcolepsy.

ADHD Medications

Generally, in treating kids with ADHD, you should start with psychostimulants, since they are the most effective options. Second-line agents include alpha-agonists, followed by atomoxetine, viloxazine, and bupropion.

STIMULANT RECOMMENDATIONS

When choosing a stimulant, the first decision is between an amphetamine or methylphenidate preparation. More recent data have suggested that, based on safety and efficacy, methylphenidates are a better choice in kids and adolescents whereas amphetamine-class agents are better in adults. Yet, even in adults, we generally recommend going with a methylphenidate preparation first based on lower side effect and misuse potential. The second decision is choosing between a long-acting or short-acting stimulant.

For kids who don't like swallowing pills, there are various options. Some long-acting stimulants can be opened and sprinkled on food. There are also short- and long-acting liquid, chewable, and disintegrating brand-name options—though they are expensive and often require pre-authorization. Finally, another option for the pill-phobics is the Daytrana or Xelstrym patch.

When initiating a trial of stimulant medication, titrating the dose on a weekly basis optimizes the response efficiently, with the added benefit of limiting the use of additional medications with their associated side effects. While valproate and risperidone have been demonstrated to be effective for aggression with ADHD, you will rarely need them if you prioritize stimulant titration.

The Case for Long-Acting Stimulants

- More practical: It's easier to take a single dose that lasts through the duration of a school day.
- Addresses acute tachyphylaxis: Response to stimulants diminishes rapidly, but most newer long-acting stimulants release an increasing amount of drug over the dose's six- to 12-hour course, which most people need for the medication to be effective. This avoids the need for multiple short-acting dosage bursts to maintain continued response.
- Decreased stimulant rebound: People sensitive to rebound irritability or worsening of ADHD symptoms often report a more attenuated rebound with long-acting stimulants.

The Case for Short-Acting Stimulants

- For situations where a child only requires a few hours of effect, such as a half day of school, an afternoon of completing homework, or a weekend activity.
- Minimizes appetite suppression during meals.
- May be less likely to interfere with sleep.

DOSE EQUIVALENTS

Some kids may need to try different stimulants, or stimulant formulations, before settling on the one that works best for them. The dose equivalents are, luckily, fairly easy to remember.

1. **From one amphetamine to another amphetamine**
   - With the exception of Vyvanse, all amphetamines, including Adderall IR and XR, are roughly equivalent in potency. For example, if a child is taking Dexedrine 10 mg TID, you can switch this to Adderall 15 mg BID or Adderall XR 30 mg QD. That said, some people believe that Dexedrine, being 100% dextroamphetamine, might be more potent than Adderall, which is 75% d-amphetamine and 25% l-amphetamine (eg, Dexedrine 30 mg/day may be closer to 40 mg/day of Adderall). In reality, the effect is likely negligible in most people.
   - Vyvanse is composed of both lysine and amphetamine, with amphetamine making up only about 30% of the drug. This means that Vyvanse is much less potent than straight Dexedrine. So when switching from another amphetamine to Vyvanse, you have to at least *double the dose,* and sometimes more.

2. **From one methylphenidate to another methylphenidate**
   - With the exception of Concerta and Focalin, all methylphenidate preparations are roughly equivalent in potency.
   - Concerta, because of its complex delivery system, delivers less methylphenidate than implied by the mg amount you prescribe. The usual conversion percentage used is 83%, meaning that the body sees 83% of Concerta in methylphenidate equivalents. Thus, Concerta 18 mg is equivalent to methylphenidate 15 mg, 36 mg is equivalent to 30 mg, and so on.
   - Focalin is the dextro-isomer of methylphenidate, which is twice as potent as methylphenidate. Thus, use about half the dose when using Focalin.

3. **From a methylphenidate to an amphetamine (or vice versa)**
   - Methylphenidate is roughly half as potent as amphetamine, so Ritalin 10 mg = Dexedrine 5 mg, etc. Consistent with this equivalency, child psychiatrists often dose methylphenidate at 1 mg/kg/immediate-release dose, whereas they dose amphetamine at 0.5 mg/kg. Conversely, if you're switching from Dexedrine to Ritalin, you would need to double the dosage.

4. **From an oral methylphenidate to the methylphenidate patch (Daytrana)**
   - According to a clinical trial of kids switched from various versions of long-acting methylphenidate to the patch, you should dose the patch at about half the dose of the oral medication.

5. **From an oral amphetamine to the dextroamphetamine patch (Xelstrym)**
   - As Xelstrym is a newer formulation, the recommendation is to titrate the patch dose from the usual starting dose rather than approximate an equivalent substitution dose.

HOW TO SWITCH

Once you've determined the dose equivalence, the actual switching is easy. Don't cross-taper; just have your patient take the last dose of stimulant A on day 1 and start stimulant B on day 2. To be prudent, start the new stimulant at a somewhat lower dose than the calculation you arrived at via the equivalent dose guideline. Those equivalencies are based on averages and may not apply to a given individual.

HOW TO STOP

When discontinuing stimulant medications, no taper is required; the medications can just be stopped given their fast action and metabolism. The same is not true for the longer-acting non-stimulant options—especially alpha-agonists, which should be tapered to avoid rebound hypertension. The bigger question is *when* to stop. About a third of young patients seem to do OK letting go of stimulants in their late teens or early 20s. Others stop due to side effects, perhaps trying non-stimulant options.

NON-STIMULANT RECOMMENDATIONS

Although their efficacy cannot compare to stimulants, atomoxetine or viloxazine may be an appropriate first step when you're concerned about diversion or substance misuse. For children with severe tic disorders, guanfacine and clonidine may be indicated with the added benefit of targeting the tics. Alpha-agonists are also helpful for addressing the frequent sleep difficulties found in children with ADHD. Patients with comorbid depression or tobacco use may benefit from bupropion. A handful of clinical trials suggest that modafinil may be an option when stimulant response is limited. Regardless of your choice, don't expect the robust and rapid response frequently seen with stimulants.

Some studies have demonstrated small improvements in ADHD symptoms with higher doses of omega-3, specifically eicosapentaenoic acid (EPA), as a supplement; however, this has not been consistently supported in meta-analyses. Limited evidence also exists for ginkgo biloba and saffron in reducing ADHD symptoms. While these should not replace the use of a stimulant or non-stimulant medication, they may be useful as an adjunct and for families who are not currently interested in medication options.

Lastly, the FDA approved a medical device, the Monarch external trigeminal nerve stimulation (eTNS) system, for children 7–12 years of age based off a single small four-week study. The cost remains significant for an option that lacks solid data. There is also an FDA-approved videogame called EndeavorRx for treatment of ADHD. Wonders never cease.

STIMULANT SIDE EFFECTS AND CLASS WARNINGS

- The most common side effects include appetite suppression and insomnia. With long-term use, due to chronic appetite suppression and acute growth hormone inhibition, some literature has reported an average decrease of half an inch in expected height, while several studies have not found significant differences with longer-term follow-up or "drug holidays." Despite this, drug holidays are still useful on weekends and school breaks for patients who struggle with appropriate weight gain, assuming their behavioral functioning remains manageable without medication. Taking stimulant medication with or after breakfast, providing snacks throughout the day, and scheduling a high-caloric evening snack when appetite has bounced back can help to manage appetite suppression, related irritability, and weight loss. High-caloric and protein milkshakes or smoothies with some combination of Ensure, whole milk, yogurt, milk powder, fruit, peanut butter, and ice cream can be on the menu. Cyproheptadine is sometimes used, but studies are limited. Additionally, stimulants should be avoided in patients with anorexia nervosa given their GI and anorectic side effects.
- Stimulants have been known to unmask underlying tics, and at times they can exacerbate an established Tourette's or tic disorder. To complicate matters further, most children present for ADHD treatment during the age range when tics begin to manifest and worsen. For patients with more severe tics, alpha-agonists are worth considering prior to a stimulant trial.
- In patients with a seizure disorder, stimulants may lower the seizure threshold, although the current data are contradictory.

- In patients with a genetic predisposition to or history of psychosis, stimulants can exacerbate symptoms in a dose-dependent fashion. Amphetamine products have at least double the psychosis risk of methylphenidate products.
- Patients with a comorbid anxiety disorder may experience a worsening of anxiety symptoms; however, anxiety and also boredom may improve.
- Research has debunked prior concerns that stimulants might not work as well and produce more side effects in autistic children and teens.
- Some patients have been known to have increased skin picking, hair pulling, and nail biting behaviors with stimulant medications. Alpha-agonists may be helpful here too.
- A few patients may experience an increase in aggressive behaviors or other adverse psychiatric effects (hallucinations, delusions, mania).
- Stimulants may increase heart rate and blood pressure, particularly in older patients; thus, vitals should be monitored at baseline and with subsequent dose adjustments. Blood pressure parameters vary in children by age, height, and sex (see Appendix C). Patients with cardiovascular symptoms, with a family history of early cardiac death or cardiac arrhythmias, or who are adopted with unknown family histories would benefit from additional consultation from their primary care physician or cardiologist.
- Black box warnings for abuse and dependence: Patients with a history of recent substance use should be followed more closely if stimulants are considered, given the risk of diversion, overuse, and dependence of these medications. Vyvanse is thought to have decreased misuse potential due to being a prodrug that becomes active only after oral ingestion.

ADHD Treatment Algorithm for Children and Adolescents

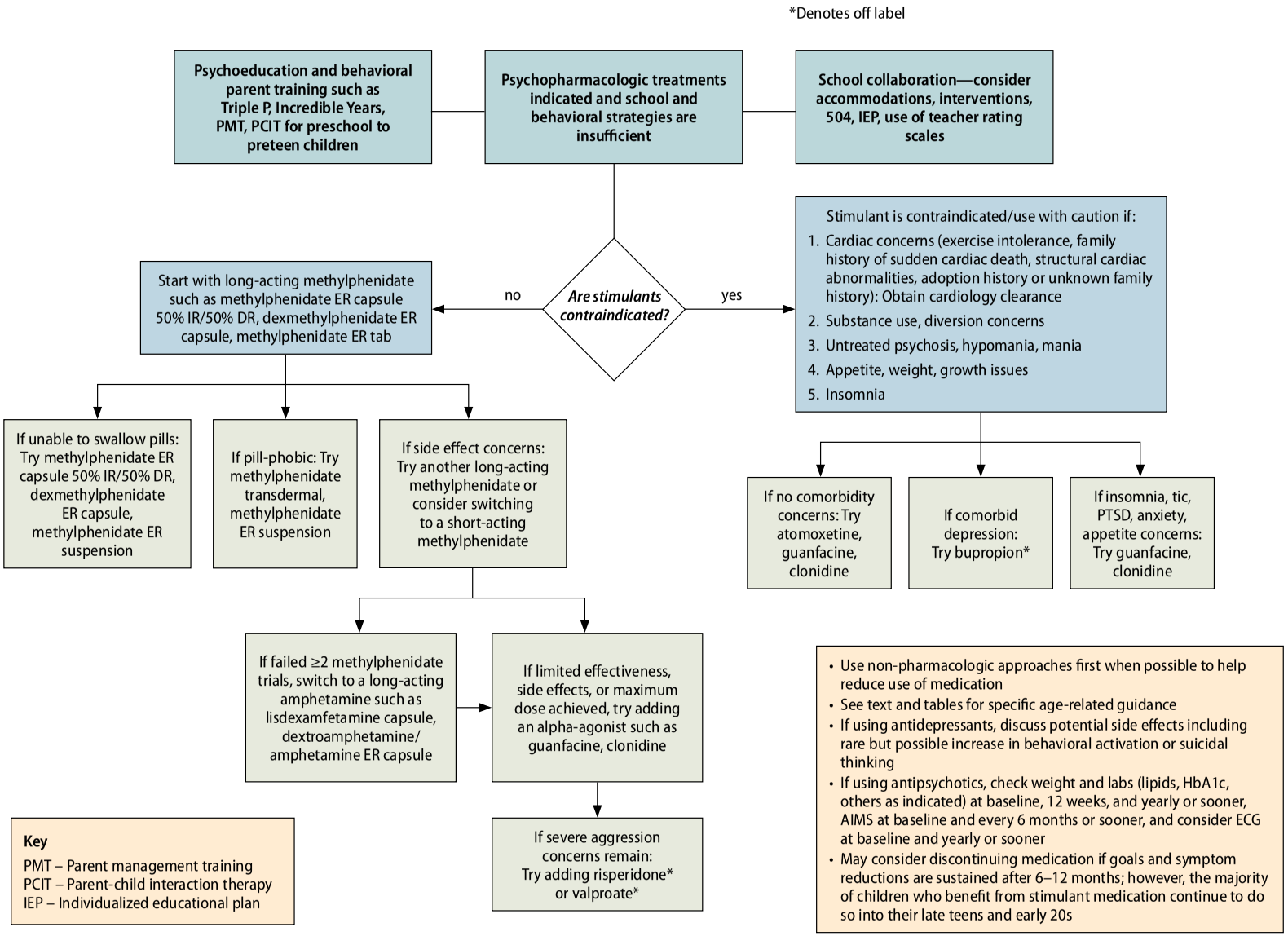

TABLE 1: ADHD Medications

Brand Name (Generic Name, if different than heading) Year FDA Approved *[G] denotes generic availability*	Available Strengths (mg except where noted)	Usual Pediatric Dosage Range (starting–max) (mg)	Onset of Action (minutes) / Duration of Action (hours)	Can It Be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate release, CR = controlled release, DR = delayed release, ER = extended release)
Methylphenidates						
Short-acting						
Focalin [G] (Dexmethylphenidate) 2001	2.5, 5, 10	2.5–10 BID	30–45 / 3–4	Yes (not scored)	6–17	Tablet; D-enantiomer of Ritalin; 2x more potent than methylphenidate
Methylin CT [G] 2003	2.5, 5, 10	2.5 BID–20 TID	30–45 / 3–4	Yes	6–17, adults	Chewable, grape-flavored tablet
Methylin oral solution [G] 2002	5 mg/5 mL, 10 mg/5 mL	2.5 BID–20 TID	30–45 / 3–4	N/A (liquid)	6–17, adults	Clear, grape-flavored liquid
Ritalin [G] 1955	5, 10, 20	2.5 BID–20 TID	30–45 / 3–4	Yes	6–17, adults	IR tablet
Intermediate-acting						
Metadate ER [G] Branded generic of Ritalin SR 1999	20	10 QAM–30 BID (max 60/day)	60–90 / 6–8	No	6–17, adults	CR tablet (less predictable because of wax matrix)
Methylin ER [G] Branded generic of Ritalin SR 2000	10, 20	20–60 QAM	60–90 / 4–8	No	6–17, adults	Hydrophilic polymer tablet; possibly more continuous than others in category
Ritalin SR [G] 1982	10, 20	10–60 QAM	60–90 / 4–8	No	6–17, adults	CR tablet (less predictable because of wax matrix)
Long-acting						
Adhansia XR 2019	25, 35, 45, 55, 70, 85	25–85 QAM	45–60 / 10–16	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 20% IR beads & 80% DR beads
Aptensio XR 2015	10, 15, 20, 30, 40, 50, 60	10–60 QAM	45–60 / 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 40% IR beads & 60% DR beads
Azstarys (Serdexmethylphenidate/ dexmethylphenidate) 2021	26.1/5.2, 39.2/7.8, 52.3/10.4	39.2/7.8–52.3/10.4 QAM	30–60 / 8–13	Can be sprinkled or added to water	6–17, adults	Combination of prodrug of dexmethylphenidate (70%) and d-MPH (30%); equivalent to 20, 30, 40 mg dexmethylphenidate (Focalin); twice as potent as methylphenidate
Concerta [G] 2000	18, 27, 36, 54	18–72 QAM	45–60 / 10–12	No	6–17, adults	CR tablet with 22% IR & 78% DR

Brand Name (Generic Name, if different than heading) Year FDA Approved *[G] denotes generic availability*	Available Strengths (mg except where noted)	Usual Pediatric Dosage Range (starting–max) (mg)	Onset of Action (minutes) / Duration of Action (hours)	Can It Be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate release, CR = controlled release, DR = delayed release, ER = extended release)
Cotempla XR-ODT 2017	8.6, 17.3, 25.9	17.3–51.8 QAM	45–60 8–12	No (ODT)	6–17	Orally disintegrating, ER with 25% IR & 75% ER
Daytrana patch (Methylphenidate transdermal system) 2006	10, 15, 20, 30	10–30 QAM Remove after 9 hours	120 8–12	No	6–17	CR patch; duration can be shortened by decreasing wear time; drug effects may persist for 5 hours after removal
Focalin XR [G] (Dexmethylphenidate XR) 2005	5, 10, 15, 20, 25, 30, 35, 40	5–30 QAM	30 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads; mimics BID dosing; 2x more potent than methylphenidate
Jornay PM 2018	20, 40, 60, 80, 100	20–100 QPM	8–10 hrs 8–12; after 10-hr delay in onset	Can be sprinkled; do not crush or chew	6–17, adults	ER capsule of DR beads; taken in evening between 6:30–9:30 pm
Metadate CD [G] 2001	10, 20, 30, 40, 50, 60	20–60 QAM	60–90 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 30% IR beads & 70% DR beads; mimics BID dosing
Quillichew ER 2015	20, 30, 40	20–60 QAM	45–60 8–12	Yes	6–17, adults	Chewable ER for those who will not swallow pills or take liquid; 30% IR & 70% ER
Quillivant XR 2012	25 mg/5 mL	20–60 QAM	45 8–12	N/A (liquid)	6–17, adults	20% IR & 80% ER in oral solution; shake prior to use
Ritalin LA [G] 2002	10, 20, 30, 40, 60	20–60 QAM	60–90 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads
Amphetamines						
Short-acting						
Desoxyn [G] (Methamphetamine) 1943	5	5 QAM–10 BID	30–45 3–5	Yes (scored)	6–17	Tablet
Dexedrine [G] (Dextroamphetamine) 1976	5, 10	3–5 yrs: 2.5 QAM–20 BID; 6–16 yrs: 5 QAM–20 BID	30–45 3–5	Yes	3–16	Scored tablet
Evekeo Evekeo ODT (Amphetamine) 2012, 2019	5, 10 ODT: 2.5, 5, 10, 15, 20	3–5 yrs: 2.5 QAM–20 BID; 6–17 yrs: 5 QAM–20 BID	30–45 3–5	Yes (scored) No (ODT)	3–17	Scored tablet or ODT; 1:1 ratio of l- and d-amphetamine

Brand Name (Generic Name, if different than heading) Year FDA Approved *[G] denotes generic availability*	Available Strengths (mg except where noted)	Usual Pediatric Dosage Range (starting–max) (mg)	Onset of Action (minutes) / Duration of Action (hours)	Can It Be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate release, CR = controlled release, DR = delayed release, ER = extended release)
ProCentra [G] (Dextroamphetamine oral solution) 2008	5 mg/5 mL	5–20 BID	30–45 3–5	N/A (liquid)	3–16	Bubblegum-flavored liquid
Zenzedi (Dextroamphetamine) 2013	2.5, 5, 7.5, 10, 15, 20, 30	3–5 yrs: 2.5–20 BID; 6–16 yrs: 5 QAM–20 BID (same as Dexedrine dosing)	30–45 3–5	Yes	3–16	Tablet; 5 mg scored, 10 mg double scored, rest unscored
Intermediate-acting						
Adderall [G] (Mixed amphetamine salts) 1960	5, 7.5, 10, 12.5, 15, 20, 30	3–5 yrs: 2.5 QAM–20 BID; 6–17 yrs: 5 QAM–20 BID	45–60 6–8	Can be crushed	3–17, adults	Tablet; mixed salt of l- and d-amphetamine
Long-acting						
Adderall XR [G] (Mixed amphetamine salts) 2001	5, 10, 15, 20, 25, 30	6–12 yrs: 5–30 QAM; 13–17 yrs: 10–40 QAM	45–60 8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads; mixed salt of l- and d-amphetamine; mimics BID dosing
Adzenys XR-ODT Adzenys ER oral suspension (Amphetamine) 2016, 2017	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 Oral suspension: 1.25 mg/mL	6–12 yrs: 6.3–18.8 QAM; 13–17 yrs: 6.3–12.5 QAM	45–60 8–12	No (ODT, liquid)	6–17, adults	ER orally disintegrating tablets; 3.1 mg is equivalent to 5 mg mixed salts product; increasing dose preparations are equivalent to 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg respectively. Solution: 1.25 mg is equivalent to 2 mg Adderall XR.
Dexedrine Spansules [G] (Dextroamphetamine) 1976	5, 10, 15	5 QAM–20 BID	30–60 6–8	Can be sprinkled; do not crush or chew	3–16	Capsule of 50% IR & 50% sustained-release beads
Dyanavel XR (Amphetamine) 2015, 2021	5, 10, 15, 20 Oral suspension: 2.5 mg/mL	2.5–20 QAM	45–60 8–12	No (oral suspension)	6–17	ER oral suspension allowing once-daily dosing (must shake well); 2.5 mg = 4 mg mixed amphetamine salts
Mydayis (Mixed amphetamine salts) 2017	12.5, 25, 37.5, 50	12.5–25 QAM	45–60 10–16	Can be sprinkled; do not crush or chew	13–17, adults	pH-dependent ER capsule formulation; may have effect up to 16 hours
Vyvanse (Lisdexamfetamine) 2007, 2017	10, 20, 30, 40, 50, 60, 70 Chewable: 10, 20, 30, 40, 50, 60	30–70 QAM	60–90 8–13	Can be dissolved in water or sprinkled into soft food	6–17, adults	Lisdexamfetamine is prodrug of dextroamphetamine
Xelstrym patch (Dextroamphetamine transdermal system) 2022	4.5, 9, 13.5, 18	4.5 QAM–18 QAM Remove after 9 hours	120 8–12	No	6–17, adults	CR patch; duration can be shortened by decreasing wear time; drug effects may persist for 5 hours after removal

Brand Name (Generic Name, if different than heading) Year FDA Approved *[G] denotes generic availability*	Available Strengths (mg except where noted)	Usual Pediatric Dosage Range (starting–max) (mg)	Onset of Action (minutes) / Duration of Action (hours)	Can It Be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate release, CR = controlled release, DR = delayed release, ER = extended release)
Non-stimulants						
Catapres [G] (Clonidine IR) 1974	0.1, 0.2, 0.3 Patch: 0.1/day, 0.2/day, 0.3/day	0.05 QHS; increase by 0.05 mg/day every 3–7 days and give divided up to QID; max 0.4 QD	N/A / 4–6 (tablets); 24 (patch)	Tablets can be crushed	Not FDA approved for ADHD; approved for adults 18+ for hypertension	Avoid abrupt discontinuation; taper slowly over 4–7 days to reduce risk of rebound hypertension
Intuniv [G] (Guanfacine ER) 2009	1, 2, 3, 4	1–4 QD (do not increase faster than 1 mg/wk) (adolescents 7 mg/day max)	N/A / 24	No	6–17	ER tablet; do not stop abruptly (rebound hypertension); not a 1:1 conversion from IR; do not give with high-fat meals
Kapvay [G] (Clonidine XR) 2010	0.1, 0.2	0.1 QHS; increase by 0.1 mg/day weekly and give divided BID; max 0.4 QD	N/A / 12–16	No	6–17	ER tablet; titrate gradually (orthostatic hypotension); avoid abrupt discontinuation; somnolence
Provigil [G] (Modafinil) 1998	100, 200	100–400 QAM	N/A / 18–24	Yes (200 mg tabs are scored)	Not FDA approved for ADHD	Tablet; studies have shown modafinil to be helpful for ADHD, but low incidence of serious rash; minimal data in children
Qelbree (Viloxazine ER) 2021	100, 150, 200	100–400 QAM	N/A / 24	Can be sprinkled	6–17, adults	ER capsule; norepinephrine reuptake inhibitor
Strattera [G] (Atomoxetine) 2002	10, 18, 25, 40, 60, 80, 100	Dosage varies[1]	N/A / 24	No	6–17, adults	Capsule; norepinephrine reuptake inhibitor
Tenex [G] (Guanfacine IR) 1986	1, 2	1–4 QD (do not increase faster than 1 mg/wk)	N/A / 17	Can be crushed	Not FDA approved for kids or ADHD; approved only for adults 18+ for hypertension	Avoid abrupt discontinuation; taper slowly over 4–7 days to reduce risk of rebound hypertension
Wellbutrin [G] (Bupropion) 1985	75, 100	1.4–6 mg/kg/day	N/A / 6–9	Yes	Not FDA approved for ADHD	Tablet; bupropion SR and XL versions exist

[1]Strattera dosing: Weight <70 kg, start 0.5 mg/kg, target 1.2 mg/kg, max 1.4 mg/kg; weight >70 kg, 40–100 mg

TABLE 2: Relative Equivalency and Conversion Guide for Stimulants[1]

Methylphenidates	
Alternative Formulation	**Regular Methylphenidate Equivalent**
Adhansia XR 25 mg QAM	5 mg IR TID
Adhansia XR 50 mg QAM	10 mg IR TID
Aptensio XR 10 mg QAM	5 mg IR BID or 10 mg ER QAM
Concerta 18, 27, 36, 54 mg tablets	10–15, 15–20, 20–30, 30–45 mg/day, respectively; use 72 mg Concerta for 45–60 mg/day
Cotempla XR-ODT 8.6, 17.3, 25.9 mg tablets	ER 10, 20, 30 mg, respectively
Daytrana patch 10 mg	5 mg IR BID or 10 mg ER QAM
Focalin 5 mg BID	10 mg IR BID
Focalin XR 10 mg QAM	20 mg IR QAM
Jornay PM 20 mg QPM	4 mg IR TID
Jornay PM 100 mg QPM	20 mg IR TID
Quillichew ER 20 mg QAM	10 mg IR BID or 20 mg ER QAM
Quillichew ER 30 mg QAM	15 mg IR BID or 30 mg ER QAM
Quillichew ER 40 mg QAM	20 mg IR BID or 40 mg ER QAM
Quillivant XR 10 mg (2 mL) QAM	5 mg IR BID or 10 mg ER QAM
Quillivant XR 20 mg (4 mL) QAM	10 mg IR BID or 20 mg ER QAM
Quillivant XR 30 mg (6 mL) QAM	15 mg IR BID or 30 mg ER QAM
Quillivant XR 40 mg (8 mL) QAM	20 mg IR BID or 40 mg ER QAM
Amphetamines	
Alternative Formulation	**Regular Mixed Amphetamine Salts Equivalent**
Adzenys XR ODT 3.1 mg QAM	2.5 mg IR BID or 5 mg ER QAM
Adzenys XR ODT 6.3 mg QAM	5 mg IR BID or 10 mg ER QAM
Adzenys XR ODT 9.4 mg QAM	7.5 mg IR BID or 15 mg ER QAM
Adzenys XR ODT 12.5 mg QAM	10 mg IR BID or 20 mg ER QAM
Adzenys XR ODT 15.7 mg QAM	12.5 mg IR BID or 25 mg ER QAM
Adzenys XR ODT 18.8 mg QAM	15 mg IR BID or 30 mg ER QAM
Adzenys ER 3.125 mg (2.5 mL) QAM	2.5 mg IR BID or 5 mg ER QAM
Adzenys ER 6.25 mg (5 mL) QAM	5 mg IR BID or 10 mg ER QAM
Adzenys ER 9.375 mg (7.5 mL) QAM	7.5 mg IR BID or 15 mg ER QAM
Adzenys ER 12.5 mg (10 mL) QAM	10 mg IR BID or 20 mg ER QAM
Adzenys ER 15.625 mg (12.5 mL) QAM	12.5 mg IR BID or 25 mg ER QAM
Adzenys ER 18.75 mg (15 mL) QAM	15 mg IR BID or 30 mg ER QAM
Dyanavel XR 6.25 mg (2.5 mL)	5 mg IR BID or 10 mg ER QAM
Dyanavel XR 12.5 mg (5 mL)	10 mg IR BID or 20 mg ER QAM
Dyanavel XR 18.75 mg (7.5 mL)	15 mg IR BID or 30 mg ER QAM
Mydayis 25 mg QAM	20 mg ER QAM
Vyvanse 30 mg QAM	5 mg IR BID or 10 mg ER QAM
Vyvanse 50 mg QAM	10 mg IR BID or 20 mg ER QAM
Vyvanse 70 mg QAM	15 mg IR BID or 30 mg ER QAM

IR = immediate release; ER = extended release

[1]These are approximate equivalencies provided as guidance; taper and titrate each agent based on recommended dosing when switching, or start the new stimulant at a somewhat lower dose than the calculation

AMPHETAMINE (Adzenys XR-ODT, Dyanavel XR, Evekeo) Fact Sheet [G]

BOTTOM LINE:
Newer formulations of an old drug come with a high price tag. Stick to the usual amphetamine products like mixed amphetamine salts unless liquid or ODT dosing is absolutely necessary.

PEDIATRIC FDA INDICATIONS:
ADHD (Adzenys XR-ODT and Dyanavel XR: children >6; Evekeo: children >3).

ADULT FDA INDICATIONS:
ADHD (Adzenys XR-ODT); narcolepsy (Evekeo); obesity (Evekeo).

OFF-LABEL USES:
Treatment-resistant depression.

DOSAGE FORMS:
- **Tablets (Evekeo, [G]):** 5 mg, 10 mg (scored); **(Evekeo ODT):** 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg.
- **ER tablets (Dyanavel XR):** 5 mg (scored), 10 mg, 15 mg, 20 mg.
- **ER orally disintegrating tablets (Adzenys XR-ODT):** 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg.
- **ER oral suspension (Dyanavel XR):** 2.5 mg/mL; **(Adzenys ER):** 1.25 mg/mL.

PEDIATRIC DOSAGE GUIDANCE:
- Tablets (Evekeo, [G]):
  - Children 3–5: Start 2.5 mg QAM, increase in 2.5 mg/day increments weekly to maximum of 40 mg/day in divided doses.
  - Children 6–17: Start 5 mg QAM, increase in 5 mg/day increments weekly to maximum of 40 mg/day in divided doses.
- ER ODT (Adzenys XR-ODT) or Adzenys ER oral suspension:
  - Start 6.3 mg QAM, increase in 3.1 mg (2.5 mL)/day–6.3 mg (5 mL)/day increments weekly. Maximum of 18.8 mg (15 mL)/day (ages 6–12) or 12.5 mg (10 mL)/day (ages 13–17).
- ER oral suspension (Dyanavel XR):
  - Start 2.5–5 mg QAM, increase in 2.5–10 mg/day increments every four to seven days. Maximum 20 mg/day.

MONITORING: Weight, height, BP/P; ECG.

COST: [G]: $$$; others: $$$$

SIDE EFFECTS:
- Most common: Abdominal pain, decreased appetite, weight loss, insomnia, headache, nervousness.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily via CYP2D6; t ½: 11 hours.
- Avoid use with MAOIs, antacids.

EVIDENCE AND CLINICAL PEARLS:
- FDA approved, many studies, history of clinical efficacy and safety, and larger effect size than non-stimulants.
- Racemic l-isomer is more potent than d-isomer in peripheral activity (more cardiovascular effects, tics).
- There may be less appetite suppressant effects with racemic mixture compared to dextroamphetamine.
- Divide IR (Evekeo) doses by intervals of four to six hours.
- Approximate equivalence doses of Adzenys XR-ODT and mixed amphetamine salts XR (Adderall XR) are: 3.1 mg = 5 mg, 6.3 mg = 10 mg, 9.4 mg = 15 mg, 12.5 mg = 20 mg, 15.7 mg = 25 mg, 18.8 mg = 30 mg.
- Shake Dyanavel XR oral suspension for extended release. 2.5 mg/mL = 4 mg of mixed amphetamine salts.
- Amphetamines are not interchangeable on a mg:mg basis. When switching, use a lowered dose and adjust.

FUN FACT:
The term "amphetamine" is the contracted form of the chemical "alpha-methylphenethylamine." Its first pharmacologic use was when pharmaceutical company Smith, Kline and French sold amphetamine under the trade name Benzedrine as a decongestant inhaler.

ATOMOXETINE (Strattera) Fact Sheet [G]

BOTTOM LINE:
Advantages: Unlike stimulants, atomoxetine has no abuse potential, causes less insomnia and anxiety, and is unlikely to worsen tics.
Disadvantages: It is generally less effective than stimulants, and takes longer to work (two to four weeks).

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD.

OFF-LABEL USES:
Treatment-resistant depression.

DOSAGE FORMS:
Capsules (G): 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg.

PEDIATRIC DOSAGE GUIDANCE:
- Children >70 kg: Start 40 mg QAM for three days, ↑ to 80 mg QAM, may ↑ to 100 mg/day after two to four weeks if needed (max 100 mg/day); may divide doses >40 mg/day (divided dosing in morning and late afternoon/early evening).
- Children <70 kg: Start 0.5 mg/kg QAM for three days, ↑ to 1.2 mg/kg QAM, may ↑ to max 1.4 mg/kg/day or 100 mg/day (whichever is less) after two to four weeks, if needed; may divide doses >0.5 mg/kg/day (divided dosing in morning and late afternoon/early evening).

MONITORING: BP/P, LFTs.

COST: $

SIDE EFFECTS:
- Most common: Headache, abdominal pain, decreased appetite, fatigue, nausea, vomiting.
- Serious but rare: Class warning for suicidal ideation in children and teens. Severe hepatic injury including increased hepatic enzymes (up to 40 times normal) and jaundice (bilirubin up to 12 times upper limit of normal). Increased blood pressure (↑ 15–20 mmHg) and heart rate (↑ 20 bpm).

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Selective norepinephrine reuptake inhibitor (NRI).
- Metabolized primarily via CYP2D6; t ½: 5 hours.
- Avoid use with MAOIs. Exercise caution with 2D6 inhibitors such as fluoxetine, paroxetine, and quinidine (increased atomoxetine serum levels); use slower titration and do not exceed 80 mg/day in presence of 2D6 inhibitors or in 2D6 poor metabolizers.

EVIDENCE AND CLINICAL PEARLS:
- Effective and FDA approved for ADHD; however, several studies clearly show it does not produce as robust of a treatment effect as stimulants.
- QAM dosing is as effective as BID, but BID dosing has better GI tolerability. Can also be dosed at bedtime if it causes fatigue.
- Appears to be more effective in improving attention than in controlling hyperactivity.
- Of the two NRIs available for ADHD, atomoxetine is cheaper than viloxazine.

FUN FACT:
Atomoxetine was originally known as "tomoxetine"; however, the FDA requested that the name be changed because the similarity to "tamoxifen" could lead to dispensing errors.

CLONIDINE (Catapres, Kapvay) Fact Sheet [G]

BOTTOM LINE:
Clonidine is a good option in kids with ADHD who also have tics, who experience excessive anxiety or insomnia on stimulants, or in whom substance misuse is a concern. Its delayed onset of effect (two to four weeks) and lower efficacy rates make it a second-line choice for ADHD generally; however, it can also be used as an add-on to stimulant medication. Commonly used off label for anxiety and insomnia, but efficacy data are limited.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years [ER formulation only]).

ADULT FDA INDICATIONS:
Hypertension.

OFF-LABEL USES:
ADHD (IR); insomnia; anxiety; PTSD; opioid withdrawal; autism; ODD; Tourette's and motor tics; migraine prophylaxis; aggression.

DOSAGE FORMS:
- **IR tablets (Catapres, [G]):** 0.1 mg, 0.2 mg, 0.3 mg.
- **ER tablets (Kapvay, [G]):** 0.1 mg, 0.2 mg.
- **Patch (Catapres-TTS, [G]):** 0.1 mg/day, 0.2 mg/day, 0.3 mg/day.

PEDIATRIC DOSAGE GUIDANCE:
- ADHD or anxiety:
  - ER: 0.1 mg QHS; increase by 0.1 mg/day weekly and give divided BID; max 0.4 mg QD.
  - IR: 0.05 mg QHS; increase by 0.05 mg/day increments every three to seven days; max 0.2 mg/day for 27–40.5 kg, 0.3 mg/day for 40.5–45 kg, or 0.4 mg/day for >45 kg; doses may be divided up to QID dosing.
- Insomnia: Start 0.05 mg IR QHS, titrate if needed by 0.05 mg (<45 kg) or 0.1 mg (>45 kg) increments every three to seven days; max 0.4 mg nightly, though most will respond to doses ≤0.2 mg at bedtime.

MONITORING: BP.

COST: $

SIDE EFFECTS:
- Most common: Somnolence, fatigue, dizziness, headache.
- Serious but rare: Hypotension, syncope, orthostasis.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Centrally acting alpha-2 adrenergic agonist.
- Metabolized primary through CYP2D6; t ½: 12–16 hours.
- Avoid use with MAOIs. Additive effects with other antihypertensives. Caution with 2D6 inhibitors (eg, paroxetine, fluoxetine, duloxetine).

EVIDENCE AND CLINICAL PEARLS:
- Studies support the use of clonidine to decrease residual hyperactivity, impulsivity, and aggression in ADHD.
- Several small limited (chart review, case series, descriptive, or retrospective) studies have supported the efficacy of clonidine as a sleep aid in autistic kids as well as children with and without ADHD, developmental delays, and genetic syndromes; however, a small systematic chart review showed significant subjective improvement in sleep in children, but only a nonsignificant trend for improvement of sleep in adolescents.
- Avoid abrupt discontinuation because of potential risk for rebound hypertension. When discontinuing, taper in no more than 0.1 mg/day decrements every three to seven days to reduce the risk of rebound hypertension. If a child misses two or more consecutive doses, consider repeating titration.
- Although a few studies support use of the patch for treating tic disorders, the patch formulation is not typically used except for treating hypertension because its effects on BP may be prolonged and continue even after patch removal.
- Many child psychiatrists prefer clonidine as an agent for sleep, but little empirical evidence exists to support this use. Still, anecdotal clinical experience suggests clonidine is generally safe and effective for insomnia, particularly in kids with ADHD.
- Generally more sedating than guanfacine.

FUN FACT:
In the early 1960s, Boehringer Ingelheim wished to synthesize a peripherally active adrenergic drug for nasal decongestion as nose drops. After administering the potential compound to a secretary, she fell asleep for 24 hours, developing low blood pressure, low pulse, and dry mouth. This compound was subsequently developed as clonidine for treating hypertension.

DEXMETHYLPHENIDATE (Azstarys, Focalin, Focalin XR) Fact Sheet [G]

BOTTOM LINE:
Focalin is just Ritalin but more potent. It's available as a generic and may mean fewer tablets for patients. Focalin XR only recently went generic. Azstarys is a newly approved (and expensive) combination of Focalin and a prodrug version of Focalin—the Focalin is absorbed quickly while the prodrug is absorbed more slowly (it's the Vyvanse of methylphenidate, with less potential misuse than Focalin).

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD (Azstarys, Focalin XR).

OFF-LABEL USES:
Narcolepsy; obesity; treatment-resistant depression.

DOSAGE FORMS:
- **Dexmethylphenidate tablets (Focalin, [G]):** 2.5 mg, 5 mg, 10 mg.
- **Dexmethylphenidate ER capsules (Focalin XR, [G]):** 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg.
- **Serdexmethylphenidate/dexmethylphenidate ER capsules (Azstarys):** 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg.

PEDIATRIC DOSAGE GUIDANCE:
- d-MPH IR: Start 2.5 mg BID, ↑ by 5–10 mg/day every seven days. Max 20 mg/day; divide IR doses by at least four hours.
- d-MPH ER: Start 5 mg QAM, ↑ by 5 mg/day every seven days. Max 30 mg/day.
- Serdex-MPH/d-MPH: Start 39.2/7.8 mg QAM, ↑ to max dose of 52.3/10.4 mg after one week if indicated.

MONITORING: Weight, height, BP/P; ECG.

COST: IR: $; ER: $$; Azstarys: $$$$

SIDE EFFECTS:
- Most common: Decreased appetite, insomnia, anxiety, GI distress, irritability, tics, headache, tachycardia, hypertension, dry mouth.
- Serious but rare: See cardiovascular class warning in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Serdexmethylphenidate (Serdex-MPH) is a prodrug of dexmethylphenidate (d-MPH). d-MPH is metabolized primarily via de-esterification, not CYP450; t ½: 2–4.5 hours (2–3 hours in children); d-MPH ER delivers 50% of dose immediately and 50% about five hours later. Azstarys t ½: 6–12 hours; delivers 30% d-MPH immediately and 70% as prodrug.
- Avoid use with MAOIs.

EVIDENCE AND CLINICAL PEARLS:
- Several randomized controlled trials and meta-analyses have shown dexmethylphenidate, like other stimulants, is effective for ADHD with a large treatment effect size.
- Focalin is the d-isomer of methylphenidate and is twice as potent as methylphenidate, which is why it is prescribed at about half the dose. Serdex-MPH is a prodrug, converted to d-MPH in the lower GI tract.
- Use the same total daily dose of Focalin IR as Focalin XR. The combined dose of Azstarys 26.1/5.2, 39.2/7.8, or 52.3/10.4 mg is equivalent to 20, 30, or 40 mg of Focalin, respectively.
- Focalin XR capsules contain two kinds of beads: Half are immediate-release beads and half are enteric-coated delayed-release beads. A single, once-daily dose of XR capsule provides the same amount of dexmethylphenidate as two IR tablets given four hours apart.
- The ER capsules cannot be split in half. However, they can be opened and the beads sprinkled over food. The patient should then eat all that food—eating half won't work to split the dose accurately because it won't be possible to determine if the eaten portion contains more immediate-release or delayed-release beads.
- Give with food if GI side effects occur.

FUN FACT:
With two stereoactive centers, methylphenidate has four possible stereoisomers. Of the four, dexmethylphenidate is the most active biologically.

DEXTROAMPHETAMINE (Dexedrine, ProCentra, Zenzedi) Fact Sheet [G]

BOTTOM LINE:
Good drug with very long history of experience, available in short- and long-acting formulations as generics.

PEDIATRIC FDA INDICATIONS:
ADHD (3–17 years); **narcolepsy** (6–17 years).

ADULT FDA INDICATIONS:
Narcolepsy.

OFF-LABEL USES:
Obesity; treatment-resistant depression.

DOSAGE FORMS:
- **Tablets (Dexedrine, [G]):** 5 mg, 10 mg (scored).
- **Tablets (Zenzedi):** 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg (5 mg scored, 10 mg double scored; rest unscored).
- **ER capsules (Dexedrine Spansules, [G]):** 5 mg, 10 mg, 15 mg.
- **Liquid (ProCentra, [G]):** 5 mg/5 mL.

PEDIATRIC DOSAGE GUIDANCE:
- ADHD (IR and ER):
  - Children >6 years: Start 5 mg QAM; ↑ by 5 mg/day at weekly intervals to max 60 mg/day, though doses >40 mg/day rarely more effective. Divide IR dose QD–TID.
  - Children 3–5 years: Start 2.5 mg QAM; ↑ by 2.5 mg/day weekly to max 60 mg/day, though doses >40 mg/day rarely more effective. Divide IR dose QD–TID.
- Narcolepsy (IR and ER):
  - Start 5 mg QAM (ages 6–11) or 10 mg QAM (ages 12–17); ↑ by 5 mg/day (ages 6–11) or 10 mg/day (ages 12–17) weekly to max 60 mg/day. Divide IR dose QD–TID.

MONITORING: Weight, height, BP/P; ECG.

COST: IR/ER: $ (ProCentra: $$$)

SIDE EFFECTS:
- Most common: Abdominal pain, anorexia, nausea, tics, insomnia, tachycardia, headache.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP450 2D6 (minor) and glucuronidation; t ½: 12 hours.
- Avoid use with MAOIs, antacids.

EVIDENCE AND CLINICAL PEARLS:
- At least five randomized clinical trials, some dating back to the 1970s, support the efficacy of dextroamphetamine in children with ADHD.
- Dextroamphetamine is the more potent d-isomer of amphetamine; it has potentially less peripheral effects (eg, motor tics) than racemic mix (eg, mixed amphetamine salts like Adderall, amphetamine, or methamphetamine).
- Doses of IR tablets and oral solution can be given at intervals of four to six hours.
- Dextroamphetamine is the only stimulant, other than Adderall IR, approved for children <6 years (approved for children >3 years).
- The newer Zenzedi brand offers more dosing flexibility options, but is more expensive than generic IR tablets.
- Available in a new patch formulation as Xelstrym (see fact sheet).
- Also available as D,L racemic mixture of amphetamine as Evekeo tablets, Adzenys XR-ODT, and Dyanavel XR oral suspension (see amphetamine fact sheet).

FUN FACT:
Dexys Midnight Runners, the British band famous for its song "Come On Eileen" (1982), derived their name from Dexedrine—"Dexys" after the drug's name and "Midnight Runners" in reference to the energy it provides.

DEXTROAMPHETAMINE TRANSDERMAL (Xelstrym) Fact Sheet

BOTTOM LINE:
A patch option in the amphetamine class of stimulants for kids who cannot use the wide array of oral stimulants available today. Minimal data and less experience than with methylphenidate transdermal (Daytrana), but similar to Daytrana in terms of high cost, lag time for onset of effect, and side effects.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD.

DOSAGE FORMS:
Transdermal patch: 4.5 mg, 9 mg, 13.5 mg, 18 mg/9 hour.

PEDIATRIC DOSAGE GUIDANCE:
Start 4.5 mg/9 hour patch QAM (for initial therapy or for patients switching from other amphetamine preparations, regardless of dose). Apply to hip, upper arm, chest, upper back, or flank two hours before an effect is needed and remove nine hours after application (drug effects may persist for five hours after removal). Increase dose at weekly intervals by using next-higher-dose system. May be removed in <9 hours if shorter duration is desired or if late-day side effects occur. Rotate application sites. Max 18 mg QD.

MONITORING: Weight, height, BP/P; ECG.

COST: $$$$

SIDE EFFECTS:
- Most common: Decreased appetite, headache, insomnia, tic, abdominal pain, vomiting, nausea, irritability, increased BP and pulse. Application site reactions and sensitization may occur.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP450 2D6 (minor) and glucuronidation; t ½: 6.4 hours (11.5 hours in adults).
- Avoid use with MAOIs, antacids.

EVIDENCE AND CLINICAL PEARLS:
- Approval was based on a two-week, randomized, double-blind, placebo-controlled, crossover, modified-analog classroom study in 110 pediatric patients with ADHD ages 6–17. Efficacy measure assessed was the Swanson, Kotkin, Angler, M. Flynn, and Pelham (SKAMP) score, a scale specific to the classroom setting.
- Dextroamphetamine is the more potent d-isomer of amphetamine; it has potentially less peripheral effects (eg, motor tics) than racemic mix (eg, mixed amphetamine salts like Adderall, amphetamine, or methamphetamine).
- The manufacturer, Noven Pharmaceuticals, Inc. recommends against cutting the patch (eg to adjust the dosage).

FUN FACT:
While Daytrana is approved for pediatric use only, Xelstrym is also approved for use in adults.

GUANFACINE (Intuniv, Tenex) Fact Sheet [G]

BOTTOM LINE:
Guanfacine's advantages over stimulants include no worsening of tic disorders, lack of misuse potential, and no insomnia. It can also be used as an add-on to stimulant medication. However, its delayed onset of effect (two to four weeks) and lower efficacy rates make it a second-line choice for ADHD generally. ER is now available in generic and easier to use than IR. Commonly used off label for anxiety and insomnia, but efficacy data are limited.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years [ER formulation only]), as monotherapy or adjunctive therapy to stimulants.

ADULT FDA INDICATIONS:
Hypertension.

OFF-LABEL USES:
Conduct disorder; Tourette's and motor tics; agitation in autistic kids; migraine prophylaxis; opioid withdrawal; anxiety and PTSD; insomnia.

DOSAGE FORMS:
- **IR tablets (Tenex, [G]):** 1 mg, 2 mg.
- **ER tablets (Intuniv, [G]):** 1 mg, 2 mg, 3 mg, 4 mg.

PEDIATRIC DOSAGE GUIDANCE:
- ADHD or anxiety:
  - IR dosing depends on weight:
    - 27–40.5 kg (55–90 lbs): Start 0.5 mg QHS, ↑ by 0.5 mg/day at weekly intervals up to 1.5 mg/day; may ↑ to 2 mg/day after two weeks; max 2 mg/day in two to four divided doses.
    - 40.5–45 kg (90–99 lbs): Start 0.5 mg QHS, ↑ by 0.5 mg/day at weekly intervals; max 1 mg per dose, 3 mg/day.
    - >45 kg (>99 lbs): Start 1 mg QHS, ↑ by 1 mg/day at weekly intervals up to 3 mg/day; may ↑ to 4 mg/day after two weeks; max 1 mg per dose, 4 mg/day.
  - ER: Start 1 mg QHS, ↑ by 1 mg/day at weekly intervals; max 4 mg/day. Alternative: 0.05–0.12 mg/kg QD or QHS; max 4 mg/day. Doses up to 7 mg/day ER studied as monotherapy in adolescents.
- Insomnia: Use IR: Start low, go slow, typically 0.5 mg QHS, increasing by 0.5 mg/day at weekly intervals; max 3 mg/day.

MONITORING: BP.

COST: $

SIDE EFFECTS:
- Most common: Dry mouth, somnolence, dizziness, constipation, fatigue, headache.
- Serious but rare: Hypotension, syncope, orthostasis.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Centrally acting, selective alpha-2 adrenergic agonist.
- Metabolized primarily through CYP3A4; t ½: 13–14 hours in children (16–18 hours in adults).
- Avoid use with MAOIs. Caution with 3A4 inhibitors (eg, clarithromycin, fluvoxamine) and inducers (eg, St. John's wort, carbamazepine).

EVIDENCE AND CLINICAL PEARLS:
- At least six randomized placebo-controlled trials and a meta-analysis show efficacy in children with ADHD.
- A pilot study of 83 children with GAD, separation anxiety, or social anxiety found guanfacine treatment resulted in greater subjective improvement of anxiety than placebo, but no improvement on other measures of anxiety.
- One negative randomized trial for insomnia in children with ADHD found decreased total sleep time of nearly an hour, with kids taking more time to fall asleep.
- Guanfacine IR and ER are not interchangeable on a mg:mg basis. When switching, taper and retitrate.
- Guanfacine tends to be less sedating than clonidine, another alpha-agonist.
- ER tablets should not be taken with a high-fat meal due to increased medication exposure.
- Minimize side effects, especially somnolence, by administering at bedtime.
- Monitor BP, especially during initial dosing titration.
- There is a risk of nervousness, anxiety, and possibly rebound hypertension two to four days after abrupt discontinuation. Taper dose in 1 mg/day decrements every three to seven days.
- If a child misses two or more consecutive doses, consider repeating titration.

FUN FACT:
Some prescribers have taken advantage of guanfacine's sympatholytic properties for the treatment of anxiety disorders in children as well as nightmares and dissociative symptoms in PTSD.

LISDEXAMFETAMINE (Vyvanse) Fact Sheet

BOTTOM LINE:
Vyvanse may have a gentler, "smoother" side effect profile than other amphetamines, and probably has a lower risk of diversion or misuse. However, its high cost means insurance companies don't like to pay for it without prior authorizations.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD; binge eating disorder (BED).

OFF-LABEL USES:
Narcolepsy; obesity; treatment-resistant depression.

DOSAGE FORMS:
- **Capsules:** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg.
- **Chewable tablets:** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg.

PEDIATRIC DOSAGE GUIDANCE:
Start 30 mg QAM, ↑ by 10–20 mg/day at weekly intervals. Target lowest effective dose; max 70 mg/day.

MONITORING: Weight, height, BP/P; ECG.

COST: $$$$

SIDE EFFECTS:
- Most common: Insomnia, anorexia, abdominal pain, irritability, agitation, tics, decreased appetite, increased heart rate, jitteriness, anxiety.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through non-CYP-mediated hepatic and/or intestinal metabolism; t ½: lisdexamfetamine (inactive prodrug) <1 hour; dextroamphetamine (active metabolite) 12 hours. Dextroamphetamine metabolized by CYP2D6.
- Avoid use with MAOIs and antacids. Caution with antihypertensives (decreased efficacy of antihypertensive). Caution with 2D6 inhibitors, which may increase stimulant effects.

EVIDENCE AND CLINICAL PEARLS:
- At least five randomized controlled trials and a meta-analysis support efficacy of lisdexamfetamine in children with ADHD.
- Lisdexamfetamine is dextroamphetamine with the chemical lysine bound to it, which renders it inactive. It remains inactive until GI enzymes cleave off lysine and convert it to active dextroamphetamine. This means that people who misuse it can't get high by snorting it or injecting it.
- Anecdotally, Vyvanse has a more gradual onset and offset than other stimulants, and may cause fewer side effects than other amphetamines.
- Taking with food decreases the effect slightly and delays peak levels by an hour. If patients feel it's not "kicking in" fast enough, have them take it earlier or on an empty stomach.
- Lisdexamfetamine 70 mg is equivalent to 30 mg of mixed amphetamine salts (Adderall).
- While indicated for BED, it is not approved for use as a weight-loss or anti-obesity agent, nor has it been studied in children.

FUN FACT:
The manufacturer of Vyvanse pursued an indication as an add-on medication for depression, but disappointing results in clinical trials put an end to this effort.

METHAMPHETAMINE (Desoxyn) Fact Sheet [G]

BOTTOM LINE:
Highly addictive substance; its use is generally not recommended. Watch the television show *Breaking Bad* if you're not convinced!

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years); **obesity** (12–17 years).

ADULT FDA INDICATIONS:
Obesity.

DOSAGE FORMS:
Tablets (G): 5 mg.

PEDIATRIC DOSAGE GUIDANCE:
ADHD: Start 5 mg QAM–BID, ↑ by 5 mg/day at weekly intervals to max 20 mg/day, divided BID.

MONITORING: Weight, height, BP/P; ECG.

COST: $$$$

SIDE EFFECTS:
- Most common: Anorexia, tachycardia, dizziness, insomnia, tremor, tics, restlessness, headache, constipation (decreased GI motility). Dental complications, such as poor dental hygiene, diffuse cavities, bruxism, and tooth wear, may develop with misuse.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP2D6 to active metabolite (amphetamine); t ½: 4–5 hours.
- Avoid use with MAOIs and antacids. Caution with 2D6 inhibitors, which may increase stimulant effects.

EVIDENCE AND CLINICAL PEARLS:
- FDA indication, but very limited published data in children.
- High risk of misuse.
- Not widely used (DEA reports that there were only 16,000 prescriptions written in 2012). When prescribed for obesity, the recommendation is for short-term (ie, a few weeks) use only and as an adjunct to caloric restriction due to its high addiction and diversion potential.
- CNS stimulating effect is approximately equal to or greater than that of amphetamine but less than that of dextroamphetamine; less BP elevation than with amphetamine.

FUN FACTS:
Desoxyn is the same as the abused street drug methamphetamine, just pharmaceutical grade. Although methamphetamine and amphetamine were long thought to be available only via laboratories, methamphetamine has been reported to occur naturally in certain acacia trees that grow in West Texas.

METHYLPHENIDATE IR (Methylin, Ritalin) Fact Sheet [G]

BOTTOM LINE:
Better side effect profile and somewhat lower misuse potential than amphetamines. However, patients often prefer the "kick" they get from Adderall.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD; narcolepsy.

OFF-LABEL USES:
Obesity; treatment-resistant depression.

DOSAGE FORMS:
- **Tablets (Ritalin, [G]):** 5 mg, 10 mg, 20 mg.
- **Chewable tablets (Methylin CT, [G]):** 2.5 mg, 5 mg, 10 mg.
- **Oral solution (Methylin, [G]):** 5 mg/5 mL, 10 mg/5 mL.

PEDIATRIC DOSAGE GUIDANCE:
- ADHD: Children 6–17 years: Start 0.3 mg/kg BID or 2.5–5 mg BID before breakfast and lunch, increase by 0.1 mg/kg/dose or 5–10 mg/day at weekly intervals to a max of 2 mg/kg/day or 60 mg/day.
- Narcolepsy: Same dosing as ADHD.

MONITORING: Weight, height, BP/P; ECG.

COST: $; chewable tablets: $$$

SIDE EFFECTS:
- Most common: Insomnia, headache, nervousness, abdominal pain, nausea, vomiting, anorexia, weight loss, affect lability, tics.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Hepatic metabolism via carboxylesterase CES1A1, not CYP450 isoenzymes; t ½: 2–4 hours.
- Avoid use with MAOIs, antacids.

EVIDENCE AND CLINICAL PEARLS:
- FDA approved with many studies and long history of clinical use supporting its efficacy and safety, with a larger treatment effect size than non-stimulant medications.
- Methylphenidate generally causes fewer side effects than amphetamine preparations—patients are less likely to report feeling "wired."
- While all stimulants may unmask tics, a Cochrane review of eight randomized trials showed that methylphenidate did not worsen tics in children with ADHD and a tic disorder; in some cases it even improved tics.
- Methylin chewable tablet: Administer with at least 8 ounces of water or other fluid.

FUN FACT:
Methylphenidate was synthesized by Ciba (now Novartis) chemist Leandro Panizzon. His wife, Marguerite, had low blood pressure and would take the stimulant before playing tennis. He named the substance "Ritaline" (yes, with the "e" on the end) after his wife's nickname, Rita.

METHYLPHENIDATE ER (Concerta, Ritalin SR and LA, others) Fact Sheet [G]

BOTTOM LINE:
There are many longer-acting methylphenidate preparations. Two good options are Concerta and Ritalin LA, available as generics.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD; narcolepsy.

OFF-LABEL USES:
Obesity; treatment-resistant depression.

DOSAGE FORMS (more commonly used):
- Tablets
  - **SR tablets (Ritalin SR, Metadate ER, Methylin ER, [G]):** 10 mg, 20 mg.
  - **ER capsule osmotic release oral system (OROS) (Concerta, [G]):** 18 mg, 27 mg, 36 mg, 54 mg (22% IR/78% ER).
- Capsules
  - **Ritalin LA, [G]:** 10 mg, 20 mg, 30 mg, 40 mg, 60 mg (50% IR/50% ER).
  - **Metadate CD, [G]:** 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (30% IR/70% ER).
  - **Aptensio XR:** 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (40% IR/60% ER).
  - **Adhansia XR:** 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg (20% IR/80% ER)
  - **Jornay PM:** 20 mg, 40 mg, 60 mg, 80 mg, 100 mg (onset delayed 10 hours).
  - **ER oral suspension (Quillivant XR):** 25 mg/5 mL (20% IR/80% ER).
  - **ER chewable tablets (Quillichew ER):** 20 mg, 30 mg (scored), 40 mg (scored) (30% IR/70% ER).
  - **ER orally disintegrating tablets (Cotempla XR-ODT):** 8.6 mg, 17.3 mg, 25.9 mg (25% IR/75% ER).

PEDIATRIC DOSAGE GUIDANCE:
- Intermediate-acting (Ritalin SR, Metadate ER, Methylin ER): Titrate to effective daily dose with IR, then switch to equivalent eight-hour SR or ER dose QAM–BID or start 10 mg QAM and increase by 10 mg/day increments weekly; max 60 mg/day.
- Long-acting (Aptensio XR, Metadate CD, Ritalin LA, Quillivant XR, Quillichew ER): Start 10–20 mg QAM; ↑ by 10 mg/day at weekly intervals; max 60 mg/day.
- Long-acting (Adhansia XR): Start 25 mg QAM; ↑ by 10–15 mg/day at weekly intervals; max 70 mg/day (children) and 85 mg/day (adults).
- Long-acting (Cotempla XR-ODT):
  - Start 17.3 mg QAM; ↑ by 8.6–17.3 mg/day at weekly intervals; max 51.8 mg/day.
  - 8.6 mg, 17.3 mg, 25.9 mg equivalent to 10 mg, 20 mg, 30 mg of other methylphenidate formulations, respectively.
- Long-acting (Concerta):
  - Start 18 mg QAM (ages 6–12) or 36 mg (ages 13–17) QAM; ↑ by 18 mg/day in weekly intervals to max 54 mg/day (ages 6–12) or 72 mg/day (ages 13–17).
  - If switching from different form of methylphenidate:
    - 10–15 mg/day: Use 18 mg QAM.
    - 20–30 mg/day: Use 36 mg QAM.
    - 30–45 mg/day: Use 54 mg QAM.
    - 40–60 mg/day: Use 72 mg QAM.
    - 27 mg dose is available for situations in which a dose between 18 mg and 36 mg is desired.
- Jornay PM: Start 20 mg daily in the evening and increase in increments of 20 mg/day up to maximum of 100 mg/day. Adjust timing between 6:30 and 9:30 p.m.

COST: $$; Aptensio XR, Cotempla XR-ODT, Concerta, Jornay PM, Quillivant XR, and Quillichew ER: $$$$

SIDE EFFECTS AND MECHANISM, MONITORING, PHARMACOKINETICS, AND DRUG INTERACTIONS:
Weight, height, BP/P; ECG. See methylphenidate IR fact sheet.

EVIDENCE AND CLINICAL PEARLS:
- FDA approved with many studies and long history of clinical use supporting its efficacy and safety, with a larger treatment effect size than non-stimulant medications.
- ER capsules contain mixture of 30% IR and 70% ER beads. Aptensio XR, a new branded formulation of ER capsules, contains a mixture of 40% IR and 60% ER beads. Ritalin LA and its generic ER capsules are a combination of 50% IR and 50% DR beads. These products mimic BID dosing of IR. Cotempla delivers a mixture of 25% IR and 75% ER in an orally disintegrating extended-release formulation. Jornay PM is dosed in evening; if early-morning awakening occurs, dose earlier in evening.
- Concerta is based on the OROS osmotic delivery system (also used for Invega). 22% of the dose is immediate (with effects in one to two hours) and 78% is delayed. If you prescribe a generic, you may need to investigate carefully to ensure that the delivery system is an OROS pump system. To avoid insomnia, dosing should be completed by noon.

METHYLPHENIDATE TRANSDERMAL (Daytrana) Fact Sheet

BOTTOM LINE:
Daytrana is helpful for kids who, for whatever reason, cannot use any of the wide variety of oral stimulant preparations. Otherwise, we don't recommend it due to high cost, lag time for onset of effect, and the side effect of rash, which is pretty common and unpleasant.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD.

DOSAGE FORMS:
Transdermal patch: 10 mg, 15 mg, 20 mg, 30 mg/9 hour.

PEDIATRIC DOSAGE GUIDANCE:
Start 10 mg/9 hour patch QAM (for initial therapy or for patients switching from other methylphenidate preparations, regardless of dose). Apply to hip two hours before an effect is needed and remove nine hours after application (drug effects may persist for five hours after removal). Increase dose at weekly intervals by using next-higher-dose system. May be removed in <9 hours if shorter duration is desired or if late-day side effects occur. Rotate application sites. Max 30 mg QD.

MONITORING: Weight, height, BP/P; ECG.

COST: $$$

SIDE EFFECTS:
- Most common: Headache, insomnia, irritability, decreased appetite, anorexia, nausea, tics, application site reaction (10%–40% incidence in children).
- Serious but rare: Allergic contact dermatitis/sensitization, characterized by intense local reactions (eg, edema, papules) that may spread beyond patch site; sensitization may subsequently manifest systemically with other routes of methylphenidate administration.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Hepatic metabolism via carboxylesterase CES1A1, not CYP450 isoenzymes; t ½: 3–4 hours.
- Avoid use with MAOIs, antacids.

EVIDENCE AND CLINICAL PEARLS:
- FDA approved with several studies supporting its efficacy and safety, with a larger treatment effect size than non-stimulant medications, including in preschoolers (albeit no FDA indication for this age group).
- Apply patch to clean, dry area of the hip; don't apply to waistline or to areas under tight clothes, as it may rub off. Alternate sites daily (eg, opposite hip). Absorption not affected by perspiration. Remove after nine hours. If dislodged, replace with a new patch but remove within the nine-hour total wear time.
- Clinical effect usually seen in two hours and lasts approximately 12 hours.
- Exposure of application site to a heat source (eg, hair dryer, heating pad, electric blanket) may increase the amount of drug absorbed.
- For localized skin reactions (redness at site), use cortisone cream (1%–2%). For persistent, severe, or systemic reactions, discontinue patch.
- In June 2015, the FDA added a warning that Daytrana can cause chemical leukoderma, a permanent loss of skin color. These reactions are irreversible and not harmful but can be disfiguring to patients. Instruct patients to contact their physician if they notice skin color changes or lightening of skin areas; in such cases, an alternative medication should be considered.
- The manufacturer recommends to not cut the patch as it may release medication inconsistently or too quickly.

FUN FACT:
Since 2006, Shire Pharmaceuticals has issued at least 10 recalls of Daytrana patches because users have had difficulty removing the protective cover from the patch. Recall costs have reached into the millions.

MIXED AMPHETAMINE SALTS (Adderall, Adderall XR, Mydayis) Fact Sheet [G]

BOTTOM LINE:
Adderall is effective but is probably the most misused and diverted of all stimulants, and it tends to have more side effects, all of which is why we recommend starting most patients on methylphenidate instead.

PEDIATRIC FDA INDICATIONS:
ADHD (3–17 years for IR, 6–17 years for XR, 13–17 years for Mydayis); **narcolepsy** (6–17 years).

ADULT FDA INDICATIONS:
ADHD; narcolepsy.

OFF-LABEL USES:
Obesity; treatment-resistant depression.

DOSAGE FORMS:
- **Tablets (Adderall, [G]):** 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg.
- **ER capsules (Adderall XR, [G]):** 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg.
- **ER capsules (Mydayis):** 12.5 mg, 25 mg, 37.5 mg, 50 mg.

PEDIATRIC DOSAGE GUIDANCE:
- ADHD:
  - For IR and ER Adderall and its generic equivalent preparation. Initial dose should be 0.3 mg/kg/day, but shoot for a target dose of 1.0 mg/kg/day and maximum dose of 2 mg/kg/day.
  - IR (ages 3–5): Start 2.5 mg QAM, increase by 2.5 mg/day increments in weekly intervals, max 40 mg/day divided BID.
  - IR (ages 6–17): Start 5 mg QAM or BID, increase by 5 mg/day increments in weekly intervals, max 40 mg/day divided BID.
  - ER (ages 6–12): Start 5–10 mg QAM, increase by 5–10 mg/day increments weekly, 30 mg/day.
  - ER (ages 13–17): Start 10 mg QAM, increase by 10 mg/day increments weekly, max 40 mg/day QAM in adolescents.
  - Mydayis (adolescents 13–17 years): Start 12.5 mg QAM, increase in increments of 12.5 mg/day weekly, max 25 mg/day.
- Narcolepsy: Start 5 mg QAM (ages 6–11) or 10 mg QAM (ages 12–17), increase by 5 mg/day (ages 6–11) or 10 mg/day (ages 12–17) at weekly increments, max 60 mg/day.

MONITORING: Weight, height, BP/P; ECG.

COST: IR/ER: $; Mydayis: $$$$

SIDE EFFECTS:
- Most common: Insomnia, headache, decreased appetite, abdominal pain, weight loss, agitation.
- Serious but rare: See class warnings in chapter introduction.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Stimulant that inhibits reuptake of dopamine and norepinephrine.
- Metabolized primarily through CYP2D6; t ½: 9–14 hours. Duration of action: 6–8 hours (IR), 8–12 hours (XR).
- Avoid use with MAOIs, antacids. Caution with 2D6 inhibitors, which may increase stimulant effects.

EVIDENCE AND CLINICAL PEARLS:
- FDA approved with many studies and long history of clinical use supporting its efficacy and safety, with a larger treatment effect size than non-stimulant medications.
- Each dose contains a mixture of amphetamine salts, resulting in a 75:25 ratio of dextro and levo isomers of amphetamine.
- When converting from IR to ER, use the same total daily dose, given QAM.
- Adderall may provide more of a "kick" than methylphenidate preparations. Roughly twice as potent (per mg) as methylphenidate.
- Mydayis is formulated with pH-dependent drug-releasing beads, with immediate-release beads and delayed-release beads that release drug at pH 5.5 and pH 7.0. Duration of effect may be up to 16 hours.
- Dextroamphetamine and mixed amphetamine salts are the only stimulants approved for children <6 years (approved for children >3 years), with the exception of Mydayis, which causes very high rates of side effects (insomnia, reduced appetite) in children <13 years and should only be used in children ≥13 years.

FUN FACTS:
Was briefly pulled from the market in Canada in 2005 because of cardiac concerns, and now counterfeit Adderall is a common vehicle for overdose and death due to adulteration with fentanyl or methamphetamine.

VILOXAZINE XR (Qelbree) Fact Sheet

BOTTOM LINE:
Like the first norepinephrine reuptake inhibitor for ADHD, atomoxetine, viloxazine has no misuse potential and is less likely than stimulants to cause insomnia, anxiety, or tics. However, it is generally less effective than stimulants and takes longer to work. While viloxazine may work faster than atomoxetine, it's unclear if it has any advantage, and unlike atomoxetine, there's no option for a cheaper generic.

PEDIATRIC FDA INDICATIONS:
ADHD (6–17 years).

ADULT FDA INDICATIONS:
ADHD.

OFF-LABEL USES:
Treatment-resistant depression.

DOSAGE FORMS:
ER capsules: 100 mg, 150 mg, 200 mg.

PEDIATRIC DOSAGE GUIDANCE:
- Children >12: Start 200 mg QD, ↑ by 200 mg/day after one week to max 400 mg QD.
- Children 6–11: Start 100 mg QD, ↑ by 100 mg/day at weekly intervals to max 400 mg QD.

MONITORING: BP/P; baseline renal function.

COST: $$$$

SIDE EFFECTS:
- Most common: Somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, irritability.
- Serious but rare: Class warning for suicidal ideation in children and teens. Mania reported. May increase pulse and BP.

MECHANISM, PHARMACOKINETICS, AND DRUG INTERACTIONS:
- Selective norepinephrine reuptake inhibitor (NRI).
- Metabolized primarily via CYP2D6, UGT1A9, UGTB15; t ½: 7 hours.
- Avoid use with MAOIs. Strong 1A2 inhibitor; exercise caution with 1A2 substrates with narrow therapeutic index (eg, clozapine, duloxetine, ramelteon, tasimelteon, tizanidine, theophylline) as combination may increase side effects of substrate.

EVIDENCE AND CLINICAL PEARLS:
- ER capsules, so do not cut, crush, or chew; can open and sprinkle contents in applesauce.
- Adjust dose in severe renal impairment (eGFR <30 mL/min); max 200 mg/day.
- Data from one of four studies suggest viloxazine may work a bit faster than atomoxetine (week one vs week three), but this finding is not based on head-to-head data and it's hard to know whether it is clinically significant.
- Effective and FDA approved for ADHD; however, not likely to produce as robust of a treatment effect as stimulants.
- Of the two NRIs available for ADHD, atomoxetine is cheaper than viloxazine.

FUN FACT:
Viloxazine has been studied and rejected for various indications since the 1970s and originally received an FDA orphan drug designation for narcolepsy.