High-dose stimulants for adult ADHD

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Multiple formulations allow clinicians to better accommodate a patient's schedule and medical history

Ms. H, age 30, presents to the outpatient clinic for a follow-up visit, where she reports difficulty paying attention to conversations, starting and completing tasks, and meeting deadlines. These challenges occur at work and home. Her psychiatric history includes attention-deficit/hyperactivity disorder (ADHD), major depressive disorder, and generalized anxiety disorder. Approximately 10 years ago, she underwent Roux-en-Y gastric bypass surgery. Following surgery, Ms. H's care team prescribed liquid formulations of medications whenever possible to minimize malabsorption. Ms. H may be a rapid metabolizer; she says the effects of her prescribed stimulants only last briefly, so she has to frequently redose. As a result, she often runs out of her monthly stimulant allotment earlier than expected.

Ms. H's current medications include dextroamphetamine/amphetamine immediate-release (IR) 30 mg 3 times daily, atenolol 50 mg/d, and escitalopram oral solution 10 mg/d. Previous unsuccessful medication trials for her ADHD include methylphenidate IR 20 mg 3 times daily and lisdexamfetamine 70 mg/d. Ms. H reports that when her responsibilities increased at work or home, she took methylphenidate IR 20 mg up to 6 times daily to relieve her symptoms.

In the United States, ADHD affects an estimated 4.4% of adults age 18 to 44.[1] The actual rate may be higher, however, as recent research has called into question the hypothesis that approximately 50% of cases of childhood ADHD remit by adulthood.[2] Prevalence estimates relying on DSM-IV criteria (which were designed with children in mind) can underestimate this condition in adults. Newer data suggest that up to 90% of individuals with ADHD in childhood continue to experience significant ADHD symptoms into adulthood.[2]

Unless contraindications are present, methylphenidate or amphetamine-based stimulants are the medications of choice for treating adult ADHD.[3] Many formulations of both medications are available,[4]

Practice Points

- The availability of multiple stimulant formulations **allows clinicians to better tailor ADHD therapy to a patient's unique pharmacokinetics and daily schedule.**
- When prescribing stimulants to a patient experiencing actual or perceived medication malabsorption, **transdermal formulations may be an option.**
- Transdermal stimulant formulations can **improve medication bioavailability, reduce dosing frequency, and stabilize medication delivery.**

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which allows clinicians to better tailor therapy to each patient's pharmacokinetics and daily schedule. Although there can be differences in response and tolerability, methylphenidate and amphetamine offer comparable efficacy and a similar adverse effect profile.[5]

Because amphetamine is more potent than methylphenidate, clinicians commonly start treatment with an amphetamine dose that is one-half to two-thirds the dose of methylphenidate.[6] While both classes of stimulants inhibit the reuptake of dopamine and norepinephrine into presynaptic neurons, amphetamines also promote the release of dopamine and norepinephrine from their storage sites in presynaptic nerve terminals.[3]

Methylphenidate

Methylphenidate IR has an average onset of action of 30 to 45 minutes and its effects last approximately 3 to 4 hours. The extended-release (XR) formulations have varying onsets of action, with durations of action up to 12 hours (***Table 1***,[3,7] ***page 36***).[4] The XR products usually immediately release a certain percentage of the medication, eliminating the need for an additional IR tablet. One methylphenidate XR product (Jornay) as well as serdexmethylphenidate/dexmethylphenidate (Azstarys) offer durations of action of 24 to 36 hours. Methylphenidate is primarily metabolized by carboxylesterase 1 (CES1) to the inactive metabolite ritalinic acid. Most of the medication (60% to 80%) is excreted in the urine as ritalinic acid.[4] Theoretically, genetic variations in the CES1 and concomitant use of medications that compete with or alter this pathway may impact methylphenidate pharmacokinetics.[8] However, plasma levels have not yet shown to be helpful in guiding treatment selection or dosing.[4]

Amphetamine

Dextroamphetamine/amphetamine IR has an average onset of action of 30 to 45 minutes and its effects last approximately 4 to 6 hours. XR formulations have varying onsets of action, with durations of action up to 13 hours (***Table 2***,[3,7,9] ***page 37***).[4] One XR product, mixed salts of single amphetamine entity (Mydayis), has a duration of action of 16 hours. In XR formulations, a certain percentage of the medication is typically released immediately, eliminating the need for an additional IR tablet. Amphetamine is primarily metabolized by cytochrome P450 (CYP) 2D6 hydroxylation and oxidative deamination. Genetic variability in amphetamine metabolism may be relevant due to CYP2D6 polymorphisms. Ultra-rapid metabolizers might need higher doses, while poor metabolizers might require smaller amounts and may be more susceptible to adverse effects.[4] However, there is currently insufficient data supporting gene/medication concentration relationships. As is the case with methylphenidate, plasma levels have not yet shown to be helpful in guiding treatment selection or dosing.[6]

Impaired medication absorption after bariatric surgery

Medication malabsorption following bariatric surgery is a significant concern. In a systematic review of 22 studies, Padwal et al[10] found that in one-third of these studies, decreased absorption following bariatric surgery may be present in patients taking medications that have poor absorption, high lipophilicity, or enterohepatic recirculation. Childress et al[11] found that methylphenidate IR and dextroamphetamine/amphetamine are both well absorbed, with bioavailability percentages of 100% and 90%, respectively. Additional research shows both stimulants have rapid absorption rates but relatively poor bioavailability.[12] In one study analyzing the dissolution of common psychiatric medications, methylphenidate was shown to dissolve slightly more in the Roux-en-Y gastric bypass surgery model (80 mg) compared to controls (70 mg).[13] One case indicated potential methylphenidate toxicity following Roux-en-Y gastric

Clinical Point

Up to 90% of those with ADHD in childhood continue to experience significant ADHD symptoms in adulthood

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Clinical Point

Plasma levels have not been shown to be helpful in guiding methylphenidate or amphetamine treatment selection or dosing

Table 1

Methylphenidate products for treating ADHD

Medication (brand name)	Onset of action (min)[a]	Duration of action (h)	Comments
Dexmethylphenidate short-acting (Focalin)	30	3 to 6	MPH dose = ½ dexmethylphenidate dose
Dexmethylphenidate long-acting (Focalin XR)	30	9 to 12	Capsule is 50% IR and 50% delayed-release beads
Methylphenidate short-acting (Ritalin, Methylin)	20 to 30	3 to 6	
Methylphenidate, intermediate-acting (Metadate ER)	60 to 180	3 to 8	
Methylphenidate long-acting (Ritalin LA, Metadate CD)	Ritalin LA: 10 to 60; Metadate CD: 20 to 60	6 to 8	Ritalin LA capsule is 50% IR and 50% delayed-release beads; Metadate CD is 30% IR and 70% delayed-release beads
Methylphenidate XR chewable (Quillichew ER)	60 to 120	10 to 12	
Methylphenidate XR suspension (Quillivant XR)	45	12	Suspension is 20% IR and 80% delayed-release
Methylphenidate osmotic release oral system (Concerta, Relexxii)	30 to 60	10 to 12	Shell of the tablet seen in stool; tablet is 22% IR and 78% delayed-release
Methylphenidate XR multilayer bead (Aptensio XR, Adhansia XR)	Aptensio XR: 20 to 60; Adhansia XR: 30 to 60	Aptensio XR: 12; Adhansia XR: 13	Aptensio is 40% IR and 60% controlled-release multilayered beads; Adhansia is 20% IR and 80% controlled-release multilayered beads
Methylphenidate XR orally disintegrating tablet (Cotempla XR-ODT)	60	12	Tablet is 25% IR and 75% controlled-release
Methylphenidate XR capsule (Jornay PM)	8 to 10 hours	24 to 36	Patients should take between 6:30 PM and 9:30 PM
Serdexmethylphenidate and dexmethylphenidate (Azstarys)	50	24 to 36	
Methylphenidate transdermal patch (Daytrana)	120	10 to 12	Transdermal patch is not equivalent to the oral MPH dose. Wear on a clean, dry area of the lateral hip beneath the underwear and rotate sites daily. After removal, patch should be folded onto itself and disposed into a lidded container; should not be cut or ripped

[a]Onset of action for methylphenidate XR capsule (Jornay PM) is 8 to 10 hours

ADHD: attention-deficit/hyperactivity disorder; CD: controlled delivery; ER: extended-release; IR: immediate-release; LA: long-acting; MPH: methylphenidate; ODT: orally disintegrating tablet; XR: extended-release

Source: References 3,7

bypass surgery,[14] while another suggested impaired absorption following the same procedure.[15] A case-control design study assessing the impact of Roux-en-Y gastric bypass surgery on the pharmacokinetic properties of lisdexamfetamine found no significant differences between the Roux-en-Y group (n = 10) and nonsurgical controls (n = 10). The investigators concluded that while data suggest adjusting

Table 2

Amphetamine products for treating ADHD

Medication (brand name)	Onset of action (min)	Duration of action (h)	Comments
Mixed amphetamine salts short-acting (Adderall)	30	5 to 8	
Amphetamine sulfate short-acting (Evekeo)		4 to 6	Also FDA-approved for narcolepsy and exogenous obesity
Dextroamphetamine short-acting (Dexedrine, Zenzedi, ProCentra)	20 to 60	4 to 6	
Dextroamphetamine intermediate-acting (Dexedrine Spansule)	60 to 90	6 to 10	Contains 50% IR and 50% delayed-release beads
Mixed amphetamine salts long-acting (Adderall XR)	30	10 to 12	Contains 50% IR and 50% delayed-release beads
Amphetamine sulfate long-acting (Adzenys ER, Adzenys XR-ODT)		10 to 12	
Amphetamine sulfate long-acting (Dyanavel XR)	60	8 to 10	
Mixed salts of a single-entity amphetamine	60	16	Should avoid need for a booster IR dose
Lisdexamfetamine (Vyvanse)	120	8 to 14	Prodrug that is hydrolyzed to its active form (dextroamphetamine) after oral ingestion
Dextroamphetamine transdermal (Xelstrym)	120	12	Apply to hip, upper arm, chest, upper back, or flank; rotate application sites each day. Upon removal, patch should be folded so adhesive side of system adheres to itself and then disposed in a lidded container

ADHD: attention-deficit/hyperactivity disorder; ER extended-release; IR: immediate-release; ODT: orally disintegrating tablet; XR: extended-release

Source: References 3,7,9

Clinical Point

Liquid stimulant formulations may be an option for patients experiencing medication malabsorption

lisdexamfetamine dosing following Roux-en-Y gastric bypass surgery is unnecessary, there may be interindividual differences, and individualized dosing regimens may be needed.[16]

When managing patients who might be experiencing medication malabsorption, it may be helpful to use dosage forms that avoid disintegration, acidic environments, and slow dissolution. Because they are more rapidly absorbed and not susceptible to disintegration and dissolution, liquid formulations are recommended.[17] For medications that are not available as a liquid, an IR formulation is recommended.[18]

Using nonoral routes of administration that avoid the anatomical changes of the gastrointestinal tract should be considered for patients who have undergone Roux-en-Y gastric bypass surgery.[17] The methylphenidate transdermal patch, a medication delivery system that avoids gut and hepatic first-pass metabolism, can improve medication bioavailability, reduce dose frequency, and stabilize medication delivery. It is available in 4 sizes/dosages: 10 mg/9 hours, 15 mg/

Clinical Point

Consider a transdermal stimulant formulation for patients who have undergone bariatric surgery

Related Resources

- DeMarco R, Rana R, Powell K, et al. How bariatric surgery affects psychotropic drug absorption. Current Psychiatry. 2022;21(8):39-44. doi:10.12788/cp.0271
- Santos MG, Majarwitz DJ, Saeed SA. Adult ADHD: 6 studies of pharmacologic interventions. Current Psychiatry. 2023;22(4):16-27. doi:10.12788/cp.0344

Drug Brand Names

Amphetamine sulfate • Adzenys ER, Adzenys XR-ODT, Dyanavel XR, Evekeo
Atenolol • Tenormin
Dexmethylphenidate • Focalin, Focalin XR
Dextroamphetamine transdermal • Xelstrym
Dextroamphetamine • Dexedrine, Dexedrine Spansule, ProCentra, Zenzedi
Escitalopram • Lexapro
Lisdexamfetamine • Vyvanse
Methylphenidate • Aptensio XR, Adhansia XR, Concerta, Cotempla, Jornay PM, Metadate CD, Metadate ER, Methylin, Quillichew ER, Quillivant XR, Relexxii, Ritalin, Ritalin LA
Methylphenidate transdermal • Daytrana
Mixed amphetamine salts • Adderall, Adderall XR
Mixed salts of a single-entity amphetamine • Mydayis
Serdexmethylphenidate and dexmethylphenidate • Azstarys

9 hours, 20 mg/9 hours, and 30 mg/9 hours. Methylphenidate is delivered at a steady rate based upon patch size. The onset of action of the patch is approximately 2 hours, and patients should wear the patch for 9 hours, then remove it. Methylphenidate will still be absorbed up to 2 to 3 hours after patch removal. Appropriate application and removal of the patch is important for optimal effectiveness and to avoid adverse effects.[4]

In March 2022, the FDA approved a dextroamphetamine transdermal patch.[9] It is available in 4 sizes/dosages: 4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours, and 18 mg/9 hours.[9] Like the methylphenidate transdermal patch, the onset of action is approximately 2 hours, and it is recommended that patients wear it for 9 hours.[9]

CASE CONTINUED

Ms. H emphasizes her desire to maintain functionality in all areas of life, while her care team reiterates the risks of continuing to take high-dose stimulants. Both Ms. H and her care team acknowledge that stimulant usage could be worsening her anxiety, and that Roux-en-Y gastric bypass surgery may be a possible explanation for her dosing challenges.

Following consultation with the pharmacist, the care team explains the possible pharmacokinetic benefits of using the methylphenidate transdermal patch. After completing the prior authorization paperwork, Ms. H is started on the 30 mg/d patch. This dose was selected because she previously tolerated high-dose stimulants, including methylphenidate IR 20 mg up to 6 times daily. At a follow-up visit 1 month after starting the patch, Ms. H reports an improvement in her ADHD symptoms and says she is not experiencing any adverse effects.

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Clinical Point

Transdermal patches avoid gut and hepatic first-pass metabolism, which can improve medication bioavailability