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CME Objective
After studying this article, you should be able to:

- Select suitable stimulant formulations for patients with attention-deficit/hyperactivity disorder using the medications' unique pharmacokinetic profiles

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Stimulant Formulations for the Treatment of Attention-Deficit/ Hyperactivity Disorder

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ABSTRACT

Objective: Clinicians have access to a variety of formulations of methylphenidate and amphetamine to treat attention-deficit/hyperactivity disorder (ADHD). However, due to new emerging formulations, clinicians may lack up-to-date knowledge about all available stimulant formulations. Presented here is a comprehensive guide to13 formulations of methylphenidate and 10 formulations of amphetamine that have US Food and Drug Administration approval to treat ADHD.

Data Sources: PubMed was searched using the following MeSH terms: *attention-deficit/hyperactivity disorder*, *ADHD*, *stimulant*, *amphetamine*, and *methylphenidate*. Inclusion criteria were randomized controlled trials and systematic reviews published through 2017.

Study Selection and Extraction: Forty-eight articles were identified; however, these included analyses using product labels and anecdotal or uncontrolled reports of apparent clinical inequivalence. Thus, 34 articles were included in the final review to provide a thorough evidence-based guide.

Results: Each formulation has a unique pharmacokinetic profile. Clinically, one formulation may not be suitable for all patients. To select the most appropriate formulation, clinicians should consider the individual patient's preferences such as dosing schedule, time required to reach peak plasma concentration and duration of action, and tolerability.

Conclusion: This review provides clinical guidance to help clinicians prescribe the most suitable treatment for an individual.

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The US Food and Drug Administration (FDA) has approved 13 formulations of methylphenidate and 10 formulations of amphetamine for the treatment of attention-deficit/hyperactivity disorder (ADHD). Immediate-release (IR) formulations of methylphenidate have been a gold standard of treatment since 1955.[1,2] While there is a historical use of amphetamines even prior to that date, the first extant IR formulation of amphetamine was not marketed until 1996. As a treatment paradigm, IR formulations generally require multiple dosing throughout the day. To address this limitation, many additional formulations have emerged that attempt to decrease the frequency of dosing using extended-release technology. Furthermore, formulations have been developed to provide additional therapeutic controls. These formulations

Clinical Points

- Many stimulant formulations are available for the treatment of attention-deficit/hyperactivity disorder (ADHD).
- Stimulant formulations for ADHD have unique properties such as type of formulation, time to reach peak plasma concentration, duration of action, and dosing schedule.
- Currently available formulations of methylphenidate and amphetamine are highly customizable for many unique patient factors.

include those that afford a more gradual increase in peak plasma concentration, liquid suspensions, chewable tablets, orally disintegrating tablets, utilization of transdermal drug delivery, enantiomers, and a prodrug that must be metabolized before the active compound is activated.

The drug delivery mechanisms of these compounds create unique parameters that differ considerably among the available formulations. We review all currently available methylphenidate and amphetamine formulations to provide a comprehensive, in-depth guide for prescribing clinicians. Each formulation is described considering individual design and pharmacokinetic parameters.

METHODS

PubMed was searched for English-language articles using the following medical subject heading (MeSH) terms: *attention-deficit/hyperactivity disorder*, *ADHD*, *stimulant*, *amphetamine*, and *methylphenidate*. Inclusion criteria were randomized controlled trials and systematic reviews published through 2017. Initial versions of the review included 48 articles. However, these articles included analyses using product labels and anecdotal or uncontrolled reports of apparent clinical inequivalence. We ultimately decided to exclude these references to provide a thorough evidence-based guide and, therefore, utilized 34 articles.[1–34]

RESULTS

Methylphenidate

Immediate release. Conventional IR methylphenidate formulation has been a standard treatment for ADHD since 1955, when the disorder was still referred to as "minimal brain dysfunction."[1,2] Brand-name IR methylphenidate is Ritalin. In the multimodality treatment study of ADHD, the gold-standard treatment was chosen as IR methylphenidate administered 3 times per day.[3] The peak serum concentration is achieved in about 1.9 hours, and the duration of action ranges from at least 3 hours to 6 hours. Clinically, IR formulations of methylphenidate can be used as monotherapy dosed 3 times daily or as adjunct therapy to extend the duration of other formulations that may not provide an adequate duration of action.

Sustained release. Although IR formulations of methylphenidate were (and continue to be) clearly efficacious, they require multiple daily dosing. To address this challenge, longer-acting preparations began to enter the market. The first generation was methylphenidate sustained release (SR), which utilizes a wax-matrix to provide slow, continual release of methylphenidate (Ritalin SR).[4] Unfortunately, this delivery mechanism lacks an IR component. Thus, plasma methylphenidate concentrations may not reach the adequate level for therapeutic action until later in the day, which may be problematic for school or work. The peak plasma concentration is achieved in about 4.7 hours, and the duration of action is up to 8 hours.[5]

Long acting. Ritalin long acting (LA) delivers methylphenidate using spheroidal oral drug absorption system (SODAS) technology. This formulation causes 50% of the methylphenidate to be released immediately and 50% over a more extended period in a conspicuously pulsatile manner.[5] This release is accomplished with polymer-coated beads; a capsule contains 50% IR beads and 50% extended-release (ER) beads. Due to this distinct dissolution property of the beads, there are 2 distinct plasma methylphenidate concentration peaks approximately 4 hours apart. The initial peak concentration is reached within 1–3 hours, and the shoulder (secondary peak) is reached within 4.7–6.3 hours.[6] The onset of action of the LA formulation is similar to the onset of action of the IR formulation, but the duration of action is extended to 8 hours.[7]

The delivery mechanism of Ritalin LA is distinct to controlled-delivery (CD) methylphenidate (Metadate CD). CD methylphenidate also consists of a capsule composed of beads; however, the composition of the beads is 30% IR and 70% ER methylphenidate. The beads were designed to begin to release methylphenidate approximately 1 hour after administration.[8] The pharmacokinetic profile of CD methylphenidate, however, tends to resemble the SR formulation, albeit a more rapid rise to peak plasma concentration followed by another secondary peak. Specifically, the early peak plasma concentration is reached within 1.5 hours, and the shoulder is reached in approximately 4.5 hours for a total duration of approximately 8 hours.[7,8]

Osmotic controlled-release delivery. Concerta utilizes osmotic controlled-release delivery system (OROS) to release 22% of its total methylphenidate content immediately, followed by a gradual release of the remaining content throughout the day. This release mechanism allows for a significantly extended duration of action with once-daily dosing of up to 12 hours.[5]

Following administration, peak plasma concentration is reached in approximately 1 hour, followed by a gradually increasing plasma concentration over the next 5–9 hours. Mean time to reach peak plasma concentrations in this phase varies between 6 and 10 hours. A unique advantage to this slowly ascending pharmacokinetic profile is the argument that it can theoretically combat the development of acute tolerance.[9–11]

Transdermal system. Daytrana is a unique methylphenidate transdermal system that provides continuous delivery via diffusion. Daytrana is the only

LA formulation to reach peak plasma methylphenidate concentration later than Concerta in head-to-head studies.[12] There is only a single peak plasma concentration, reached approximately 7.5–10.5 hours after administration.[5] The advantage to this transdermal system is once-daily dosing and a slowly ascending pharmacokinetic profile. To some patients, however, the very slow ascension of peak plasma concentration of methylphenidate may be reached too late into the school or work day for adequate symptom control. This formulation has several other limitations and complications including adhesive backing recalls, incidences of dermatitis, and inconsistent delivery of methylphenidate into the systemic circulation.

Chewable tablets. Methylphenidate chewable tablet, eg, Methylin chewable tablets, is an IR formulation that is readily absorbed after oral administration. The peak plasma concentration of methylphenidate following administration of IR chewable is reached within 1–2 hours.[13] In 2015, Pfizer received FDA approval to release Quillichew ER, a longer-acting preparation of this delivery system consisting of flavored tablets composed of 15% IR and the remainder as ER methylphenidate.[14] The peak plasma methylphenidate concentration of the ER formulation is reached within 4–5 hours after administration. Whereas twice-daily dosage of an IR chewable tablet reaches a higher peak plasma concentration, a single dose of ER chewable tablet entails a more gradual increase of plasma concentration followed by a broader peak and fewer fluctuations in plasma concentration of methylphenidate.[13]

Dexmethylphenidate. Methylphenidate consists of a racemic mixture of *d*- and *l*-enantiomers. The major mechanism of action of methylphenidate in the treatment of ADHD symptoms is accomplished by the reuptake inhibition of dopamine in the synaptic cleft. Specifically, this reuptake inhibition is primarily accomplished by the *d*-enantiomer. The *l*-enantiomer, on the other hand, is a largely inactive isomeric ballast.[15–18] Therefore, in an effort to minimize systemic toxicity, the *d*-enantiomer was isolated and marketed as Focalin (IR formulation) and Focalin XR.

The pharmacokinetic profile of dexmethylphenidate is similar to *dl*-methylphenidate. Dexmethylphenidate is formulated as a tablet; upon administration, peak plasma dexmethylphenidate concentration is reached within 1–2 hours for a total duration of approximately 4 hours.[19] Dexmethylphenidate ER uses the SODAS technology as described previously for LA formulations, which allows for an immediate release of 50% of the dexmethylphenidate and, therefore, an initial peak followed by a shoulder more than 4 hours later.[16]

Suspension solution. Quillivant XR is a powder that forms an extended-release formulation consisting of 20% IR and 80% ER after reconstitution with water.[14] This formulation allows for an oral solution that can be easily administered to individuals who cannot tolerate tablets or capsules. The peak plasma methylphenidate concentration after administration of this formulation is reached within 5–6 hours for a total duration of approximately 12 hours.[14,20] Clinically, using a reconstitution solution will require more extensive patient education and more close monitoring for safe preparation and administration.

Orally disintegrating tablets. In 2017, another novel mechanism for methylphenidate delivery received FDA approval for market entry: ER orally disintegrating tablets (Cotempla XR-ODT). This formulation is placed on the tongue, where it undergoes rapid absorption. Randomized controlled studies[14,21] on this formulation have showed symptom control of up to 12 hours.

Multilayer-release beads. Another newly developed delivery of methylphenidate is a multilayer-release (MLR) bead formulation contained in a hard gelatin capsule (Aptensio XR). This medication received FDA approval for market entry in 2016. The formulation consists of 37% IR beads and 63% controlled-release beads with a layer of coating that slowly releases the drug over a more extended time period. Pharmacokinetic information on this formulation, available from 2 randomized controlled trials, demonstrates a rapid initial peak in plasma methylphenidate concentration followed by a decline in plasma methylphenidate concentration over the subsequent 5 hours and a gradual increase in concentration in the subsequent 2 hours to reach a shoulder at approximately 7 hours after initial administration. Total duration of action of this formulation is approximately 12 hours, regardless whether the capsule is administered whole or the contents of the capsule are sprinkled on a food item.[14,22,23]

Amphetamines

Mixed amphetamine salts. Although amphetamines have been used since 1935, the first extant formulation of IR mixed amphetamine salts was marketed in 1996 as Adderall.[24] The IR formulation contains both enantiomers, *d*-amphetamine and *l*-amphetamine, in a ratio of 3:1. The peak plasma amphetamine concentration is reached approximately 3 hours after administration, and the duration of action of this formulation is approximately 4–6 hours.[24,25]

The success of Adderall led Shire Pharmaceuticals to introduce the ER formulation in 2001 (Adderall XR). Like the IR formulation, the XR formulation also consists of *d*-amphetamine and *l*-amphetamine in a ratio of 3:1. The XR formulation is composed of a capsule with 50% IR beads and 50% ER beads.[24] The XR formulation reaches a peak plasma concentration approximately 7 hours after administration, which allows for once-daily dosing. Therapeutic efficacy does not appear to be altered if the XR capsule is ingested whole or the contents of the capsule are sprinkled over a food item.[26–28]

Dextroamphetamine immediate release and sustained release. During the 1930s, Smith, Kline, and French manufactured racemic amphetamine as Benzedrine tablets. In 1937, the firm began marketing only the D-isomer of amphetamine (dextroamphetamine) under the trade name Dexedrine. The use of Benzedrine to treat ADHD declined dramatically after 1976, when it was reported that Dexedrine was more effective.[29] In 1975, Shire Pharmaceuticals received FDA approval for Dextrostat tablets (dextroamphetamine

Table 1. Currently Available Formulations of Methylphenidate and Amphetamine

Formulations	Time to Reach Peak Plasma Concentration	Duration of Action	Dosing
Methylphenidate			
Concerta (osmotic controlled-release delivery)	1 h, overall peak 6–10 h	12 h	Once daily
Daytrana (transdermal)	7.5–10.5 h	12 h	Once daily
Quillivant XR (suspension)	5–6 h	12 h	Once daily
Aptensio XR (multilayer beads)	5 h, shoulder at 7 h	12 h	Once daily
Cotempla CR-ODT (orally disintegrating tablets)	<6 h	Up to 12 h	Once daily
Focalin XR (dextromethylphenidate)	1–3 h, shoulder at 4.7–6.3 h	8 h	Once daily
Quillichew ER (chewable tablets)	4–5 h	8 h	Once daily
Ritalin LA (long acting)	1–3 h, shoulder at 4.7–6.3 h	8 h	Once daily
Ritalin SR (sustained release)	4.7 h	8 h	Once daily
Focalin IR (dextromethylphenidate)	1–2 h	4 h	3 times daily
Methylin IR (chewable tablets)	1–2 h	3–6 h	3 times daily
Ritalin (immediate release)	1.9 h	3–6 h	3 times daily
Amphetamine			
Mydayis XR (dextroamphetamine)	7–10 h	16 h	Once daily
Vyvanse (lisdexamfetamine)	3–5 h for active compound	>8 h	Once daily
Adderall XR (extended release)	7 h	>8 h	Once daily
Adzenys XR (orally disintegrating tablets)	5 h	>8 h	Once daily
Evekeo IR (dextroamphetamine/levoamphetamine)	4 h	9 h	Once daily
Dynavel XR (dextroamphetamine/ levoamphetamine suspension)	4 h	8 h	Once daily
Procentra IR (dextroamphetamine suspension)	<3 h	<6 h	2 times daily/3 times daily
Adderall (immediate release)	3 h	4–6 h	3 times daily

Abbreviations: CR = controlled release, ER = extended release, IR = immediate release, XR = extended release.

IR). In 1976, GlaxoSmithKline received FDA approval for Dexedrine tablets (dextroamphetamine IR), elixir (dextroamphetamine IR oral solution), and spansule (dextroamphetamine SR). Currently, all of these trade formulations have been discontinued. The generic formulation of Dexedrine spansule (dextroamphetamine SR) is available, and dextroamphetamine IR became available under the brand name Zenzedi in 2015.

Lisdexamfetamine: expanded analysis of a prodrug. Shire Pharmaceuticals received FDA approval for lisdexamfetamine in 2007 as Vyvanse. This approval filled a yet uninhabited niche in the stimulant market as the first and only prodrug formulation. A prodrug is a biologically inactive compound that must be metabolized prior to becoming a drug that can induce effects. Furthermore, there is significant potential for the application of this prodrug if there is concern for substance abuse, as it is not possible to insufflate or inject this formulation. Lisdexamfetamine consists of the pharmacologically inactive parent compound dextroamphetamine linked to L-lysine; this inactive compound is absorbed in the small intestine and transported into the blood. Finally, when it is in the blood, lisdexamfetamine is hydrolyzed by a hydrolase into the pharmacologically active dextroamphetamine.[30]

Although the time to reach peak plasma concentration for lisdexamfetamine is 1 to 2 hours, the time needed for the active compound dextroamphetamine is 3–5 hours because of the necessary process of conversion of the prodrug (lisdexamfetamine) to this active compound (dextroamphetamine). The time to reach peak plasma concentration of dextroamphetamine following lisdexamfetamine administration (3–5 hours) is approximately 1 hour later than administration of dextroamphetamine (2–3 hours).[31] Therapeutic efficacy of lisdexamfetamine has been demonstrated up to 14 hours after administration, and, as is the case for OROS-methylphenidate, it can be argued that the slowly ascending plasma concentration of lisdexamfetamine would theoretically combat the development of acute tolerance.[30–32]

Dextroamphetamine extended release. In June 2017, Shire Pharmaceuticals announced the release of its latest amphetamine formulation, dextroamphetamine ER, Mydayis. Currently available, the formulation contains dextroamphetamine and levoamphetamine in a ratio of 3:1. There is a paucity of clinical research available on this formulation to confidently delineate its unique pharmacokinetic properties. One distinguishing feature, however, is a delayed time course to reach a single peak plasma concentration approximately 7–10 hours after administration and a duration of action of up to 16 hours.

Amphetamine extended-release orally disintegrating tablet. Adzenys received FDA approval in 2016. It is the first formulation of amphetamine ER orally disintegrating tablet. This formulation is a tablet that is placed on the tongue where it disintegrates rapidly. There is a paucity of clinical research available on this formulation. Amphetamine ER orally disintegrating tablets offer an alternative route of administration for patients who cannot swallow tablets or capsules. The peak plasma concentration of this formulation is reached approximately 5 hours after administration.[33]

Amphetamine immediate release. Unlike mixed amphetamine salts, the formulation of Evekeo is 1:1 dextroamphetamine and levoamphetamine. This formulation received FDA approval in 2012. Purportedly, the onset of action is debated to be 45 minutes after administration, with greatest efficacy observed at 4 hours, and a duration

of action of at least 9 hours.[34] Hence, the duration of action of amphetamine IR is suggested to be significantly longer than the duration of action of mixed amphetamine salts IR (4–6 hours).

Amphetamine oral solution. Dynavel XR contains IR and ER components of dextroamphetamine and levoamphetamine in a ratio of 3.2:1. This formulation is suitable for patients who are unable to swallow tablets and allows for once-daily dosing. The peak plasma concentration is reached in approximately 4 hours, with at least an 8-hour duration of action. This formulation does not have FDA approval for children younger than 6 years.

On the other hand, ProCentra is a dextroamphetamine oral solution with FDA approval for children as young as 3 years. Because there are no XR components to this formulation, it requires multiple dosing throughout the day.

CONCLUSION

Currently available stimulant formulations for the treatment of ADHD offer similar efficacy with customizable differences. For example, most LA formulations are considerably more expensive than short-acting formulations. If affordability is a significant concern, short-acting formulations administered 2 or 3 times daily may be a more appropriate treatment approach. If the development of tolerance or abuse potential is a concern, then LA methylphenidate, OROS-methylphenidate, mixed amphetamine salts-XR, or more expensive newer formulations such as lisdexamfetamine may be the most appropriate approach. Table 1 provides a list of currently available formulations, along with guidelines concerning time to reach peak plasma concentration, duration of action, and dosing.

To select the most appropriate formulation for each patient, we recommend taking into consideration the individual patient's preferences such as dosing schedule, time required to reach peak plasma concentration and duration of action, and tolerability. Evidence suggests that currently available formulations of methylphenidate and amphetamine are highly customizable for many unique patient factors.

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Posttest

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1. **Heather is a 35-year-old woman whose attention-deficit/hyperactivity disorder (ADHD) symptoms are adequately controlled throughout her workday with 54 mg of methylphenidate osmotic controlled release. Heather is concerned because by the time she arrives home, she is unable to fulfill her family obligations. Which of the following pharmacologic approaches is most likely to address this issue?**
   a. Ask Heather to take her current dose later in the morning
   b. Increase her dose to 72 mg
   c. Add low-dose lisdexamfetamine in the afternoon
   d. Titrate upward with the addition of an immediate-release formulation for the evening
2. **Which of the following stimulant formulations would be expected to reduce ADHD symptoms for the longest duration of time?**
   a. Methylphenidate long acting 60 mg
   b. Methylphenidate osmotic controlled release 36 mg
   c. Extended-release mixed amphetamine salts 20 mg
   d. Dexmethylphenidate extended release 30 mg
3. **If the potential for abuse is at all a concern, which of the following formulations would be most appropriate?**
   a. Methylphenidate immediate release
   b. Extended-release mixed amphetamine salts
   c. Lisdexamfetamine
   d. Mixed amphetamine salts