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Options for the Management of Attention Deficit/Hyperactivity (ADHD)

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A wide array of products are currently on the market in the United States for the management of ADHD. Over the past decade, a number of new treatment options have been introduced, including once-daily products, oral liquid and transdermal dosage formulations, and several generic products (Table).¹⁻¹⁴ This issue of *Pediatric Pharmacotherapy* will provide a brief review of some of these products and highlight their unique properties.

Methylphenidate OROS Tablets

In 2000, McNeil introduced Concerta[®], a once-daily methylphenidate product using Alza's osmotic-controlled release oral delivery system (OROS[®]).⁴ This technology had been used successfully for several other drugs, including nifedipine and doxazosin. The tablet has an outer coating of methylphenidate that is absorbed rapidly after ingestion, providing approximately 20% of the dose immediately.¹⁻⁶ After the coating has dissolved, penetration of gastric fluid through the semipermeable outer membrane expands an osmotic agent in the push layer of the core, causing it to slowly force the methylphenidate contained in the core out a laser-drilled opening in the tablet over 12 hours.

Once-Daily Methylphenidate Capsules

Like Concerta[®] tablets, all of the once-daily capsule products are considered to have a double pulse or biphasic release, producing a rapid initial peak as well as a second later peak in serum concentrations following a single dose. There are considerable differences, however, in how these products are absorbed.¹⁻³ Two capsule products are available that deliver methylphenidate over approximately an 8 to 10 hour period, Metadate CD[®] and Ritalin LA[®].^{7,8} Metadate CD[®] is a Diffucaps[®] formulation, a mix of 30% immediate-release beads and 70% delayed-release beads. The delayed-release beads dissolve more slowly and are typically absorbed in the intestine, providing a later second peak in serum concentrations.^{1-3,7}

Ritalin LA[®] differs in that the coated beads are designed to release drug in two relatively equal

amounts.^{1-3,8} With the spheroidal oral drug absorption system (SODAS[®]) technology used for this preparation, 50% of the beads are immediate-release and 50% are enteric-coated delayed-release beads that dissolve more slowly in the intestine. This provides an initial peak serum concentration shortly after administration and a second peak at 4 hours. With a larger percentage of drug released immediately compared to Concerta[®] and Metadate CD[®], Ritalin LA[®] may be a better choice for patients needing early morning symptom control.

Dexmethylphenidate, the active d-enantiomer of methylphenidate, is also available in a once-daily capsule formulation (Focalin XR[®]) which uses SODAS[®] technology.^{1-3,9} This product provides drug release over an 8 to 12 hour period, with an initial peak at approximate 1½ hrs and a second peak at 6.5 hrs (range 4.5-7 hrs). All three capsule products can be opened and the beads mixed with a spoonful of applesauce. As long as the beads are not chewed or crushed, the delayed-release properties will be retained.

Transdermal Methylphenidate

The Daytrana[®] transdermal patch was approved by the Food and Drug Administration in 2006.^{1-3,10-12} The three layer patch consists of a polyester/ethylene vinyl acetate laminate film backing, an adhesive layer that contains methylphenidate combined with acrylic and silicone adhesives, and a protective liner that is removed prior to application. Dose varies by patch size. The patch is designed to be worn for 9 hours to provide 12 hours of symptom control, but adjustment of wear times to tailor duration remains the primary reason for selecting this formulation. The location of the patch should be changed daily to reduce skin reactions. Patients and family members must understand the need to carefully dispose of patches to prevent accidental contact or ingestion by children or pets.

Mixed Dextroamphetamine Salts

The branded mixed dextroamphetamine salts product, Adderall XR[®], uses Microtrol[®] technology to provide an 8-10 hour duration.¹⁻³

Half of the beads within the capsule are immediate-release; the remaining beads are coated with a polymer that degrades in the higher pH of the intestine which prolongs absorption and results in sustained drug effect. Generic versions of mixed dextroamphetamine salts are available with similar absorption characteristics.

Lisdexamfetamine

In 2008, a prodrug of dextroamphetamine, lisdexamfetamine (Vyvanse®), was introduced in the US.¹³ The prodrug is inactive until hydrolyzed in the blood and liver to dextroamphetamine and the amino acid l-lysine.^{1-3,13}

The product was designed to reduce the potential for abuse, but also provides a prolonged duration of action (up to 13 hours in some patients). For patients unable to swallow the capsule whole, lisdexamfetamine capsules can be opened and the contents dissolved in water. The resulting solution should be ingested immediately and not stored for later use.

Extended-Release Guanfacine

Immediate release guanfacine, a selective α_{2A} -agonist, has been used off-label for many years in the management of ADHD.^{1-3,14} A once-daily guanfacine product, Intuniv™, became available in 2009 which provides symptom control up to 24 hours. The extended-release tablets come in 4 strengths, with a recommended starting dose of 1 mg or 0.05-0.08 mg/kg given once daily. There have been only mild changes in blood pressure with guanfacine in clinical trials; but due to the potential for hypotension, the dose should be increased by a maximum of 1 mg/week. When discontinuing therapy, the dose should be reduced by 1 mg increments every 3-7 days to prevent rebound hypertension.

Summary

Pediatric health care providers have a wide array of options for the treatment of ADHD, including products with varying durations of effect and different routes of administration. These options allow providers to tailor therapy to individual children as part of optimizing their care.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/25/11:

1. Perflutren protein-type A microspheres injection (Optison™) was added to the Formulary for cardiac imaging.
2. Poractant (Curosurf®) was added for prevention and treatment of RDS in infants < 27 weeks gestational age.
3. Eribulin (Halaven™) was added for the treatment of metastatic breast cancer.
4. Denosumab (Xgeva™) was added for patients with bone metastases of solid tumors.

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Table. Medication Options for the Management of ADHD¹⁻¹⁴

Product (Manufacturer)	Formulation	Approximate Duration of Action	Available Strengths	Dosing Considerations
Methylphenidate				
Ritalin [®] or generic (Novartis and others)	Immediate-release tablets, chewable tablets, or oral solution*	3-4 hours	5, 10, 20 mg tablets 5 mg/5 mL, 10 mg/5 mL solutions	Provides flexibility for initial dose titration
Concerta [®] (McNeil Pediatrics)	Tablet with OROS [®] osmotic pump technology; biphasic release with initial peak at 1 hr (20% of dose) and gradual release over 9 hrs	12 hours	18, 27, 36, 54 mg	Must be swallowed whole; non-absorbable shell may be passed in stool
Daytrana [®] (Noven Therapeutics)	Transdermal patch with drug dispersed in adhesive layer; applied daily	12 hours with 9 hour wear time	10, 15, 20, 30 mg/9 hr	Can vary wear time to control duration of action; monitor for skin sensitization; discard patches appropriately
Metadate CD [®] (UCB, Inc.)	Diffucaps [®] capsule with 30% immediate-release beads and 70% delayed-release beads*	8-10 hours	10, 20, 30, 40, 50, 60 mg	Capsule may be opened and beads swallowed whole with applesauce.
Metadate ER [®] (UCB, Inc.)	Extended-release tablet*	6-8 hours	10, 20 mg	Swallow whole; do not break, crush, or chew
Methylin [™] Chewable (Mallinckrodt Inc.)	Chewable tablet*	3-4 hours	2.5, 5, 10 mg	Contains phenylalanine
Methylin ER [™] (Mallinckrodt Inc.)	Extended-release tablet*	6-8 hours	10, 20 mg	Swallow whole; do not break, crush, or chew
Ritalin SR [®] (Novartis)	Extended-release tablet*	6-8 hours	20 mg	Swallow whole; do not break, crush, or chew
Ritalin LA [®] (Novartis)	Capsule with Spheroidal Oral Drug Absorption System (SODAS [®]) technology; 50% immediate-release beads and 50% delayed-release (2 nd peak 4 hrs later)*	8-10 hours	10, 20, 30, 40 mg	Capsule may be opened and beads swallowed whole with applesauce. Do not give with antacids or acid suppressants.
Dexmethylphenidate				
Focalin [®] or generic (Novartis and others)	Immediate-release tablets*	4-6 hours	2.5, 5, 10 mg	Active isomer; give approx. ½ methylphenidate dose
Focalin XR [®] (Novartis)	Capsule with SODAS [®] technology*	12 hours	5, 10, 15, 20, 30, 40 mg	Capsule may be opened and beads swallowed whole with applesauce. Do not give with antacids or acid suppressants.

Product (Manufacturer)	Formulation	Approximate Duration of Action	Available Strengths	Dosing Considerations
Amphetamines				
Dextroamphetamine (various manufacturers)	Immediate-release tablets, capsules, or liquid	3-6 hours	5, 10 mg	Provides flexibility during initial titration
Adderall [®] or generic (Teva and others)	Immediate-release tablet	4-6 hours	5, 7.5, 10, 12.5, 15, 20, 30 mg	Mixture of amphetamine salts provides slightly longer half-life
Adderall XR [®] (Teva)	Capsule with Micotrol [®] delivery system: 50% immediate-release and 50% delayed-release beads*	10-12 hours	5, 10, 15, 20, 25, 30 mg	Capsule may be opened and beads swallowed whole with applesauce.
Vyvanse [®] (Shire)	Capsule containing lisdexamfetamine (dextroamphetamine linked to l-lysine); peak dextroamphetamine reached in approx. 3.5 hrs*	10-13 hours	20, 30, 40, 50, 60, 70 mg	Capsule may be opened and contents dissolved in water; use immediately after dissolving.
Atomoxetine				
Strattera [®] (Lilly)	Capsule*	24 hours	10, 18, 25, 40, 60, 80, 100 mg	Selective norepinephrine inhibitor; may take several weeks to achieve full effect; swallow capsule whole; powder is irritating to eyes
Clonidine				
Catapres [®] or generic (Boehringer Ingelheim and others)	Immediate-release tablets	3-6 hours (wide interpatient variability)	0.1, 0.2, 0.3 mg	Sedating, typically initiated at bedtime; increase weekly by adding morning and then mid-day doses
Catapres-TTS [®] (Boehringer Ingelheim and others)	Transdermal patch, applied weekly	5-7 days	0.1, 0.2, 0.3 mg/24 hours	Potential for skin irritation; if patch loosens, cover with adhesive overlay; discard patches appropriately
Guanfacine				
Tenex [®] or generic (Promius and others)	Immediate-release tablets	6-12 hours	1, 2 mg	
Intuniv [™] (Shire)	Extended-release tablet	12-24 hours	1, 2, 3, 4 mg	Swallow tablet whole; a high-fat meal may increase absorption and lead to toxicity

* Administration with a high-fat meal may delay the time to peak serum concentrations, but has no significant effect on total absorption.