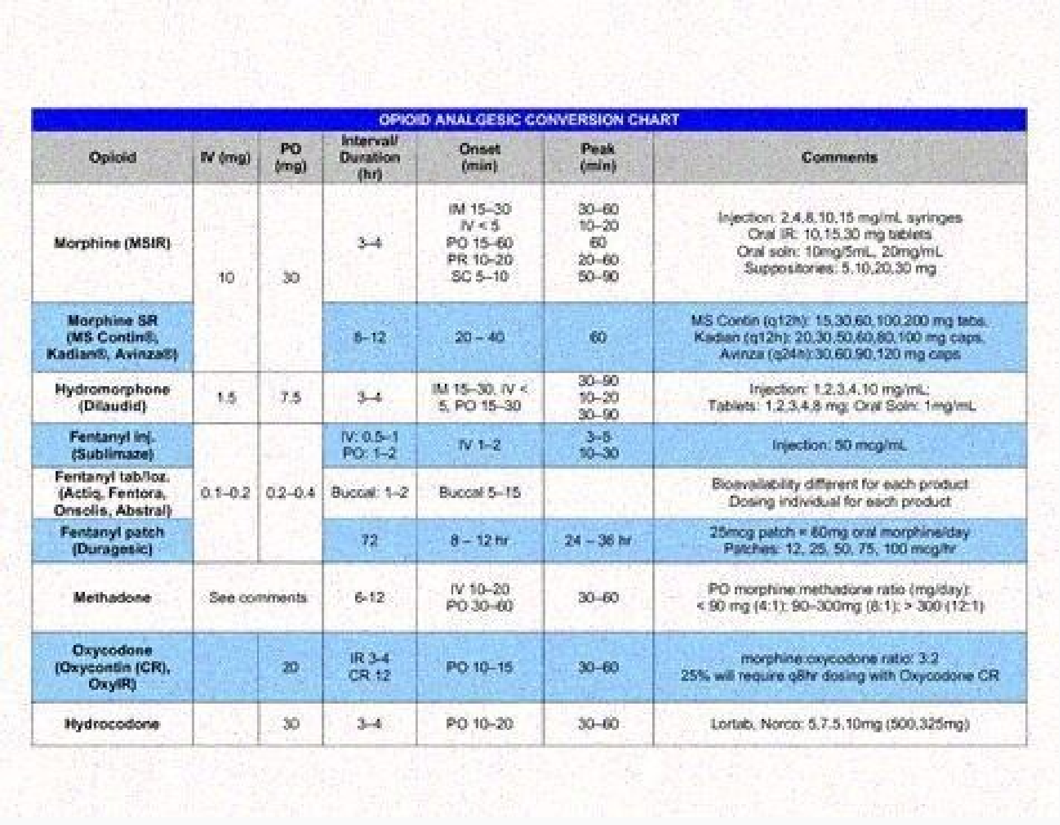
Dose equivalent stimulants. Dose conversion stimulants. Stimulant dose equivalency chart.

In the last 15 years, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets, chewable tablets, extended-release liquid formulations, transdermal patches, and novel “beaded” technology. All of these formulations involve changes to the pharmaceutical delivery systems of the two existing compounds most commonly employed to treat attention-deficit/hyperactivity disorder (ADHD), amphetamine (AMP) and methylphenidate (MPH).

In addition to these new formulations, our knowledge about the individual differences in response has advanced and contributes to a more nuanced approach to treatment.

The clinician can now make increasingly informed choices about these formulations and more effectively individualize treatment in a way that had not been possible before. In the absence of reliable biomarkers that can predict individualized response to ADHD treatment, clinical knowledge about differences in MPH and AMP pharmacodynamics, pharmacokinetics, and metabolism can be utilized to personalize treatment and optimize response. Different properties of these new formulations (delivery modality, onset of action, duration of response, safety, and tolerability) will most likely weigh heavily into the clinician's choice of formulation. To manage the broad range of options that are now available, clinicians should familiarize themselves in each of these categories for both stimulant compounds. This review is meant to serve as an update and a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties.Keywords: attention-deficit/hyperactivity disorder, stimulants, pharmacotherapy, treatment, pharmacokinetics, reviewIn 2004, “New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder” was published (Connor and Steingard 2004). The 2004 article discussed the following formulations: OROS, methylphenidate (MPH) modified release, MPH extended-release capsules, and mixed amphetamine (AMP) salts (MAS) extended release (ER).

That review suggested that “Future pharmaceutical development of stimulants for ADHD will emphasize long-acting formulations.” Since the publication of that article, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets (ODT), chewable tablets, ER liquid formulations, transdermal patches, and novel “beaded” technology. This review is meant to serve as an update and guide to newer stimulant formulations and includes a brief review of attention-deficit/hyperactivity disorder (ADHD) and stimulant properties which were covered in the original article.ADHD is a common neuropsychiatric disorder that has an estimated prevalence of 5%–9%.

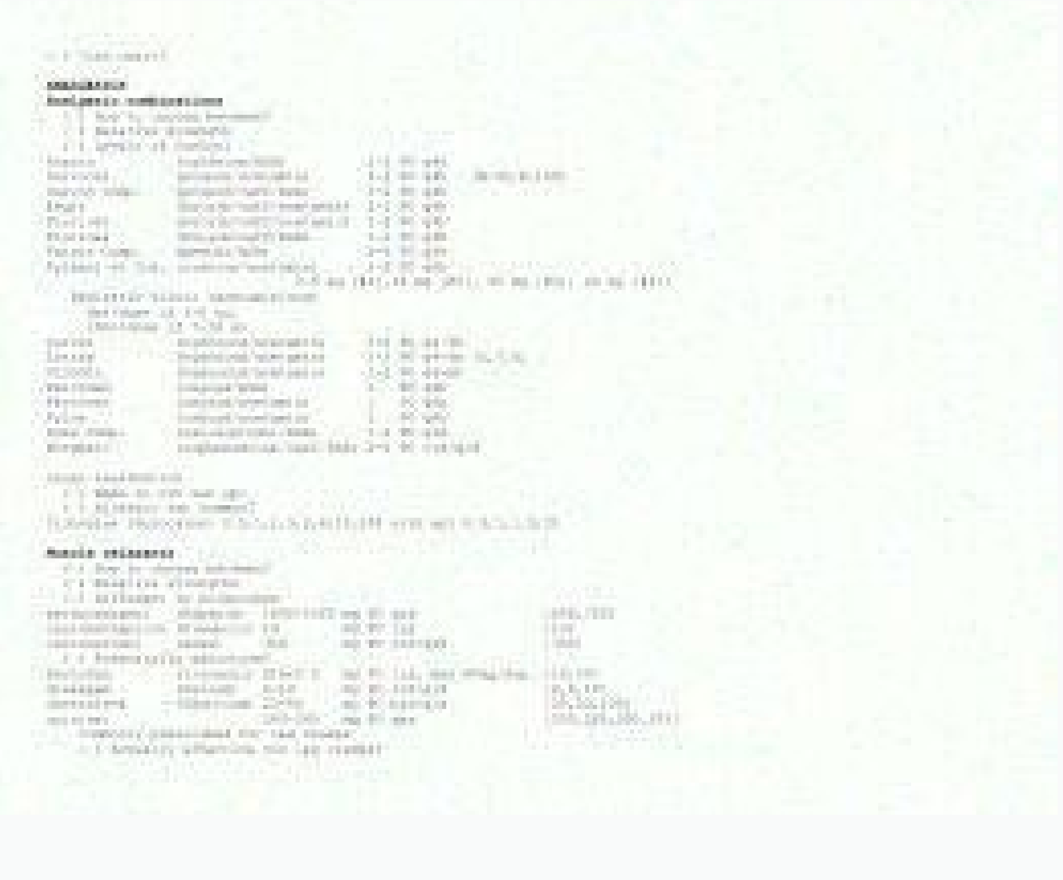


OPIOID ANALGESIC CONVERSION CHART

Opioid	IV (mg)	PO (mg)	Interval/ Duration (hr)	Onset (min)	Peak (min)	Comments
Morphine (MSIR)	10	30	3–4	IM 15–30 IV < 5 PO 15–60 PR 10–20 SC 5–10	30–60 10–20 60 20–60 50–90	Injection: 2,4,8,10,15 mg/mL syringes Oral IR: 10,15,30 mg tablets Oral soln: 10mg/5mL, 20mg/mL Suppositories: 5,10,20,30 mg
Morphine SR (MS Contin®, Kadian®, Avinza®)			8–12	20 – 40	60	MS Contin (q12h): 15,30,60,100,200 mg tabs. Kadian (q12h): 20,30,50,60,80,100 mg caps. Avinza (q24h):30,60,90,120 mg caps
Hydromorphone (Dilaudid)	1.5	7.5	3–4	IM 15–30, IV < 5, PO 15–30	30–90 10–20 30–90	Injection: 1,2,3,4,10 mg/mL; Tablets: 1,2,3,4,8 mg; Oral Soln: 1mg/mL
Fentanyl inj. (Sublimaze)	0.1–0.2	0.2–0.4	IV: 0.5–1 PO: 1–2	IV 1–2	3–5 10–30	Injection: 50 mcg/mL
Fentanyl tab/loz. (Actiq, Fentora, Onsolis, Abstral)			Buccal: 1–2	Buccal 5–15		Bioavailability different for each product Dosing individual for each product
Fentanyl patch (Duragesic)			72	8 – 12 hr	24 – 36 hr	25mcg patch = 60mg oral morphine/day Patches: 12, 25, 50, 75, 100 mcg/hr
Methadone	See comments		6-12	IV 10–20 PO 30–60	30–60	PO morphine:methadone ratio (mg/day): < 90 mg (4:1); 90–300mg (8:1); > 300 (12:1)
Oxycodone (Oxycontin (CR), OxyIR)		20	IR 3-4 CR 12	PO 10–15	30–60	morphine:oxycodone ratio: 3:2 25% will require q8hr dosing with Oxycodone CR
Hydrocodone		30	3–4	PO 10–20	30–60	Lortab, Norco: 5,7.5,10mg (500,325mg)

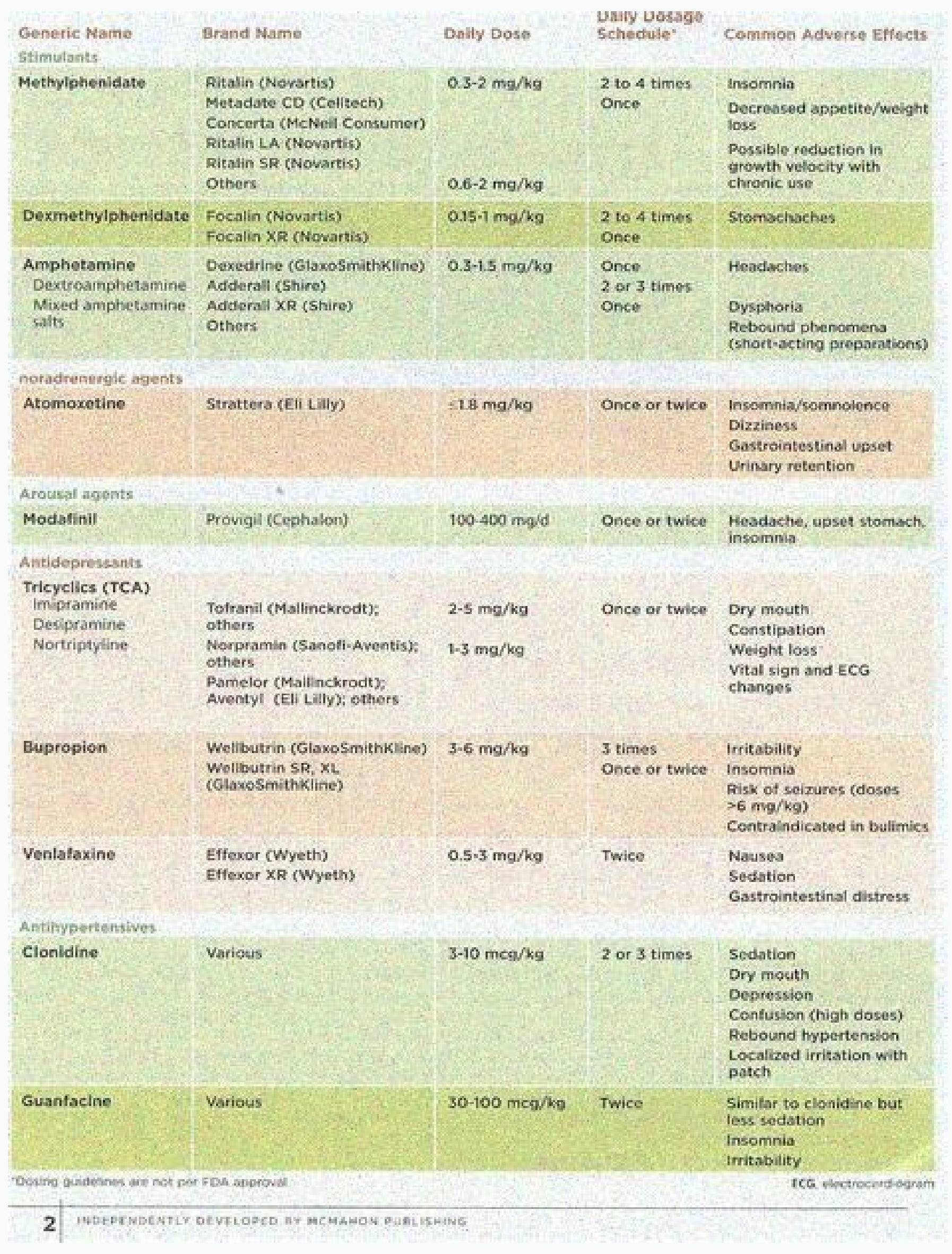
This review is meant to serve as an update and a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties.Keywords: attention-deficit/hyperactivity disorder, stimulants, pharmacotherapy, treatment, pharmacokinetics, reviewIn 2004, “New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder” was published (Connor and Steingard 2004). The 2004 article discussed the following formulations: OROS, methylphenidate (MPH) modified release, MPH extended-release capsules, and mixed amphetamine (AMP) salts (MAS) extended release (ER). That review suggested that “Future pharmaceutical development of stimulants for ADHD will emphasize long-acting formulations.” Since the publication of that article, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets (ODT), chewable tablets, ER liquid formulations, transdermal patches, and novel “beaded” technology. This review is meant to serve as an update and guide to newer stimulant formulations and includes a brief review of attention-deficit/hyperactivity disorder (ADHD) and stimulant properties which were covered in the original article.ADHD is a common neuropsychiatric disorder that has an estimated prevalence of 5%–9%. The symptoms of ADHD include developmentally inappropriate motor restlessness, impulsivity, and difficulty maintaining and shifting attention, which result in significant and often cumulative impairments in family, academic, and social functioning. ADHD has an onset in childhood and often persists into adulthood. While treatment often includes behavioral and educational strategies for associated problems, in children above 6 years, the core symptoms of ADHD are often treated with medications. Stimulant medications are slightly less effective and more poorly tolerated in preschoolers, compared to older children and adolescents (Greenhill et al. 2006).While nonstimulant options are available as monotherapy or combination treatment, stimulant medications have been and continue to be the most common first-line medication treatment for ADHD (MTA Cooperative Group 1999; Pediatrics 2011; Feldman et al. 2018). MPH and AMP are the core stimulants that are used to treat ADHD.

These compounds appear to have comparable clinical efficacy, yet there are individuals who responded preferentially to only one compound (Stein et al. 2011; Coghill et al. 2014). Acute response rate to stimulant treatment is ~70%, but the response rate can increase to close to 90% with carefully managed sequential trials of different stimulants and stimulant formulations that are carefully titrated (Stein et al. 2011; Coghill et al. 2014). Nevertheless, adherence to stimulants is modest, especially in adolescents who often discontinue medication, despite persistence of symptoms and impairments (Adler and Nierenberg 2010).Methylphenidate MPH has a typical onset of action of 30–45 minutes after administration and the mean duration of the clinical effect for immediate release (IR) MPH is 3–4 hours postadministration and up to 12 hours for ER formulations.



To manage the broad range of options that are now available, clinicians should familiarize themselves in each of these categories for both stimulant compounds. This review is meant to serve as an update and a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties.Keywords: attention-deficit/hyperactivity disorder, stimulants, pharmacotherapy, treatment, pharmacokinetics, reviewIn 2004, “New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder” was published (Connor and Steingard 2004). The 2004 article discussed the following formulations: OROS, methylphenidate (MPH) modified release, MPH extended-release capsules, and mixed amphetamine (AMP) salts (MAS) extended release (ER).

That review suggested that “Future pharmaceutical development of stimulants for ADHD will emphasize long-acting formulations.” Since the publication of that article, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets (ODT), chewable tablets, ER liquid formulations, transdermal patches, and novel “beaded” technology. This review is meant to serve as an update and guide to newer stimulant formulations and includes a brief review of attention-deficit/hyperactivity disorder (ADHD) and stimulant properties which were covered in the original article.ADHD is a common neuropsychiatric disorder that has an estimated prevalence of 5%–9%. The symptoms of ADHD include developmentally inappropriate motor restlessness, impulsivity, and difficulty maintaining and shifting attention, which result in significant and often cumulative impairments in family, academic, and social functioning. ADHD has an onset in childhood and often persists into adulthood. While treatment often includes behavioral and educational strategies for associated problems, in children above 6 years, the core symptoms of ADHD are often treated with medications. Stimulant medications are slightly less effective and more poorly tolerated in preschoolers, compared to older children and adolescents (Greenhill et al. 2006).While nonstimulant options are available as monotherapy or combination treatment, stimulant medications have been and continue to be the most common first-line medication treatment for ADHD (MTA Cooperative Group 1999; Pediatrics 2011; Feldman et al. 2018). MPH and AMP are the core stimulants that are used to treat ADHD. These compounds appear to have comparable clinical efficacy, yet there are individuals who responded preferentially to only one compound (Stein et al. 2011; Coghill et al. 2014). Acute response rate to stimulant treatment is ~70%, but the response rate can increase to close to 90% with carefully managed sequential trials of different stimulants and stimulant formulations that are carefully titrated (Stein et al. 2011; Coghill et al. 2014). Nevertheless, adherence to stimulants is modest, especially in adolescents who often discontinue medication, despite persistence of symptoms and impairments (Adler and Nierenberg 2010).Methylphenidate MPH has a typical onset of action of 30–45 minutes after administration and the mean duration of the clinical effect for immediate release (IR) MPH is 3–4 hours postadministration and up to 12 hours for ER formulations. The time to reach maximum plasma concentration (Tmax) is typically in the range of 1.5–2 hours. Unless otherwise noted, all MPH formulations are racemic formulations (1:1 d-MPH to l-MPH) (Markowitz et al. 2003; Connor and Steingard 2004; Patrick et al. 2018).MPH undergoes de-esterification (hydrolysis) to the inactive metabolite ritalinic acid by carboxylesterase 1 (CES1) in the liver. This is the primary metabolic pathway for MPH with little contribution from other metabolic enzymes. Sixty to 80% of the drug is excreted in the urine as ritalinic acid.



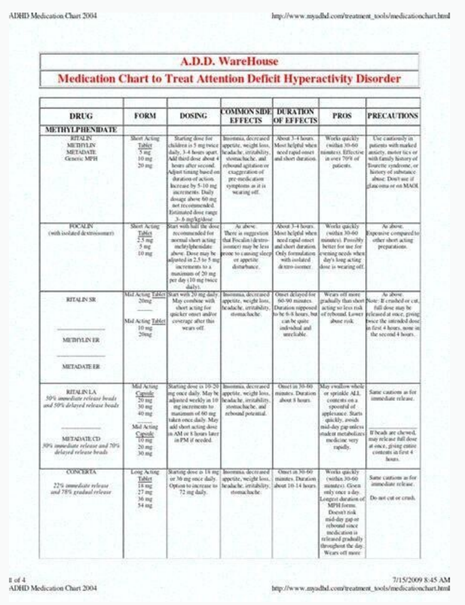
Generic Name	Brand Name	Daily Dose	Daily Dosage Schedule*	Common Adverse Effects
Stimulants				
Methylphenidate	Ritalin (Novartis) Metadate CD (Celltech) Concerta (McNeil Consumer) Ritalin LA (Novartis) Ritalin SR (Novartis) Others	0.3-2 mg/kg 0.6-2 mg/kg	2 to 4 times Once	Insomnia Decreased appetite/weight loss Possible reduction in growth velocity with chronic use
Dexmethylphenidate	Focalin (Novartis) Focalin XR (Novartis)	0.15-1 mg/kg	2 to 4 times Once	Stomachaches
Amphetamine Dextroamphetamine Mixed amphetamine salts	Dexedrine (GlaxoSmithKline) Adderall (Shire) Adderall XR (Shire) Others	0.3-1.5 mg/kg	Once 2 or 3 times Once	Headaches Dysphoria Rebound phenomena (short-acting preparations)
noradrenergic agents				
Atomoxetine	Strattera (Eli Lilly)	≤1.8 mg/kg	Once or twice	Insomnia/somnolence Dizziness Gastrointestinal upset Urinary retention
Arousal agents				
Modafinil	Provigil (Cephalon)	100-400 mg/d	Once or twice	Headache, upset stomach, insomnia
Antidepressants				
Tricyclics (TCA) Imipramine Desipramine Nortriptyline	Tofranil (Mallinckrodt); others Norpramin (Sanofi-Aventis); others Pamelor (Mallinckrodt); Aventyl (Eli Lilly); others	2-5 mg/kg 1-3 mg/kg	Once or twice	Dry mouth Constipation Weight loss Vital sign and ECG changes
Bupropion	Wellbutrin (GlaxoSmithKline) Wellbutrin SR, XL (GlaxoSmithKline)	3-6 mg/kg	3 times Once or twice	Irritability Insomnia Risk of seizures (doses >6 mg/kg) Contraindicated in bulimics
Venlafaxine	Effexor (Wyeth) Effexor XR (Wyeth)	0.5-3 mg/kg	Twice	Nausea Sedation Gastrointestinal distress
Antihypertensives				
Clonidine	Various	3-10 mcg/kg	2 or 3 times	Sedation Dry mouth Depression Confusion (high doses) Rebound hypertension Localized irritation with patch
Guanfacine	Various	30-100 mcg/kg	Twice	Similar to clonidine but less sedation Insomnia Irritability

*Dosing guidelines are not per FDA approval

ECG, electrocardiogram

2 INDEPENDENTLY DEVELOPED BY MCMAHON PUBLISHING

The 2004 article discussed the following formulations: OROS, methylphenidate (MPH) modified release, MPH extended-release capsules, and mixed amphetamine (AMP) salts (MAS) extended release (ER). That review suggested that “Future pharmaceutical development of stimulants for ADHD will emphasize long-acting formulations.” Since the publication of that article, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets (ODT), chewable tablets, ER liquid formulations, transdermal patches, and novel “beaded” technology. This review is meant to serve as an update and guide to newer stimulant formulations and includes a brief review of attention-deficit/hyperactivity disorder (ADHD) and stimulant properties which were covered in the original article.ADHD is a common neuropsychiatric disorder that has an estimated prevalence of 5%–9%. The symptoms of ADHD include developmentally inappropriate motor restlessness, impulsivity, and difficulty maintaining and shifting attention, which result in significant and often cumulative impairments in family, academic, and social functioning.



ADHD Medication Chart 2004

http://www.myadhd.com/treatment_tools/medicationchart.html

A.D.D. WareHouse

Medication Chart to Treat Attention Deficit Hyperactivity Disorder

DRUG	FORM	DOSING	COMMON SIDE EFFECTS	DURATION OF EFFECTS	PROS	PRECAUTIONS
METHYLPHENIDATE						

1 of 4

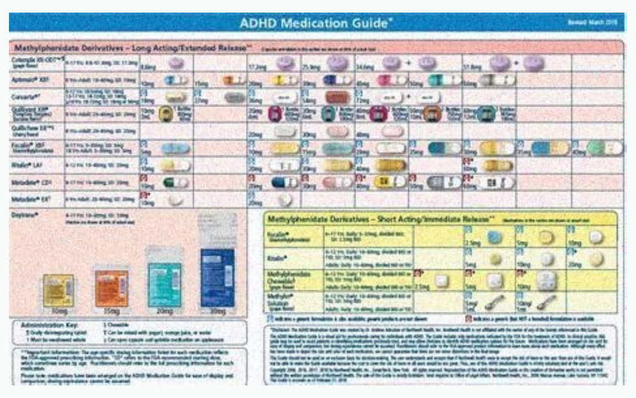
7/15/2009 8:45 AM

ADHD Medication Chart 2004

http://www.myadhd.com/treatment_tools/medicationchart.html

In the last 15 years, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets, chewable tablets, extended-release liquid formulations, transdermal patches, and novel “beaded” technology. All of these formulations involve changes to the pharmaceutical delivery systems of the two existing compounds most commonly employed to treat attention-deficit/hyperactivity disorder (ADHD), amphetamine (AMP) and methylphenidate (MPH). In addition to these new formulations, our knowledge about the individual differences in response has advanced and contributes to a more nuanced approach to treatment. The clinician can now make increasingly informed choices about these formulations and more effectively individualize treatment in a way that had not been possible before. In the absence of reliable biomarkers that can predict individualized response to ADHD treatment, clinical knowledge about differences in MPH and AMP pharmacodynamics, pharmacokinetics, and metabolism can be utilized to personalize treatment and optimize response. Different properties of these new formulations (delivery modality, onset of action, duration of response, safety, and tolerability) will most likely weigh heavily into the clinician's choice of formulation. To manage the broad range of options that are now available, clinicians should familiarize themselves in each of these categories for both stimulant compounds. This review is meant to serve as an update and a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties.Keywords: attention-deficit/hyperactivity disorder, stimulants, pharmacotherapy, treatment, pharmacokinetics, reviewIn 2004, “New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder” was published (Connor and Steingard 2004). The 2004 article discussed the following formulations: OROS, methylphenidate (MPH) modified release, MPH extended-release capsules, and mixed amphetamine (AMP) salts (MAS) extended release (ER). That review suggested that “Future pharmaceutical development of stimulants for ADHD will emphasize long-acting formulations.” Since the publication of that article, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets (ODT), chewable tablets, ER liquid formulations, transdermal patches, and novel “beaded” technology. This review is meant to serve as an update and guide to newer stimulant formulations and includes a brief review of attention-deficit/hyperactivity disorder (ADHD) and stimulant properties which were covered in the original article.ADHD is a common neuropsychiatric disorder that has an estimated prevalence of 5%–9%.

The symptoms of ADHD include developmentally inappropriate motor restlessness, impulsivity, and difficulty maintaining and shifting attention, which result in significant and often cumulative impairments in family, academic, and social functioning. ADHD has an onset in childhood and often persists into adulthood. While treatment often includes behavioral and educational strategies for associated problems, in children above 6 years, the core symptoms of ADHD are often treated with medications. Stimulant medications are slightly less effective and more poorly tolerated in preschoolers, compared to older children and adolescents (Greenhill et al. 2006).While nonstimulant options are available as monotherapy or combination treatment, stimulant medications have been and continue to be the most common first-line medication treatment for ADHD (MTA Cooperative Group 1999; Pediatrics 2011; Feldman et al. 2018). MPH and AMP are the core stimulants that are used to treat ADHD. These compounds appear to have comparable clinical efficacy, yet there are individuals who responded preferentially to only one compound (Stein et al. 2011; Coghill et al. 2014). Acute response rate to stimulant treatment is ~70%, but the response rate can increase to close to 90% with carefully managed sequential trials of different stimulants and stimulant formulations that are carefully titrated (Stein et al. 2011; Coghill et al. 2014). Nevertheless, adherence to stimulants is modest, especially in adolescents who often discontinue medication, despite persistence of symptoms and impairments (Adler and Nierenberg 2010).Methylphenidate MPH has a typical onset of action of 30–45 minutes after administration and the mean duration of the clinical effect for immediate release (IR) MPH is 3–4 hours postadministration and up to 12 hours for ER formulations.



ADHD Medication Guide*

Methylphenidate Derivatives – Long Acting/Extended Release**

Methylphenidate Derivatives – Short Acting/Immediate Release**

Administration Key:

Different properties of these new formulations (delivery modality, onset of action, duration of response, safety, and tolerability) will most likely weigh heavily into the clinician's choice of formulation. To manage the broad range of options that are now available, clinicians should familiarize themselves in each of these categories for both stimulant compounds.

This review is meant to serve as an update and a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties.Keywords: attention-deficit/hyperactivity disorder, stimulants, pharmacotherapy, treatment, pharmacokinetics, reviewIn 2004, “New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder” was published (Connor and Steingard 2004). The 2004 article discussed the following formulations: OROS, methylphenidate (MPH) modified release, MPH extended-release capsules, and mixed amphetamine (AMP) salts (MAS) extended release (ER). That review suggested that “Future pharmaceutical development of stimulants for ADHD will emphasize long-acting formulations.” Since the publication of that article, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations, and the introduction of several novel delivery systems such as orally dissolving tablets (ODT), chewable tablets, ER liquid formulations, transdermal patches, and novel “beaded” technology. This review is meant to serve as an update and guide to newer stimulant formulations and includes a brief review of attention-deficit/hyperactivity disorder (ADHD) and stimulant properties which were covered in the original article.ADHD is a common neuropsychiatric disorder that has an estimated prevalence of 5%–9%. The symptoms of ADHD include developmentally inappropriate motor restlessness, impulsivity, and difficulty maintaining and shifting attention, which result in significant and often cumulative impairments in family, academic, and social functioning.

ADHD has an onset in childhood and often persists into adulthood. While treatment often includes behavioral and educational strategies for associated problems, in children above 6 years, the core symptoms of ADHD are often treated with medications. Stimulant medications are slightly less effective and more poorly tolerated in preschoolers, compared to older children and adolescents (Greenhill et al. 2006).While nonstimulant options are available as monotherapy or combination treatment, stimulant medications have been and continue to be the most common first-line medication treatment for ADHD (MTA Cooperative Group 1999; Pediatrics 2011; Feldman et al. 2018). MPH and AMP are the core stimulants that are used to treat ADHD. These compounds appear to have comparable clinical efficacy, yet there are individuals who responded preferentially to only one compound (Stein et al. 2011; Coghill et al. 2014). Acute response rate to stimulant treatment is ~70%, but the response rate can increase to close to 90% with carefully managed sequential trials of different stimulants and stimulant formulations that are carefully titrated (Stein et al. 2011; Coghill et al. 2014). Nevertheless, adherence to stimulants is modest, especially in adolescents who often discontinue medication, despite persistence of symptoms and impairments (Adler and Nierenberg 2010).Methylphenidate MPH has a typical onset of action of 30–45 minutes after administration and the mean duration of the clinical effect for immediate release (IR) MPH is 3–4 hours postadministration and up to 12 hours for ER formulations.

The time to reach maximum plasma concentration (Tmax) is typically in the range of 1.5–2 hours. Unless otherwise noted, all MPH formulations are racemic formulations (1:1 d-MPH to l-MPH) (Markowitz et al. 2003; Connor and Steingard 2004; Patrick et al. 2018).MPH undergoes de-esterification (hydrolysis) to the inactive metabolite ritalinic acid by carboxylesterase 1 (CES1) in the liver. This is the primary metabolic pathway for MPH with little contribution from other metabolic enzymes. Sixty to 80% of the drug is excreted in the urine as ritalinic acid. Both d-MPH and l-MPH undergo this transformation. However, the presystemic metabolism and clearance of MPH are an enantioselective process favoring the metabolism of l-MPH, resulting in markedly higher concentrations of d-MPH, the therapeutically active isomer (Markowitz et al. 2003; Connor and Steingard 2004; Patrick et al.

2005, 2018; Quinn 2008). In theory, variation in the CES1 gene influencing the activity of the CES1 enzyme and co-administration with compounds that compete with or alter the CES1 pathway can impact the pharmacokinetics of MPH (Zhu et al. 2008). However, as there is significant interindividual variability in the dose–response relationship for MPH, plasma levels are not recommended for routine care and have not proven useful as guidance for dosing and management.Typically, this medication can be taken with food as this appears not to have a significant impact on bioavailability of MPH (Midha et al. 2001). However, you may see a delay in absorption (i.e., Tmax), which appears to be greatest with high-fat meals and theoretically could alter clinical response profile (Midha et al. 2001; Markowitz et al. 2003).Amphetamines Like MPH, AMP has a typical onset of action 30–45 minutes after administration, but has a slightly longer Tmax (3–4 hours) as well as duration of clinical effect: 4–6 hours for IR formulations, 8–12 hours for most ER formulations, and up to 16 hours for the formulation Mydayis®. AMP is more potent than MPH and recommendations generally suggest dose that is roughly half to two thirds the dose of MPH (Markowitz and Patrick 2017).AMP is highly metabolized and subject to two primary oxidative pathways: hydroxylation catalyzed by CYP2D6 and oxidative deamination. There is evidence to support preferential metabolism of d-AMP, which results in d-AMP having a shorter half-life relative to l-AMP. However, the difference is far less in magnitude than that described for racemic MPH. Unlike MPH, the l-isomer of AMP has significant therapeutic activity. AMP is eliminated through the kidneys in a pH-dependent manner, and alkalization of the urine can significantly protract AMP excretion (Markowitz and Patrick 2017).It is noted that genetic variability in AMP metabolism may be clinically relevant due to highly polymorphic nature of CYP2D6. In theory, CYP2D6 poor metabolizers might be expected to require smaller doses of AMP and/or be more prone to adverse effects from routine clinical doses, while CYP2D6 ultra-rapid metabolizers might be anticipated to have higher dosing requirements. However, since there are other metabolic pathways involved in the metabolism of AMP, this may mitigate the impact of this genetic variability. Given this observation and the lack of sufficient data documenting gene-drug concentration relationships, routine pharmacogenetic testing of genes encoding for drug metabolizing enzymes involved in AMP metabolism is not recommended. Furthermore, therapeutic drug monitoring of AMP blood levels has not proven useful in the management of ADHD, and there appears to be little correlation between blood concentrations of AMP and behavioral effects in adults or children (Markowitz and Patrick 2017).While food has been reported to have little effect on the bioavailability of d-AMP, as noted before, high-fat meals may delay absorption of the drug. Furthermore, acidifying agents/foods may lower absorption of AMP, while alkalinizing agents/foods may increase absorption (Markowitz and Patrick 2017).Pharmacodynamics The primary action of stimulants is to increase the synaptic availability of dopamine and norepinephrine, although AMP and MPH achieve this in slightly different ways. Both compounds inhibit dopamine (DAT) and norepinephrine (NET) transporter, thus slowing reuptake of these transmitters from the synaptic cleft and thereby elevating extracellular levels and increasing their effect. Unlike MPH, AMP is transported into the presynaptic cell. Through several intracellular processes, AMP nonspecifically displaces monoamines from intraneuronal storage vesicles, creating an increase of monoamines in the cytosolic pool. This increase of monoamines in the cell's cytosolic pool results in a reversal of flow at the reuptake pump, which further results in an increased flow of monoamines from the cell into the synaptic cleft.Therefore, AMP impacts the availability of other monoamines as well (e.g., serotonin) and thus may have broader effects than MPH either as a direct effect of the increased release of monoamines in the synapse or through downstream effects of these monoamines (Markowitz et al. 2003; Markowitz and Patrick 2017; Faraone 2018).However, the counterpoint to this argument is the evidence that MPH may also have a broader impact on other transmitter systems through a direct effect at receptor sites. For example, studies have suggested that MPH has affinity for 5-HT1A and 5-HT2B receptors and may exert an independent effect on this system (Markowitz et al. 2006, 2009).Enantiomers Methylphenidate The vast majority of clinical experience has centered around the administration of racemic MPH, that is, a 50:50 mixture of d-MPH and l-MPH (d,l-MPH). Dexmethylphenidate (d-MPH; Focalin®) was the first enantiopure form of MPH to reach the market.

It is apparent from studies that equipotent doses of d,l-MPH and d-MPH have comparable efficacy and d-MPH is the active enantiomer, roughly twice as potent as l-MPH (Markowitz and Patrick 2008; Quinn 2008). Furthermore, it has been shown that, while the presence of l-MPH does not impact the activity of d-MPH, its presence can prolong the elimination of d-MPH, thus extending the duration of action of the d-MPH enantiomer (Markowitz and Patrick 2008).Amphetamine While both isomers (d-AMP and l-AMP) are clinically effective, they have different pharmacokinetic properties. The mean elimination half-life is reported as ranging from 9 to 11 hours for d-AMP and 11 to 14 hours for l-AMP. Furthermore, when combined in a racemic mixture, the two isomers compete metabolically and thus prolong the elimination of both isomers, possibly extending the duration of response (Markowitz and Patrick 2017).As noted before, both isomers nonselectively release monoamines into the synaptic cleft. While d-AMP has a fourfold greater impact on dopamine than l-AMP, this needs to be put in context as a relative assessment because both isomers can increase striatal dopamine by greater than 5000% of the baseline value (Heal et al.

2013). In a similar vein, l-AMP has a comparable or greater impact on norepinephrine when compared to d-AMP, but both isomers have a very potent effect (Heal et al. 2013; Markowitz and Patrick 2017). This must be interpreted in the context of nonracemic mixtures of AMP isomers in which d-AMP predominates (e.g., mixed AMP salt formulations) (Markowitz and Patrick 2017).The typical response duration or behavioral half-life for IR formulations is 3–5 hours. Thus, until the advent of longer acting formulations of stimulant medication, treatment required the administration of multiple doses throughout the day. This created encumbrances that often interfered with access to effective treatment. IR formulations continue to play a role in the overall management of ADHD. They can be useful in the initial treatment of young children, those with autism spectrum disorder or intellectual disability, and managing afternoon or evening functioning. However, the ER formulations have become the core of treatment and there is no need to initiate treatment with IR and then transition to ER formulations.Safety Side effects and tolerability are comparable between the two stimulants. The most commonly observed side effect for all stimulant formulations are appetite suppression and delays in sleep onset. These adverse effects are often transitory, and adjustments in dosage, timing, or changing formulations can be helpful, as well as consultation regarding meal management, especially with younger children, and sleep hygiene. Mild changes in pulse and blood pressure also can occur and warrant monitoring during initiation of treatment and periods of dose adjustment (Graham et al. 2011; Pediatrics 2011; Feldman et al. 2018). While routine ECG screening is not indicated, patients with either a family or personal history of cardiovascular risk should undergo ECG testing or cardiology consultation before starting stimulants (Bélanger et al. 2009; Cooper et al.

2011; Hailpern et al. 2014). Comorbid tics are not a contraindication to use, but tics should be monitored (Cohen et al. 2015). Individuals with Raynaud's' syndrome can experience an exacerbation of symptoms (Coulombe et al. 2015). Hallucinations are a very rare side effect that typically remit with discontinuation (Coghill et al. 2014).The biggest clinical implication of the differences between MPH and AMP is the potential for a preferential response to one compound versus the other. As yet, there are no reliable clinical or biological predictors of response to a specific stimulant.

When the initial stimulant choice fails to deliver an optimal response, the evidence clearly supports the need for carefully managed sequential trials of the two compounds before deeming a stimulant trial unsuccessful in any given patient.Furthermore, isomeric mixtures are not equivalent. The ratio of enantiomers in the mixture can have an impact on both potency and duration of response, and single enantiomer formulations may have a tendency to be more potent milligram per milligram than mixed isomer formulations, although few head-to-head trials have been conducted.While the majority of drug development has focused on long-acting formulations, several IR formulations have been FDA approved and marketed since the publication of the 2004 review. All IR formulations can be modified for use with children who have difficulty swallowing. In addition to the obvious value of solutions and chewable tablets in this population, IR tablets can be crushed and mixed with food as well. As mentioned previously, the limitation of these formulations is the brief duration of action and accordingly, the need for twice- or thrice-daily dosing schedules.Racemic AMP (Evekeo®) Racemic AMP was originally marketed as Benzedrine® in the 1930s and was approved for clinical use by the FDA in 1976 (FDA 1976a, 2019a, 2019c). While Benzedrine is no longer available, racemic AMP sulfate marketed as Evekeo received FDA approval in 2012. A separate formulation, Evekeo ODT®, received FDA approval in 2019. As a racemic formulation, it contains a ratio of 1:1 d-AMP to l-AMP. It is available in 5 mg scored and 10 mg multiscored tablets and as a 5, 10, 15, and 20 mg ODT (FDA 2019a).AMP sulfate is water soluble and there is no recommendation against chewing or crushing the tablets, although there are no reports available describing palatability or comparative pharmacokinetics of tablets swallowed whole versus crushed and given with food or drink. Evekeo ODT allows for the drug to be taken without water and the disintegrated portions of the tablet along with the drug are swallowed with saliva.In children from 3 to 5 years of age, the recommended initial dose is 2.5 mg daily. Dosage may be raised in increments of 2.5 mg at weekly intervals until an optimal response is obtained. In children 6 years of age or older, the recommended starting dose is 5 mg once or twice daily; daily dosage may be increased in increments of 5 mg at weekly intervals until an optimal response is obtained. It is recommended to give first dose on awakening, and additional doses (1–2) at intervals of 4 to 6 hours.In a multicenter, dose-optimized, double-blind crossover study that measured reduction of ADHD symptoms at 2 hours postdose in a laboratory classroom setting, subjects were started on 10 mg/day given in two divided doses 4–6 hours apart, and dose was titrated in 5 mg increments until optimal dose was achieved based on efficacy and tolerability. Median final dose was 20 mg; however, efficacy was shown between doses of 10–40 mg, regardless of final daily dose (Childress et al. 2015). Evekeo also carries FDA-labeled indications to treat narcolepsy and exogenous obesity.Dextroamphetamine (Zenzedi®) Dexedrine sulfate was initially approved for use in 1976 and is available generically from multiple manufacturers (FDA 1976b, 2011). Zenzedi is the brand name of for a recently released formulation of d-AMP sulfate tablets. It is available in six different dosage strength tablets: 2.5, 5, 7.5, 10, 15, 20, and 30 mg.Zenzedi is indicated for treatment of narcolepsy and ADHD in children, adolescents, and adults. It is not recommended for pediatric patients younger than 3 years.

In pediatric patients from 3 to 5 years of age, recommended starting dose is 2.5 mg daily. It is recommended that daily dosage be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In patients older than 6 years, an initial dose of 5 mg once or twice daily is recommended with a titration schedule of 5 mg at weekly increments until optimal response is achieved. Doses exceeding 40 mg/day is only recommended for rare cases. The first daily dose should be given on awakening with one or two additional doses throughout the day at intervals of 4 to 6 hours depending on clinical response.MPH oral solution and MPH chewable tablet MPH Oral Solution was approved by the FDA as Methylin® Oral Solution in 2002 and is now available from multiple manufacturers (FDA 2002a, 2002b, 2003a, 2003b). It is a grape-flavored liquid form of MPH. It comes in two solutions of different concentrations: 5 mg/5 mL (each mL has 1 mg of MPH) and 10 mg/5 mL (each mL has 2 mg of MPH).An MPH Chewable Tablet was approved by the FDA as Methylin Chewable Tablet in 2003. While the original manufacturer has discontinued production, it is now available from multiple manufacturers. It is a grape-flavored chewable tablet, which contains MPH. It is available as 2.5, 5, and 10 mg tablets.Both formulations are a racemic mixture (dl-MPH) and have been shown to be bioequivalent to MPH tablets. Thus, recommended dosing, dosing schedule, pharmacokinetics, response profile, and side effects for both formulations are comparable to MPH tablets.Dextroamphetamine oral solution (Procentra®) Dexedrine® Elixir was originally approved by the FDA in 1976 (FDA 2010). When the original manufacturer discontinued production, other manufacturers began to produce the compound as a replacement.Procentra is the brand name for one of these formulations. Procentra is colorless, has bubble gum flavor, and contains 5 mg of d-AMP in each teaspoon (5 mL).Procentra should be taken orally. The dosing recommendations are those used for all other d-AMP formulations.There are no studies showing safety and tolerability of this preparation as it received FDA approval by replacing Dexedrine Elixir.Cotempla XR ODT® (MPH) Cotempla XR ODT was approved by the FDA in 2017 (Childress et al. 2016, 2017; FDA 2017b, 2017c).

It is the brand name for the first ER orally disintegrating tablet formulation of dl-MPH. The formulation comprised two types of MPH microparticles (MPH bound to a polymer).

One set of microparticles is uncoated and considered an IR component. The other set is coated with a film that delays absorption of the MPH and leads to the extended release (ER) of the drug in the body.

Thirty percent of the microparticles in this formulation are designed for IR. These microparticles are incorporated into an ODT that allows the drug to be taken without water, and the disintegrated portions of the tablet along with the drug are swallowed with saliva.Cotempla XR ODT is available as 8.6, 17.3, and 25.9 mg tablets, which contain the same amount of MPH (base equivalent) found in other 10, 20, and 30 mg ER MPH formulations, respectively. The tablets are dispensed in blister packs.Cotempla XR ODT has a pharmacokinetic profile similar to a comparable dose of MPH ER capsule with a slightly higher peak concentration and overall bioavailability. Cotempla XR ODT can be administered once a day. The onset of action is again comparable to MPH ER capsule with onset of action within the first hour following administration and a significant clinical response still evident at least 8 hours and extending up to 12 hours postdose, with gradual loss of effect over between 8 and 12 hours.The recommended starting dose in 6–17-year-old patients is 17.3 mg, given once in the morning. The dose can be increased by 8.6 to 17.3 mg weekly. Doses above 51.8 mg have not been studied and are therefore not advised.Like other formulations, Cotempla XR ODT can be taken with food. There is a small decrease in median time to peak concentrations when consumed with food that could have a small impact on response time. High-fat meals could decrease peak concentrations and overall bioavailability. Given these issues, patients should try to be consistent with regard to the presence of food during administration.Response characteristics and safety and tolerability profiles are comparable to other dl-MPH formulations.Adzenys XR-ODT® and Adzenys ER® (oral suspension) (AMP) Adzenys XR-ODT was approved for use in 2016 and Adzenys ER (oral suspension) was approved for use in 2017 (FDA 2016a, 2016b, 2017a, 2107; Stark et al. 2016, 2017; Sikes et al. 2017, 2018).

Adzenys XR-ODT is an ER orally disintegrating tablet and Adzenys ER is an oral suspension. Both formulations contain MAS, comprising both d- and l-enantiomers of AMP in a 3:1 ratio. The formulations comprised two types of AMP microparticles. Fifty percent of the microparticles are uncoated (IR), while the balance of microparticles is coated with a film that delays absorption of the AMP, providing for an ER profile of the formulation. These microparticles are incorporated into an ODT (Adzenys XR-ODT) or dissolved in an oral suspension (Adzenys ER). Like Cotempla XR-ODT®, the ODT allows for the drug to be taken without water and the disintegrated portions of the tablet along with the drug are swallowed with saliva. This medication is bioequivalent to other MAS ER formulations.Adzenys XR-ODT is available in 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg tablets, which are equivalent to 5, 10, 15, 20, 25, and 30 mg of Adderall XR®, respectively. The individual tablets are dispensed in a blister pack. Adzenys ER contains 1.25 mg of MAS per mL, roughly the equivalent of 2 mg of Adderall XR.For pediatric patients, the recommended starting dose is 6.3 mg (5 mL of the oral suspension) once daily. The dose can be increased by increments of 3.1 or 6.3 mg weekly as indicated by response. The maximum recommended dose is 18.8 mg for patients 6 to 12 years of age. For older children and adults, the maximum recommended dose is 12.5 mg daily.Patients taking Adderall XR may be switched to Adzenys XR-ODT at an equivalent dose taken once daily. When switching from other AMP products, discontinuation of that treatment followed by slow upward titration with Adzenys XR-ODT is recommended.Adzenys XR-ODT and Adzenys ER are bioequivalent to other MAS ER formulations that comprised 3:1 d- and l-AMP, such as Adderall XR and pharmacokinetic profiles are comparable. Maximum plasma levels for d-AMP occur at 5.6 hours, and a delayed Tmax is observed in younger children.

Elimination half-life is 9.5 hours, in line with other ER formulations. Peak plasma levels (Cmax) for l-AMP are reached at 5.9 hours.Adzenys XR-ODT can be taken with or without food. However, when taken with high-fat meals, studies in adults showed 19% reduction in peak plasma levels and the median Tmax to reach peak plasma levels is prolonged by ~2 hours. Onset of action (45–60 minutes) and mean duration of action (up to 12 hours) are comparable to other MAS ER formulations.Adzenys XR-ODT and Adzenys ER have the same clinical efficacy as other MAS XR formulations at equivalent doses and share similar response characteristics as well as safety and tolerability.Quillivant XR® (MPH) Quillivant XR was approved for use in 2012 (Childress and Berry 2010; FDA 2012a, 2012b; Childress and Sallee 2013; Robb et al. 2017; Sallee et al. 2017). It is a powder containing dl-MPH microparticles, which are proportioned as ~20% uncoated (IR) microparticles and 80% film coated (for ER). When reconstituted in water, it forms a 25 mg/5 mL oral solution.The recommended starting dose for patients 6 years of age and older is 20 mg (4 mL). However, studies in adults suggest that Quillivant XR 60 mg is bioequivalent to two 30 mg doses of dl-MPH IR oral solution. Thus, a starting dose of 2 mL (10 mg) may be more in line with recommended starting doses of MPH IR in this population.

Increments of 10 mg (2 mL)–20 mg (4 mL) are recommended with the provision that doses above 60 mg (12 mL) have not been studied and are not recommended.Pharmacokinetic studies demonstrate the expected profile of an effective ER preparation: initial release that emulates IR uptake with an extended pattern of release. Peak plasma levels are usually achieved within 2–4 hours and there is evidence of "clinically meaningful plasma concentrations" up to 12 hours later. Thus, Quillivant XR has an onset of action at 45 minutes postdose and duration of action for up to 12 hours.As noted before, a study of single-dose pharmacokinetics in adults demonstrated that the 60 mg dose was equivalent to two doses of 30 mg IR given 6 hours apart. The peak plasma level for Quillivant XR in this study was higher for the IR preparation. Similar studies in children and adolescents, using weight-adjusted analysis, revealed comparable characteristics in all age groups.Quillivant XR can be taken with food as the presence of food appears to have no impact on overall exposure to MPH.Efficacy studies suggested significant response beginning at ~45 minutes postdose, which is maintained for at least 8 hours, and extending up to 12 hours postdose with gradual loss of effect over between 8 and 12 hours.The side effect and tolerability profiles are comparable to other dl-MPH-based products.Dynavel XR® (AMP) Dynavel XR was approved for use in 2015 (FDA 2015c, 2105; Childress et al. 2018b). It is an ER oral suspension that contains 3.2 to 1 ratio of d- to l-AMP. One milliliter of Dynavel XR suspension contains 2.5 mg of MAS base. The suspension should be stored at room temperature and shaken vigorously before dosing and administration.Following a single 18.8 mg oral dose of Dynavel XR in 29 healthy adult subjects in a crossover study under fasting conditions, the median time to peak plasma concentrations was 4.0 (range 2–7) hours after dosing and the peak concentration was comparable to IR MAS tablets. The mean elimination half-life was ~12 hours for d-AMP and 15 hours for l-AMP, respectively, following a single 18.8 mg oral administration. After rapid initial absorption, levels peak 4–5 hours postdosing and then slowly decline over the remainder of the day.The clinical efficacy of Dynavel XR was demonstrated in a recent laboratory classroom study with an open-label dose optimization phase followed by a double-blind placebo-controlled week on patients with ADHD. In the study, statistically significant improvements in attention and deportment measures were shown at all time points tested (1, 2, 4, 6, 8, 10, 12, and 13 hours postdose). Thus, Dynavel XR has an onset of action by 1 hour postdose and duration of response lasting as long as 13 hours postdose.The recommended starting dose is 2.5 or 5 mg once daily for children older than 6 years. The dosage may be increased in increments of 2.5 mg to 10 mg/day every 4–7 days until an optimal response is obtained. The maximum recommended dose is 20 mg/day.A high-fat meal delays average peak concentrations (Cmax) by 1 hour, but actual changes in Cmax are small and considered clinically insignificant.Dynavel XR is well tolerated and its side effect profile is comparable to other MAS formulations.Lisdexamfetamine: Vyvanse® Capsule and Chewable Tablet Vyvanse is the proprietary name for lisdexamfetamine (LDX) dimesylate (FDA 2006e, 2007; Biederman et al. 2007a, 2007b; Boellner et al. 2010; Jain et al. 2011, 2013; Katic et al. 2012; Coghill et al. 2013, 2014, 2017; Findling et al. 2013; Childress et al. 2014; Dolder et al. 2017; Newcorn et al. 2017). As a prodrug, LDX is the pharmacologically inactive parent molecule, consisting of d-AMP covalently bonded to l-lysine. The intact prodrug is not believed to cross the blood–brain barrier. The compound is rapidly and actively absorbed in the small gut.

LDX is then hydrolyzed in the red blood cells, liberating the pharmacologically active d-AMP molecule from lysine. This process of hydrolyzation is rate limited and contributes to the lag in response time and the longer duration of response.Vyvanse is available in two forms, a capsule and a chewable tablet. There is no dosing difference between the two forms. Vyvanse is available as 10, 20, 30, 40, 50, and 60 mg capsules and chewable tablet. The capsule is also available as 70 mg.The capsule form of the medication can be taken two ways: (1) swallowed whole or (2) mixed thoroughly into edibles like yogurt or liquids like water or orange juice. If taken in edibles or liquid, it must be taken immediately and not stored for later use. The chewable tablets must be chewed thoroughly before swallowing.The recommended starting dose is 30 mg in ages 6 and older. Dosage adjustments of 10–20 mg can occur on a weekly basis to a maximum recommended dose of 70 mg.The pharmacokinetics and pharmacodynamics of d-AMP liberated from the LDX are comparable to those of the active metabolite, d-AMP. Pharmacokinetic curves are monophasic and linear between 30 and 70 mg in pediatric patients and between 50 and 250 mg in adults. When compared in a head-to-head manner using equivalent doses, there is a lag time in reaching peak plasma level of d-AMP (about 1 hour) when administered as LDX, but the overall pharmacokinetics are practically identical.LDX has been shown to be effective in reducing ADHD symptoms in children, adolescents, and adults. Doses between 30 and 70 mg result in significant improvements in ADHD symptoms on standardized measures of response and this response is maintained from 1.5 (onset of action) to 13 hours (duration of action) postadministration. Clinical response appears to be maintained over time in long-term follow-up studies in children and adolescents.Clinical response characteristics, safety, and tolerability are comparable to other d-AMP formulations.QuilliChew ER® tablets (MPH) Like Quillivant XR, Quillichew® Tablets contain MPH microparticles that are both uncoated and coated, which determine the rate of release of the ER MPH component (FDA 2015e, 2015d; Wigal et al. 2017, 2018).Quillichew ER tablets contain 30% uncoated (IR) microparticles and 70% film coated ER microparticles of MPH.

The MPH microparticles are incorporated into a cherry-flavored tablet that can either be chewed or swallowed whole. There is no difference in pharmacokinetic characteristics if the tablet is swallowed whole or chewed.QuilliChew ER is available as 20, 30, and 40 mg tablets. The 20 and 30 mg tablets are scored. While a 40 mg dose of QuilliChew ER is comparable to two 20 mg dose of IR MPH given 6 hours apart, the peak concentration (−20%) and the overall bioavailability (−11%) are slightly lower when QuilliChew ER is administered.While the recommended starting dose for patients 6 years and above is 20 mg, in some patients, starting with 10 mg may be prudent. Thus, a starting dose of 10 mg may be more in line with recommended starting doses of MPH IR in this population.

Increments of 10–20 mg are recommended with the provision that doses above 60 mg have not been studied and are not recommended.Pharmacokinetic studies demonstrate the generally accepted profile of an effective ER formulation, that is, an initial release that emulates IR absorption with an extended pattern of release over the ensuing hours. Peak plasma concentrations are usually achieved 5 hours later, with a steady decline in plasma levels after that is achieved. Efficacy studies suggested significant response beginning at ~45 minutes postdose, which is maintained for up to 8 hours with gradual loss of effect over between 8 and 10 hours.QuilliChew ER can be taken with food as the presence of food appears to have no impact on overall exposure to the core compound; however, as noted before, high-fat meals can impact time to peak levels and overall bioavailability.The side effect and tolerability profiles are comparable to other dl-MPH formulations.LDX Chewable Tablet-Vyvanse (see Prodrug section) Daytrana® (dl-MPH) Daytrana is "an adhesive-based matrix transdermal system (MTS)" patch (Pelham et al.

2005, 2011; Pelham Jr et al. 2005; FDA 2006a, 2006b, 2006c, 2006d; Faraone and Giefer 2007; Findling et al. 2008; Faraone et al. 2009; Gonzalez et al. 2009; Patrick et al. 2009; Arnold et al. 2010; Findling and Dinh 2014; Pastore et al. 2015). The active moiety is dl-MPH. The dl-MPH is incorporated into an adhesive in a way that ensures the dosage strength across the patch is uniform. The medication is delivered transdermally and the total dose delivered is dependent upon (1) the size of the patch and (2) the wear time.The patch is available in four sizes: 10 mg (12.5 cm2), 15 mg (18.75 cm2), 20 mg (25 cm2), and 30 mg (37.5 cm2).

Starting dose of this medication is 10 mg. The onset of action of transdermal dl-MPH is ~2 hours after application, but the effects last for the duration of wear time.

It is recommended that the patch be worn no longer than 9 hours postapplication. The patch can be removed before 9 hours and thus provides some control over response duration.

Once the patch is removed, absorption may continue for several hours (2–3 hours), but the plasma concentrations of MPH and hence, the clinical response, begin to decline steadily.The patch should be applied to a clean, dry area of the hip, avoiding any breaks in the skin or areas that are prone to being rubbed by clothing.

The patch should not be damaged in any manner and it should not be cut. If the patch becomes damaged during use, or becomes partially or fully detached, it should be removed and discarded. If a new patch is applied, it should be applied in a different site.The site of patch application should be changed daily, and it is suggested that it be applied in an alternating manner, right or left hip. Studies have shown variation in absorption between different sites in the body (e.g., less absorption at the scapula vs. the hip). Therefore, general location should remain constant (hip), but alternating right and left side is acceptable.Care must be taken when the patch is removed. Only 36% of the MPH in the transdermal patch is absorbed after 9 hours. Thus, the patch is still "active" after removal. Improper disposal carries the risk of accidental exposure or overdose. Skin contact with the active surface should be avoided when removed and it is advisable that any visible adhesive residue should be removed to avoid continued systemic absorption.As noted above, there is a lag time of ~2 hours before response. As a result of this delay, MPH IR is often prescribed concomitantly to decrease the onset of action.The MPH is delivered at a steady rate based on patch size: 10 mg delivers 1.1 mg/h, 15 mg delivers 1.6 mg/h, 20 mg delivers 2.2 mg/h, and 30 mg delivers 3.3 mg/h.Of note, transdermal dl-MPH is the only racemic formulation of the drug that delivers ~50:50 ratio of d- and l-MPH into the systemic circulation.As noted previously, oral absorption of dl-MPH can favor the d-MPH enantiomer. Transdermal absorption circumvents this first-pass effect. This results in higher levels of the l-MPH enantiomer. Since the l-isomer is largely inactive, the therapeutic significance of this isomer delivery is likely to be minimal.Results of RCT trials demonstrate that children exhibit significant improvement when compared to placebo treatment and comparable improvement when compared with the ER oral dosage form Concerta®.As the core compound is MPH, the safety and tolerance profiles are comparable to other dl-MPH products.However, this formulation brings some unique risks. Localized contact dermatitis is a frequently reported side effect, typically manifests by slight and transient redness at the application site. The technology used in the patches minimizes the risk of dermatitis compared to other transdermal products, but the risk exists. Alternating the application site can minimize this risk. This limited dermatitis appears to be a reaction to the adhesives in the patch as opposed to the drug itself. Cortisone cream (1%–2%) can be applied to the affected area.

One study set out to explore the risk for more serious skin sensitization. In this study, 133 individuals intentionally applied the patch to the same site for 3 weeks. Eighteen of these individuals developed a more severe and systemic sensitization that precluded further use of the patch.

The concern has been raised that some MTS-sensitized individuals may not be able to be reexposed to MPH in any form.Furthermore, some people report discomfort when removing the patch regardless of the presence of dermatitis. This can also be minimized by alternating sites.Finally, there is a risk of accidental poisoning. The large patch contains 82.5 mg of MPH. If a child were to chew or swallow a patch, this would constitute a medical emergency. Again, as stated earlier, there are also concerns surrounding previously used patches as over 60% of the MPH content remains in the patch after use.Aptensio XR® (MPH) Aptensio® XR was approved for use in 2015 (FDA 2015a, 2015b; Teuscher et al. 2015; Wigal et al. 2015; Owens et al. 2016). It is an ER dl-MPH compound in capsule form that utilizes coated and uncoated MPH microparticles, similar to other MPH ER capsules. In this preparation, 37% of the beads are uncoated for IR and the remainder of the beads are coated for ER.Aptensio XR is available in 10, 15, 20, 30, 50, and 60 mg capsules.

Recommended starting dose is 10 mg and the dose can be increased weekly by 10 mg, as indicated by clinical response and tolerance.The response to Aptensio XR appears comparable to other MPH ER oral dosage formulations with an onset of action within 1 hour of administration and duration of up to 12 hours.Response characteristics and safety and tolerability profiles are comparable to other dl-MPH formulations.Adhansia XR (MPH) At the time of this review, information available on the newly approved Adhansia XR® was limited to the information on the FDA website (FDA 2019b). Adhansia XR was approved for use in 2019. It is a dl-MPH formulation that utilizes beads composed of an immediate release layer which contains approximately 20% of the MPH dose and a controlled release layer which contains approixmately 80% of the MPH dose. Clinical trials suggest that this formulation maintains a response as long as 16 hours postadministration. Adhansia XR is approved for use in children, adolescents, and adults.Adhansia XR comes in 25, 35, 45, 55, 70, and 85 mg capsules.

The recommended starting dose for 6 years of age and older is 25 mg with weekly increments of 10–15 mg. In short term controlled trials in pediatric patients, doses of 70 mg/day and higher were associated with a disproportionate increase in the incidence of certain adverse reactions. Daily doses greater than 100 mg in adults and 85 mg in pediatric patients have not been evaluated in clinical trials.

Adhansia XR is given once in the morning and the long duration of response obviates the need for a second dose of medication.The construction of this formulation results in an extended duration with a biphasic pattern of absorption. Steady state is achieved by day 3 and no further accumulation was observed following the administration of 100 mg/day in healthy adult subjects. The onset of response is comparable to the onset seen with a standard dose of IR dl-MPH. When Adhansia 100 mg qam is compared to MPH IR 20 mg TID, Adhansia XR exhibits a significantly higher initial peak (Cmax 22% higher). Furthermore, the formulation exhibits greater mean extent of exposure (AUC0–24 hours: 50%) and minimum concentration (Cmin: 288%) at steady state, which is achieved at day 3.The capsules can be taken whole or opened and sprinkled in small amount of food such as limited applesauce or yogurt portions.

If the sprinkle method is used, the entire sprinkled contents should be consumed immediately and not chewed or crushed.Adhansia XR has been shown to be effective in reducing ADHD symptoms in children, adolescents, and adults within the suggested dose range. Adhansia XR results in significant improvements on standardized measures of response and this response appears to be maintained from 1 to 16 hours postadministration.The side effect and tolerance profiles are comparable to other dl-MPH formulations. However, given the extended duration of response, the most common concerns are insomnia and decreased appetite.Mydayis (AMP) Mydayis was approved for use in 2017 (FDA 2017e, 2017d; Adler et al. 2017; Weisler et al. 2017; Brams et al. 2018; Wigal et al. 2019). It is an MAS formulation that utilizes three different types of drug releasing beads, which achieve a prolonged duration of action of up to 16 hours. The first bead releases MAS immediately after ingestion. The second bead is coated in a film that releases the core compound at pH 5.5 in the proximal small intestine. The third bead has two coatings. The first coat is porous and allows for the slow release of the MAS, while the second coating is designed to release the medication at a pH of 7.0 corresponding to the distal small colon.Mydayis is recommended for patients 13 years of age and older. Patients 12 years of age and younger experienced higher plasma levels at the same dose and higher rates of adverse reactions, mainly insomnia and decreased appetite. At the time of this publication, Mydayis had not been approved for use is children 12 of age or younger.Mydayis comes in 12.5, 25, 37.5, and 50 mg capsules. As with other MAS formulations, Mydayis is a mixture of d-AMP and l-AMP in a ratio of 3:1.

The recommended starting dose is 12.5 mg with weekly increments to a maximum recommended dose of 25 mg in 13–17 year olds and 50 mg in adult patients. Mydayis can be given once in the morning. The response profile is such that the use of Mydayis obviates the need for a second late-afternoon dose of medication.After absorption, the pharmacokinetics of the compound is the same as with other MAS formulations. Given the design of the dosage form, absorption is extended and monophasic, and the onset of response is comparable to the onset seen with a standard dose of IR MAS, but has an extended duration of response lasting as long as 16 hours postingestion. Administration of one Mydayis 37.5 mg capsule results in similar plasma concentrations as with a dose of MAS-ER 25 mg followed by a dose of 12.5 mg of MAS IR given 8 hours later.The capsules can be taken whole or opened and sprinkled in small amount of food such as limited applesauce portions. If the sprinkle method is used, the entire sprinkled contents should be consumed immediately and not chewed. There is no difference in absorption of this formulation if taken whole or as sprinkles.Mydayis has been shown to be effective in reducing ADHD symptoms in children, adolescents, and adults within the suggested dose range. Mydayis results in significant improvements on standardized measures of response and this response is maintained from 2 to 16 hours postadministration.The side effect and tolerance profiles are comparable to other MAS formulations. However, given the extended duration of response, in clinical trials, the most common side effects reported were insomnia and decreased appetite in adults and decreased appetite in adolescentsJornay PM® (dl-MPH) Jornay PM was approved for use in 2018 (Pliszka et al. 2017; Childress et al. 2018a; FDA 2018a, 2018b).

It is the first "delayed release/extended release" (DR/ER) dl-MPH formulation. This dosage form permits nighttime administration of medication with an onset of action targeted for the following morning. This is achieved utilizing a proprietary delivery system called Delexis®. Delexis delivery system is based on a microbead technology and comes in a capsule form. Each microbead in the capsule comprised a drug core surrounded by two layers of functional film coatings. The outer layer delays the release of the drug core and the inner layer regulates the release of the drug core to achieve a delayed, yet extended dispersal pattern.Jornay PM is available in 20, 40, 60, and 80 mg capsules. The recommended starting dose is 20 mg.

If clinically indicated, the dose can be titrated weekly in increments of 20 mg. The mean dose in an open flexible dosing trial of 6–12-year olds was 67 mg, while the mean dose in a randomized, forced-dose titration study of 6–12-year olds was 68.1 mg. Doses between 20 and 80 mg are well tolerated; however, doses above 100 mg have not been studied.Jornay PM is intended for evening administration only. Given the unique characteristic of the medication, it is recommended that treatment be initiated with an 8 PM administration (the most commonly prescribed time in clinical trials). However, given apparent variability that exists in the population tested, it is also suggested that the timing of the evening dose can be adjusted between 6:30 and 9:30 PM based on an individual's response.There is an intended initial delay of 8–10 hours before drug begins to be released. Following this delay, the drug concentrations rise rapidly and generally produce an ascending absorption profile. Peak concentrations are achieved at 16–18 hours and this is followed by a slow decline in concentrations. It appears that more than half of the MPH exposure occurs after the peak concentration is achieved, thus achieving an extended duration of action.Thus, this is a formulation that can be taken at night and functions like an ER preparation taken in the morning. Clinical response is seen for 10–12 hours after onset of delayed release (22–24 hours postdose).Unlike other MPH formulations, the target for drug delivery is the colon, which is less absorptive. This results in a prolonged absorption window and, perhaps, the extended duration of response. Pharmacokinetic studies suggest that the drug has a monophasic profile and there are no significant differences in pharmacokinetic findings across all age groups when a weight-adjusted dose analysis is used.In clinical trials, Jornay PM has been shown to significantly reduce symptoms of ADHD. Significant improvement was noted in the first week of treatment during a randomized fixed-dose titration study where the starting dose was 40 mg. Furthermore, given the unique response profile, Jornay PM was able to effectively reduce early morning functional impairment, while maintain comparable benefit throughout the afternoon and into the early evening.Doses ranging from 20 to 80 mg are generally well tolerated.The capsules can be taken whole or opened and sprinkled in a small portion of food such as applesauce. When the sprinkling method is used, the entire sprinkled contents should be consumed immediately and not chewed. There is no difference in pharmacokinetics of this formulation swallowed whole versus sprinkled on food.The pattern of adverse events is comparable to that seen with other dl-MPH formulations. However, the pattern of sleep interruption is different than that experienced with other formulations. Instead of interfering with sleep onset, Jornay PM can result in early morning awakening.

This can usually be addressed by adjusting the timing of the evening dose.In the last 15 years, numerous new ADHD medication formulations have appeared on the market. All of these formulations involve changes to the pharmaceutical delivery systems of the two existing compounds most commonly employed to treat ADHD, AMP and MPH. Much of this new round of drug development centers on the use of microparticles, increasingly more sophisticated "coats" on these microparticles, and the development of pH-dependent, transdermal, and prodrug technologies. In addition to these new formulations, our knowledge of individual variability with regard to response and metabolism has also advanced and contributes to a more nuanced approach to treatment. Concomitantly, knowledge about individual differences in response as well as interindividual and intraindividual pharmacokinetic variability has increased. The clinician can now make increasingly informed choices about these formulations and more effectively individualize treatment in a way that had not been possible before.In the absence of reliable biomarkers that can predict individualized response to ADHD treatment, clinical knowledge about differences in MPH and AMP pharmacodynamics, pharmacokinetics, and metabolism can be utilized to personalize treatment and optimize response. For example, we know that MPH and AMP are sufficiently different, so there can be a preferential individual response to one compound versus the other. Clinical practice now recommends the use of sequential trials of both compounds, when indicated, to maximize the response rate. In another example, we know that these two compounds are metabolized differently. This means that metabolic variations can apply to one compound, but not the other. For instance, an individual who is a rapid metabolizer of AMP may normally metabolize MPH, or a variation in the CES1 gene may have a profound impact on an individual's response to MPH, but will have no impact on AMP.

Likewise, drug-drug interaction liability is substantially different between the two stimulants. For example, AMP is partially metabolized by CYP2D6, but not MPH. Thus, the potential exists for competitive metabolic interactions between AMP and other compounds metabolized by CYP2D6, but this is not the case for MPH. Finally, recent research suggests that age may play a role in determining the primary agent. In a recent meta-analysis of comparative efficacy and tolerability, Cortese et al. have suggested that MPH may be the preferred agent in children and adolescents, while AMP may be preferred in adults.Currently, different properties of these new formulations (delivery modality, onset of action, duration of response, safety, and tolerability) will most likely weigh heavily into the clinician's choice of formulation (see above Tables). Treatment typically emphasizes the use of an ER formulation. Extended-release formulations loosely fall in to the range of medium duration (6–10 hours), long duration (8–12 hours), and very long duration (>12 hours) and a number of the formulations can accommodate patients who have difficulty swallowing oral dosage forms. In certain individuals, younger children for instance, the clinician may choose to initiate treatment with an IR compound to assess tolerability and determine appropriate daily dose requirements. Treatment with an ER formulation can be supplemented or "sculpted" with an additional dose of IR medication to provide an enhanced response with the morning dose or to extend coverage into the early evening if required. Dosing is typically started at the lowest available dosage strength and titrated against response and tolerability to determine the optimal dose. This allows for the clinician to carefully manage the metabolic variability that exists in the population. To manage the broad range of options that are now available, a clinician should familiarize themselves in each of these categories for both stimulant compounds. We have provided 4 tables (Tables 1–4) that provide guidelines in tabular form for the use of the formulations that have been reviewed in this article.Immediate-Release Formulations: MethylphenidateDrugFormulation(s)Dose rangeCommentsMPH oral solution5 mg/5 mL and 10 mg/5 mL solutions• Starting dose:4–5-year old: 2.5–5 mg6 years and older: 5–10 mg• Dosage range:4–5-year old: 2.5–30 mg/day6 years and older: 5–60 mg/day. Given in divided dose qd-tid• Dose can be increased by 5–10 mg/day weekly• Max dose 60 mg/day• Dose the same as other dl-MPH formulations• Onset of response 30–45 minutes• Duration of response 3–4 hours postdose• Multiple manufacturersMPH chewable tablet2.5, 5, and 10 mg tablets• Starting dose:4–5-year old: 2.5–5 mg6 years and older: 5–10 mg• Dosage range:4–5-year old: 2.5–30 mg/day6 years and older: 5–60 mg/day. Given in divided dose qd-tid• Dose can be increased by 5–10 mg/day weekly• Max dose 60 mg/day• Dose the same as other dl-MPH formulations• Onset of response 30–45 minutes• Duration of response 3–4 hours postdose• Multiple manufacturersImmediate-Release Formulations: AmphetamineDrugFormulation(s)Dose rangeCommentsEvekeo®5 and 10 mg scored tablets• Starting dose:4–5-year old: 2.5 mg6 years and older: 5 mg• Dosage range:4–5-year old: 2.5–30 mg/day6 years and older: 5–60 mg/day. Given in divided dose qd-tid• Dose can be increased by 5 mg/day weekly• Doses above 40 mg/day rarely more effective• Racemic mixture (1;1 d- to l-ratio)• Originally marketed as Benzedrine• Onset of response 30–45 minutes• Duration of response 4–6 hours postdoseZenzedi®2.5, 5.7.5, 10, 15, 20, and 30 mg tablets• Starting dose:4–5-year old: 2.5 mg6 years and older: 5 mg• Dosage range:4–5-year old: 2.5–30 mg/day6 years and older: 5–60 mg/day. Given in divided dose qd-tid• Dose can be increased by 5 mg/day weekly• Max dose 60 mg/day• Branded formulation of dexedrine sulfate• Dose the same as other d-amphetamine formulations• Onset of response 30–45 minutes• Duration of response 4–6 hours postdoseProcentra®5 mg/5 mL solution• Starting dose:4–5-year old: 2.5 mg6 years and older: 5 mg• Dosage range:4–5-year old: 2.5–30 mg/day6 years and older: 5–60 mg/day. Given in divided dose qd-tid• Dose can be increased by 5 mg/day weekly• Max dose 60 mg/day• Dose the same as other d-amphetamine formulations• Onset of response 30–45 minutes• Duration of response 4–6 hours postdoseExtended-Release Formulations: MethylphenidateDrugFormulation(s)Dose rangeClinical tipsCotempla XR ODT®8.6, 17.3, and 25.9 mg tablets• Starting dose: 6–17 years old: 17.3 mg• Given QD in am• Dose can be increased by 8.6 to 17.3 mg/day weekly• Dose above 51.8 have not been studied• Onset of response within 1 hour• Duration of response 8–12 hours postdose• Can be swallowed without waterQuillivant XR®25 mg/5 mL suspension• Starting dose: 6 years and older: 10–20 mg (2–4 mL)• Given QD in am• Concentration = 25 mg/5 mL• Dose can be increased by 10–20 mg/day weekly• Max dose 60 mg/day• Onset of response 45 minutes• Duration of response 10–12 hours postdoseQuillichew ER®20 and 30 mg scored tablets40 mg tablets• Starting dose: 6 years and older: 10–20 mg• Given QD in am• Dose can be increased by 10–20 mg/day weekly• Doses above 60 mg/day have not been studied• Onset of response within 1 hour• Duration of response 8–10 hours postdose• Can be chewed or swallowed wholeDaytrana®10, 15, 20, and 30 mg patch• Starting dose: 6 years and older: 10 mg patch• Given QD in am• Dose can be increased to next patch size weekly• Max dose 30 mg patch/day• Onset of response within 2 hours• Duration of response depends on wear time• Maximum wear time 9 hours• Response may persist for 2–3 hours after patch removal• Lag time to response in the morning may necessitate the use of a morning dose of immediate-release methylphenidateAptensio XR®10, 15, 20, 30, 40, 50, and 60 mg capsules• Starting dose 10 mg• Given QD in the am• Increase by 10 mg/day weekly• Max dose: 60 mg/day• Onset of response within 1 hour• Duration of response 12 hours postdose• Capsule can be opened, and contents can be mixed with a small amount of food (applesauce, yogurt, etc.)Adhansia XR®25, 35, 45, 55, 70, and 85 mg capsules• Starting dose: 6 years and older: 25 mg• Given QD in am• Dose can be increased by 10 to 15 mg/day weekly• Dose above 70 mg in pediatric patients and above 85 mg in adults result in greater incidence of adverse events• Onset of response within 1 hour• Duration of response 16 hours postdose• Achieves steady state plasma level in 3 days• Capsule can be opened, and contents can be mixed with a small amount of food (applesauce, yogurt, etc.)Jornay PM®20, 40, 60, and 80 mg capsules• Starting dose: 6 years and older: 20 mg• Given QD in the evening between 6:30 and 9:30 pm• Dose can be increased by 20 mg/day weekly• Doses between 20 and 80 mg well tolerated• Dose above 100 mg has not been studied• Onset of response within 8–10 hours after administration• Duration of response 22–24 hours postdose (10–12 hours after delayed onset)• Capsule can be opened, and contents can be mixed with a small amount of food (applesauce, yogurt, etc.)Extended-Release Formulations: AmphetamineDrugFormulation(s)Dose rangeClinical tipsAdzenys XR-ODT®3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg tablets• Starting dose: 6 years and older: 6.3 mg• Given QD in the am• Increase by 3.1–6.3 mg/day weekly• Max dose:6–12 years old: 18.8 mg13 years and older: 12.5 mg• Bioequivalent to other 3:1 MAS formulations• Onset of response 45–60 minutes• Duration of response up to 12 hours• Can be swallowed without waterAdzenys ER®1.25 mg/mL suspension• Starting dose: 6 years and older: 6.3 mg (5 mL)• Given QD in the am• Increase by 3.1–6.3 mg/day weekly• Max dose:6–12 years old: 18.8 mg13 years and older: 12.5 mg• Bioequivalent to other 3:1 MAS formulations• Onset of response 45–60 minutes• Duration of response up to 12 hoursDynavel XR®2.5 mg/mL suspension• Starting dose: 6 years and older: 2.5–5 mg (1–2 mL)• Given QD in the am• Increase by 2.5–10 mg/day weekly• Max dose: 20 mg/day• Bioequivalent to other 3:1 MAS formulations• Onset of response by 60 minutes• Duration of response up to 13 hoursVyvanse® Capsule10, 20, 30, 40, 50, 60, and 70 mg capsule• Starting dose 30 mg• Given QD in the am• Increase by 10–20 mg/day weekly• Max dose: 70 mg/day• Bioequivalent to other d-amphetamine• Onset of response by 60–90 minutes• Duration of response up to 13 hours• Capsule can be opened, and contents can be mixed with a small amount of food (applesauce, yogurt, etc.) or liquidVyvanse Chewable Tablet10, 20, 30, 40, 50, 60 mg tablet• Starting dose 30 mg• Given QD in the am• Increase by 10–20 mg/day weekly• Max dose: 70 mg/day• Bioequivalent to other d-amphetamine• Onset of response by 60–90 minutes• Duration of response up to 13 hoursMydayis®12.5, 25, 37.5, 50 mg capsules• Starting dose 30 mg• Given QD in the am• Increase by 10–20 mg/day weekly• Max dose: 70 mg/day• Bioequivalent to other 3:1 MASa formulations• Onset of response by 45–60 minutes• Duration of response up to 16 hours• Capsule can be opened and contents can be mixed with a small amount of food (applesauce, yogurt, etc.)• Not approved for use in children younger than 13 yearsFurthermore, given the shifting nature of costs for various stimulant formulations as determined by the insurer, pharmacy benefits manager, and/or pharmacy, it remains difficult for the patient and clinician to make treatment decisions solely on the basis of formulation alone. This argues for the importance of clinician flexibility based on an understanding of the available agents, so if the patient's formulary changes, the clinician can make an informed decision about alternative options.There are occasions when a patient cannot access the formulation that they have been taking and the clinician needs to consider a formulation substitution to provide interim coverage. While the preferred methodology for switching formulations is to discontinue the current formulation and optimize the dose of the new formulation according to the guideline we provided, however, in some instances, the clinician is faced with the need to provide comparable coverage quickly without a lapse in response. We have provided 2 tables (Tables 5 and 6) that are meant to provide a reference point in these instances, based on data available in the references that we have cited. We strongly recommend erring on the side of using lower estimated doses and retitrating the dose based on response and tolerability.Substitution Tables Methylphenidate Extended-Release FormulationsDrugConversionaCommentsCotempla XR ODT8.6 mg -> 10 MPH ER or 5 mg MPH IR BID17.3 mg -> 20 MPH ER or 10 mg MPH IR BID25.9 -> 30 MPH ER or 15 mg MPH IR BID8.6, 17.3, and 25.9 mg tablets contain the same amount of MPH (base equivalent) found in other 10, 20, and 30 mg ER MPH formulationsQuillivant XR2 mL -> 10 mg MPH ER or 5 mg MPH IR BID4 mL -> 20 mg MPH ER or 10 mg MPH IR BID6 mL -> 30 mg MPH ER or 15 mg MPH IR BID8 mL -> 40 MPH ER or 20 mg MPH IR BIDStudies in adults suggest that Quillivant XR® 60 is bioequivalent to two 30 mg doses of dl-MPH IR oral solution. (Concentration = 25 mg/5 mL)Quillichew ER20 mg -> 20 mg MPH ER or 10 mg MPH IR BID30 mg -> 20 mg MPH ER or 15 MPH IR BID40 mg -> 40 mg MPH ER or 20 mg MPH IR BIDA 40 mg dose of QuilliChew ER is comparable to two 20 mg doses of IR MPH given 6 hours apart; however, the peak concentration (−20%) and the overall bioavailability (−11%) are slightly lower when QuilliChew ER is administeredDaytrana10 mg patch -> 10 mg MPH ER or 5 mg MPH IR BID10 mg patch delivers 1.1 mg/h with a delayed onsetAptensio XR10 mg -> 10 mg of MPH ER or 5 mg MPH IR BIDAptensio® XR® appears comparable to other MPH oral dosage formulations with an onset of action of 1 hour following administration and duration of up to 12 hoursAdhansia XR25 mg -> 5 mg MPH IR TID100 mg -> 20 mg MPH IR TIDWhen Adhansia 100 mg qam is compared to MPH IR 20 mg TID, Adhansia XR exhibits a significantly higher initial peak (Cmax 22% higher)Jornay PM20 mg -> 4 mg MPH IR TID given in the am40 mg -> 8 mg MPH IR TID given in the am60 mg -> 12 mg MPH IR PO TID given in the am80 mg -> 16 mg MPH IR PO TID given in the am100 mg -> 20 mg MPH IR PO TID given in the amAfter a delayed onset of action, 100 mg comparable to 20 mg TIDSubstitution Tables Amphetamine Extended-Release FormulationsDrugConversionaCommentsAdzenys XR-ODT3.1 mg -> 5 mg MAS XR or 2.5 mg MAS IR BID6.3 mg -> 10 mg MAS XR or 5 mg MAS IR BID9.4 mg -> 15 mg MAS XR or 7.5 mg MAS IR BID12.5 mg -> 20 mg MAS XR or 10 mg MAS IR BID15.7 mg -> 25 mg MAS XR or 12.5 mg MAS IR BID18.8 mg -> 30 mg MAS XR or 15 mg MAS IR BIDAdzenys XR-ODT 18.8 mg tablet is equivalent to 30 mg of Adderall XR® (MAS ER) or 15 mg MAS IR BIDAdzenys ER2.5 mL -> 5 mg MAS XR or 2.5 mg MAS IR BID5 mL -> 10 mg MAS XR or 5 mg MAS IR BID7.5 mL -> 15 mg MAS XR or 7.5 mg MAS IR BID10 mL -> 20 mg MAS XR or 10 mg MAS IR BID12.5 mL -> 25 mg MAS XR or 12.5 mg MAS IR BID15 mL -> 30 mg MAS XR or 15 mg MAS IR BID18.8 mg (15 mL) is equivalent to 30 mg Adderall XR (MAS ER) or 15 mg MAS IR BIDDynavel XR2.5 mL -> 10 mg MAS XR or 5 mg MAS IR BID5 mL -> 20 mg MAS XR or 10 mg MAS IR BID7.5 mL -> 30 mg MAS XR or 15 mg MAS IR BID1 mL of Dynavel XR suspension contains 2.5 mg of MAS base10 mg of Adderall XR contains 6.3 mg MAS baseVyvanse Capsule30 mg -> 10 mg MAS XR or 5 mg MAS IR BID50 mg -> 20 mg MAS XR or 10 mg MAS IR BID70 mg -> 30 mg MAS XR or 15 mg MAS IR BIDStudies indicate that AUC and Cmax for d-amphetamine from 75 mg NRP 104 (LDX) were comparable to (d-l-amphetamine) from 35 mg Adderall XR. The data also show d-amphetamine equivalence for AUC for 75 mg NRP 104 (LDX) and 30 mg Dexedrine, while peak exposure was 48% higher from NRP 104 than from Dexedrine.Vyvanse Chewable Tablet30 mg -> 10 mg MAS XR or 5 mg MAS IR BID50 mg -> 20 mg MAS XR or 10 mg MAS IR BID70 mg -> 30 mg MAS XR or 15 mg MAS IR BIDStudies indicate that AUC and Cmax for d-amphetamine from 75 mg NRP 104 (LDX) were comparable to (d-l-amphetamine) from 35 mg Adderall XR.

The data also show d-amphetamine equivalence for AUC for 75 mg NRP 104 (LDX) and 30 mg Dexedrine, while peak exposure was 48% higher from NRP 104 (LDX) than from Dexedrine.Mydayis37.5 mg -> 25 MAS XR +12.5 MAS IR 8 hours laterBecause of long duration of action, substitution requires two doses as notedEarly ADHD treatment with stimulants was greatly limited by the available formulations. IR formulations required the use of multiple doses throughout the day. Not only did this contribute to issues with general compliance in school dosing and associated stigma, as well as security concerns, IR formulations did not permit a more individualized drug regimen that took into account individual metabolic variation and response. This often created significant logistical complications. Over the past 15 years there has been a significant expansion in the number of available medications available to ADHD patients and clinicians. This widened armamentarium hopefully will lead to greater personalizing of ADHD treatment in hopes of improving adherence and long-term outcomes.Over the last 15 years, there has been a marked increase in the number of available stimulant formulations with the emphasis on long-acting formulations and the introduction of several novel delivery systems such as ODT, chewable tablets, ER liquid formulations, transdermal patches, and novel "beaded" technology. This review is meant to serve as a guide to newer stimulant formulations and includes a brief review of ADHD and stimulant properties.Adler LA, Frick G, Yan B.

A long-term, open-label, safety study of triple-bead mixed amphetamine salts (SHP465) in adults with ADHD. J Atten Disord 2017:1087054717696770 [PubMed] [Google Scholar]Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. Postgrad Med 122:184–191, 2010 [PubMed] [Google Scholar]Arnold L, Bozzolo D, Hodgkins P, McKay M, Beckett-Thurman L, Greenbaum M, Bukstein O, Patel A. Switching from oral extended-release methylphenidate to the methylphenidate transdermal system: Continued attention-deficit/hyperactivity disorder symptom control and tolerability after abrupt conversion. Curr Med Res Opin 26:129–137, 2010 [PMC free article] [PubMed] [Google Scholar]Bélanger S, Warren A, Hamilton R, Gray C, Sanatani S, Côté J, Lougheed J, LeBlanc J, Martin S, Miles B. Cardiac risk assessment before the use of stimulant medications in children and youth. Paediatr Child Health 14:579–585, 2009 [PMC free article] [PubMed] [Google Scholar]Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: A double-blind, placebo-controlled, crossover analog classroom study. J Biol Psychiatry 62:970–976, 2007a [PubMed] [Google Scholar]Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: A phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther 29:450–463, 2007b [PubMed] [Google Scholar]Boellner SW, Stark JG, Krishnan S, Zhang Y. Pharmacokinetics of lisdexamfetamine dimesylate and its active metabolite, d-amphetamine, with increasing oral doses of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder: A single-dose, randomized, open-label, crossover study. Clin Ther 32:252–264, 2010 [PubMed] [Google Scholar]Brams M, Childress AC, Greenbaum M, Yu M, Yan B, Jaffee M, Robertson B.

SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in children and adolescents: Results of a randomized, double-blind placebo-controlled study. J Child adolesc Psychopharmacol 28:19–28, 2018 [PMC free article] [PubMed] [Google Scholar]Childress A, Mehrotra S, Gobburu J, McLean A, DeSousa NJ, Incledon B. Single-dose pharmacokinetics of HLD200, a delayed-release and extended-release methylphenidate formulation, in healthy adults and in adolescents and children with attention-deficit/hyperactivity disorder. J Child adolesc Psychopharmacol 28:10–18, 2018a [PMC free article] [PubMed] [Google Scholar]Childress A, Newcorn J, Stark JG, McMahen R, Tengler M, Sikes C.

A single-dose, single-period pharmacokinetic assessment of an extended-release orally disintegrating tablet of methylphenidate in children and adolescents with attention-deficit/hyperactivity disorder.

J Child Adolesc Psychopharmacol 26:505–512, 2016 [PMC free article] [PubMed] [Google Scholar]Childress A, Sallee FR. The use of methylphenidate hydrochloride extended-release oral suspension for the treatment of ADHD. Expert Rev Neurother 13:979–988, 2013 [PubMed] [Google Scholar]Childress AC, Berry SA. The single-dose pharmacokinetics of NWP06, a novel extended-release methylphenidate oral suspension. Postgrad Med 122:35–41, 2010 [PubMed] [Google Scholar]Childress AC, Brams M, Cutler AJ, Kollins SH, Northcutt J, Padilla A, Turnbow JM. The efficacy and safety of evekeo, racemic amphetamine sulfate, for treatment of attention-deficit/hyperactivity disorder symptoms: A multicenter, dose-optimized, double-blind, randomized, placebo-controlled crossover laboratory classroom study. J Child Adolesc Psychopharmacol 25:402–414, 2015 [PMC free article] [PubMed] [Google Scholar]Childress AC, Cutler AJ, Saylor K, Gasior M, Hamdani M, Ferreira-Cornwell MC, Findling RL. Participant-perceived quality of life in a long-term, open-label trial of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 24:210–217, 2014 [PMC free article] [PubMed] [Google Scholar]Childress AC, Kollins SH, Cutler AJ, Marraffino A, Sikes CR. Efficacy, safety, and tolerability of an extended-release orally disintegrating methylphenidate tablet in children 6–12 years of age with attention-deficit/hyperactivity disorder in the laboratory classroom setting. J Child Adolesc Psychopharmacol 27:66–74, 2017 [PMC free article] [PubMed] [Google Scholar]Childress AC, Wigal SB, Brams MN, Turnbow JM, Pincus Y, Belden HW, Berry SA. Efficacy and safety of amphetamine extended-release oral suspension in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 28:306–313, 2018b [PMC free article] [PubMed] [Google Scholar]Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, Anderson C, Civil R, Higgins N, Lyne A. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol 23:1208–1218, 2013 [PubMed] [Google Scholar]Coghill DR, Banaschewski T, Nagy P, Otero IH, Soutullo C, Yan B, Caballero B, Zuddas AJCD. Long-term safety and efficacy of lisdexamfetamine dimesylate in children and adolescents with ADHD: A phase IV, 2-year, open-label study in Europe.

CNS Drugs 31:625–638, 2017 [PMC free article] [PubMed] [Google Scholar]Coghill DR, Caballero B, Sorooshian S, Civil R. A systematic review of the safety of lisdexamfetamine dimesylate.

CNS Drugs 28:497–511, 2014 [PMC free article] [PubMed] [Google Scholar]Cohen SC, Mulqueen JM, Ferracioli-Oda E, Stuckelman ZD, Coughlin CG, Leckman JF, Bloch MH. Meta-analysis: Risk of tics associated with psychostimulant use in randomized, placebo-controlled trials. J Am Acad Child Adolesc Psychiatry 54:728–736, 2015 [PubMed] [Google Scholar]Connor DF, Steingard RJ. New formulations of stimulants for attention-deficit hyperactivity disorder. CNS Drugs 18:1011–1030, 2004 [PubMed] [Google Scholar]Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 365:1896–1904, 2011 [PMC free article] [PubMed] [Google Scholar]Coulombe J, Powell J, Hatami A, McCuaig C, Renet S, Marcoux D. Diseases of abnormal sensitivity to cold in children on psychostimulant drugs. J Cutan Med Surg 19:121–124, 2015 [PubMed] [Google Scholar]Dolder PC, Strajhar P, Vizeli P, Hammann F, Odermatt A, Liechti ME. Pharmacokinetics and pharmacodynamics of lisdexamfetamine compared with D-amphetamine in healthy subjects. Front Pharmacol 8:617, 2017 [PMC free article] [PubMed] [Google Scholar]Faraone SV. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehav Rev 87:255–270, 2018 [PMC free article] [PubMed] [Google Scholar]Faraone SV, Giefer EE.

Long-term effects of methylphenidate transdermal delivery system treatment of ADHD on growth. J Am Acad Child Adolesc Psychiatry 46:1138–1147, 2007 [PubMed] [Google Scholar]Faraone SV, Glatt SJ, Bukstein OG, Lopez FA, Arnold LE, Findling RL. Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. J Atten Disord 12:308–315, 2009 [PubMed] [Google Scholar]FDA. Center for Drug Evaluation and Research, Benzedrine® medical review: Application Number: 83900. 1976a. 20Sulfate_Medrpdf Accessed March13, 2019FDA. Dexedrine®, Product Monograph, Application Number:ANDA084935. 1976b. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Methylin Oral Solution® medical review: Application Number: 21–419. 2002a. ��419_Methylin_Medrpdf Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Methylin® Oral Solution clinical pharmaceuticals and biopharmaceuticals review: Application Number: 021419.

2002b. ��419_Methylin_BioPharmrpdf Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Methylin® Chewable Tablet clinical pharmaceuticals and biopharmaceuticals review: Application Number: 021475, 2003. 2003a. Accessed March13, 2019FDA.

Center for Drug Evaluation and Research; Methylin® Chewable Tablet medical review: Application Number: 021475. 2003b.

Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Daytrana® clinical pharmaceuticals and biopharmaceuticals review (Part 1): Application Number: 021514s000. 2006a. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Daytrana® clinical pharmaceuticals and biopharmaceuticals review (Part 2): Application Number: 021514s000. 2006b. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Daytrana® medical review (Part 1): Application Number: 021514s000. 2006c. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Daytrana® medical review (Part 2): Application Number: 021514s000. 2006d. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Lisdexamfetamine clinical pharmacology and bio[harmaceutics review: Application Number:21–977, 2006. 2006e. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Lisdexamfetamine medical review: Application Number:21–977, 2007. 2007. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; ProCentra® Product Label, Application Number: ANDA040776. 2010. Accessed March13, 2019FDA. Zenzedi® Product Monograph, Application Number: ANDA090533. 2011.

Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Quillivant XR® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 202100Orig1s000. 2012a. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Quillivant XR® medical review: Application Number: 202100Orig1s000. 2012b.

Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Aptensio XR® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 205831Orig1s000. 2015a. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Aptensio XR® medical review: Application Number: 205831Orig1s000. 2015b.

Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Dynavel XR® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 208147Orig1s000. 2015c. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; QuilliChew ER® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 207960Orig1s000.

2015d. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; QuilliChew ER® medical review: Application Number: 207960Orig1s000, 2015. 2015e. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Adzenys XR-ODT® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 204326Orig1s000. 2016a. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Adzenys XR-ODT® medical review: Application Number: 204326Orig1s000. 2016b. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Adzenys ER® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 204325Orig1s000, 2017. 2017a. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Cotempla XR ODT® clinical pharmacology and biopharmaceutics review: Application Number: 205489Orig1s000. 2017b. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Cotempla XR ODT® medical review: Application Number: 205489Orig1s000, 2017. 2017c. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Mydayis® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 022063Orig1s000, 2017. 2017d. Accessed March13, 2019FDA.

Center for Drug Evaluation and Research; Mydayis® medical review: Application Number: 022063Orig1s000. 2017e. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Jornay PM® clinical pharmaceuticals and biopharmaceuticals review: Application Number: 209311Orig1s000. 2018a.

Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Jornay PM® medical review: Application Number: 209311Orig1s000. 2018b. Accessed March13, 2019FDA. Center for Drug Evaluation and Research (CDER);Evekeo ODT® Label, Application Number 209905. 2019a. Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Adhansia XR® Product Label, Application Number: 212038. 2019b. Accessed March13, 2019FDA. Evekeo® Label, Application Number 200166. 2019c. Accessed March13, 2019FDA.

Center for Drug Evaluation and Research; Dynavel XR® medical review: Application Number: 2208147Orig1s000.

2015.

Accessed March13, 2019FDA. Center for Drug Evaluation and Research; Adzenys ER® medical review: Application Number: 204325Orig1s000, 2017.

Accessed March13, 2019Feldman ME, Charach A, Bélanger SA. ADHD in children and youth: Part 2—Treatment. Paediatr Child Health 23:462–472, 2018 [PMC free article] [PubMed] [Google Scholar]Findling RL, Bukstein OG, Melmed RD, López FA, Sallee FR, Arnold LE, Pratt RD. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry 69:149–159, 2008 [PubMed] [Google Scholar]Findling RL, Cutler AJ, Saylor K, Gasior M, Hamdani M, Ferreira-Cornwell MC, Childress AC. A long-term open-label safety and effectiveness trial of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 23:11–21, 2013 [PubMed] [Google Scholar]Findling RL, Dinh S. Transdermal therapy for attention-deficit hyperactivity disorder with the methylphenidate patch (MTS). CNS Drugs 28:217–228, 2014 [PMC free article] [PubMed] [Google Scholar]Gonzalez MA, Campbell D, Rubin J. Effects of application to two different skin sites on the pharmacokinetics of transdermal methylphenidate in pediatric patients with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 19:227–232, 2009 [PubMed] [Google Scholar]Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann R, Döpfner M, Hamilton R, Hollis C, Holtmann M. European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 20:17–37, 2011 [PMC free article] [PubMed] [Google Scholar]Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, McGough J, Wigal S, Wigal T, Vitiello B. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 45:1284–1293, 2006 [PubMed] [Google Scholar]Hailpern SM, Egan BM, Lewis KD, Wagner C, Shattat GF, Al Qaoud DI, Shatat IF. Blood pressure, heart rate, and CNS stimulant medication use in children with and without ADHD: Analysis of NHANES data. Front Pediatr 2:100, 2014 [PMC free article] [PubMed] [Google Scholar]Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present—A pharmacological and clinical perspective. J Psychopharmacol 27:479–496, 2013 [PMC free article] [PubMed] [Google Scholar]Jain R, Babcock T, Burtea T, Dirks B, Adeyi B, Scheckner B, Lasser R. Efficacy of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder previously treated with methylphenidate: A post hoc analysis. Child Adolesc Psychiatry Mental Health 5:35, 2011 [PMC free article] [PubMed] [Google Scholar]Jain R, Babcock T, Burtea T, Dirks B, Adeyi B, Scheckner B, Lasser R, Renna J, Duncan D. Efficacy and safety of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder and recent methylphenidate use. Adv Ther 30:472–486, 2013 [PMC free article] [PubMed] [Google Scholar]Katic A, Ginsberg L, Jain R, Adeyi B, Dirks B, Babcock T, Scheckner B, Richards C, Lasser R, Turgay A. Clinically relevant changes in emotional expression in children with ADHD treated with lisdexamfetamine dimesylate. J Atten Disord 16:384–397, 2012 [PubMed] [Google Scholar]Markowitz J, DeVane C, Ramamoorthy S, Zhu H.-J. The psychostimulant d-threo-(R, R)-methylphenidate binds as an agonist to the 5HT1A receptor. Die Pharmazie 64:123–125, 2009 [PubMed] [Google Scholar]Markowitz JS, DeVane CL, Pestreich LK, Patrick KS, Muniz R. A comprehensive in vitro screening of d-, l-, and dl-threo-methylphenidate: An exploratory study. J Child Adolesc Psychopharmacol 16:687–698, 2006 [PubMed] [Google Scholar]Markowitz JS, Patrick KS. Differential pharmacokinetics and pharmacodynamics of methylphenidate enantiomers: Does chirality matter? J Clin Psychopharmacol 28:S54–S61, 2008 [PubMed] [Google Scholar]Markowitz JS, Patrick KS. The clinical pharmacokinetics of amphetamines utilized in the treatment of attention-deficit/hyperactivity disorder.

J Child Adolesc Psychopharmacol 27:678–689, 2017 [PubMed] [Google Scholar]Markowitz JS, Straughn AB, Patrick KS. Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: Focus on methylphenidate formulations. Pharmacotherapy 23:1281–1299, 2003 [PubMed] [Google Scholar]Midha K, McKay G, Rawson M, Korchinski E, Hubbard J. Effects of food on the pharmacokinetics of methylphenidate. Pharm Res 18:1185–1189, 2001 [PubMed] [Google Scholar]MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56:1073–1086, 1999 [PubMed] [Google Scholar]Newcorn JH, Nagy P, Childress AC, Frick G, Yan B, Pliszka S. Randomized, double-blind, placebo-controlled acute comparator trials of Lisdexamfetamine and extended-release methylphenidate in adolescents with attention-deficit/hyperactivity disorder.

CNS Drugs 31:999–1014, 2017 [PMC free article] [PubMed] [Google Scholar]Owens J, Weiss M, Nordbrock E, Mattingly G, Wigal S, Greenhill LL, Chang W.-W, Childress A, Kupper RJ, Adjei A. Effect of aptensio XR (methylphenidate HCl extended-release) capsules on sleep in children with attention-deficit/hyperactivity disorder.

J Child Adolesc Psychopharmacol 26:873–881, 2016 [PMC free article] [PubMed] [Google Scholar]Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: History, development and pharmacology. Br J Pharmacol 172:2179–2209, 2015 [PMC free article] [PubMed] [Google Scholar]Patrick KS, González MA, Straughn AB, Markowitz JS. New methylphenidate formulations for the treatment of attention-deficit/hyperactivity disorder.

Expert Opin Drug Deliv 2:121–143, 2005 [PubMed] [Google Scholar]Patrick KS, Radke JL, Raymond JR, Koller L, Nguyen LV, Rodriguez W, Straughn AB. Drug regimen individualization for attention-deficit/hyperactivity disorder: Guidance for methylphenidate and dexmethylphenidate formulations.

Pharmacotherapy 2018. [Epub ahead of print]; DOI: 10.1002/phar.2190 [PubMed] [CrossRef] [Google Scholar]Patrick KS, Straughn AB, Perkins JS, González MA. Evolution of stimulants to treat ADHD: Transdermal methylphenidate.

Hum Psychopharmacol 24:1–17, 2009 [PMC free article] [PubMed] [Google Scholar]Pediatrics. Subcomittee on ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 128:1007–1022, 2011 [PMC free article] [PubMed] [Google Scholar]Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, Coles EK, Tresco KE, Chacko A, Wymbs BT, Wienke AL, Walker KS. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD.

Exp Clin Psychopharmacol 13:111, 2005 [PubMed] [Google Scholar]Pelham WE, Jr, Manos MJ, Ezzell CE, Tresco KE, Gnagy EM, Hoffman MT, Onyango AN, Fabiano GA, Lopez-Williams A, Wymbs BT. A dose-ranging study of a methylphenidate transdermal system in children with ADHD. J Am Acad Child Adolesc Psychiatry 44:522–529, 2005 [PubMed] [Google Scholar]Pelham WE, Waxmonsky JG, Schentag J, Ballow CH, Panahon CJ, Gnagy EM, Hoffman MT, Burrows-MacLean L, Meichenbaum DL, Forehand GL. Efficacy of a methylphenidate transdermal system versus tid methylphenidate in a laboratory setting. J Atten Disord 15:28–35, 2011 [PubMed] [Google Scholar]Pliszka SR, Wilens TE, Bostrom S, Arnold VK, Marraffino A, Cutler AJ, López FA, DeSousa NJ, Sallee FR, Incledon B.

Efficacy and safety of HLD200, delayed-release and extended-release methylphenidate, in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 27:474–482, 2017 [PMC free article] [PubMed] [Google Scholar]Quinn D. Does chirality matter?: Pharmacodynamics of enantiomers of methylphenidate in patients with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 28:S62–S66, 2008 [PubMed] [Google Scholar]Robb AS, Findling RL, Childress AC, Berry SA, Belden HW, Wigal SB. Efficacy, safety, and tolerability of a novel methylphenidate extended-release oral suspension (MEROS) in ADHD. J Atten Disord 21:1180–1191, 2017 [PubMed] [Google Scholar]Sallee FR, Palumbo DR, Abbas R, Berry SA, Puthli SP, Kathala KK. Effect of food intake on the pharmacokinetics of a novel methylphenidate extended-release oral suspension for attention deficit hyperactivity disorder. Clin Pharmacol Drug Dev 6:476–483, 2017 [PubMed] [Google Scholar]Sikes C, Stark JG, McMahen R, Engelking D. Pharmacokinetics of a new amphetamine extended-release oral liquid suspension under fasted and fed conditions in healthy adults: A randomized, open-label, single-dose, 3-treatment study. Clin Ther 39:2389–2398, 2017 [PubMed] [Google Scholar]Sikes CR, McMahen RL, Stark JG, Engelking D. Pharmacokinetics of a new amphetamine extended-release oral suspension in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 28:29–35, 2018 [PubMed] [Google Scholar]Stark JG, Engelking D, McMahen R, Sikes C. A randomized crossover study to assess the pharmacokinetics of a novel amphetamine extended-release orally disintegrating tablet in healthy adults. Postgrad Med 128:648–655, 2016 [PubMed] [Google Scholar]Stark JG, Engelking D, McMahen R, Sikes C. Pharmacokinetics of a novel amphetamine extended-release orally disintegrating tablet in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 27:216–222, 2017 [PubMed] [Google Scholar]Stein MA, Waldman ID, Charney EAryal S, Sable C, Gruber R, Newcorn JH. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts.

J Child Adolesc Psychopharmacol 21:581–588, 2011 [PMC free article] [PubMed] [Google Scholar]Teuscher NS, Adjei A, Findling RL, Greenhill LL, Kupper RJ, Wigal S. Population pharmacokinetics of methylphenidate hydrochloride extended-release multiple-layer beads in pediatric subjects with attention deficit hyperactivity disorder. Drug Des Devel Ther 9:2767, 2015 [PMC free article] [PubMed] [Google Scholar]Weisler RH, Greenbaum M, Arnold V, Yu M, Yan B, Jaffee M, Robertson B. Efficacy and safety of SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in adults: Results of a randomized, double-blind, placebo-controlled, forced-dose clinical study. CNS Drugs 31:685–697, 2017 [PMC free article] [PubMed] [Google Scholar]Wigal S, Lopez F, Frick G, Yan B, Robertson B, Madhoo M. A randomized, double-blind, 3-way crossover, analog classroom study of SHP465 mixed amphetamine salts extended-release in adolescents with ADHD. Postgrad Med 131:212–224, 2019 [PubMed] [Google Scholar]Wigal SB, Childress A, Berry SA, Belden H, Walters F, Chappell P, Sherman N, Orazem J, Palumbo D. Efficacy and safety of a chewable methylphenidate extended-release tablet in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 27:690–699, 2017 [PMC free article] [PubMed] [Google Scholar]Wigal SB, Childress A, Berry SA, Belden HW, Chappell P, Wajsbrot DB, Nagraj P, Abbas R, Palumbo D. Optimization of methylphenidate extended-release chewable tablet dose in children with ADHD: Open-label dose optimization in a laboratory classroom study. J Child Adolesc Psychopharmacol 28:314–321, 2018 [PMC free article] [PubMed] [Google Scholar]Wigal SB, Nordbrock E, Adjei AL, Childress A, Kupper RJ, Greenhill L. Efficacy of methylphenidate hydrochloride extended-release capsules (Aptensio XR™) in children and adolescents with attention-deficit/hyperactivity disorder: A phase III, randomized, double-blind study. CNS Drugs 29:331–340, 2015 [PMC free article] [PubMed] [Google Scholar]Zhu H-J, Patrick KS, Yuan H.-J, Wang J.-S, Donovan JL, DeVane CL, Malcolm R, Johnson JA, Youngblood GL, Sweet DH. Two CES1 gene mutations lead to dysfunctional carboxylesterase 1 activity in man: Clinical significance and molecular basis. Am J Hum Genet 82:1241–1248, 2008 [PMC free article] [PubMed] [Google Scholar]