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REVIEW



An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations

Ann C. Childress^a, Marina Komolova^b and F. Randy Sallee^c

^aCenter for Psychiatry and Behavioral Medicine, Inc., Las Vegas, NV, USA; ^bHighland Therapeutics Inc., Toronto, ON, Canada; ^cIronshore Pharmaceuticals Inc., Durham, NC, USA

ABSTRACT

Introduction: Long-acting stimulant formulations are recommended as first-line pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD). Over the past 20 years, extended-release (ER) methylphenidate (MPH) and amphetamine (AMP) formulations have evolved to include varying drug delivery technologies, enantiomers/salts, and dosage forms. All formulations are characterized by a unique pharmacokinetic profile that is closely mirrored by pharmacodynamic response allowing clinicians to individualize therapy based on their patient's clinical needs and dosing preferences.

Areas covered: This review provides an update on the pharmacokinetic properties of approved and investigational ER MPH and AMP formulations and highlights pharmacokinetic features that clinicians should consider when selecting a long-acting stimulant.

Expert opinion: Since there are no reliable biomarkers that can predict individualized response to long-acting stimulants, clinicians need to consider their distinctive pharmacokinetic properties, including the pharmacokinetic profile, rate and extent of absorption, variability, dose proportionality, bioequivalence, and potential for accumulation. Clinicians also need to understand that certain factors can contribute to increased variability in pharmacokinetics and potentially affect outcomes. Less invasive, high-throughput techniques and novel time-based scales are being developed to advance research on the pharmacokinetic-pharmacodynamic relationships of stimulants. Model-based pharmacokinetic-pharmacodynamic approaches can be applied to aid the development of novel formulations and individualize therapy with existing drugs.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by persistent and developmentally inappropriate levels of inattention, impulsivity, and hyperactivity that interfere with functioning from the time of awakening until bedtime [1–4]. The estimated prevalence of ADHD in U.S. is approximately 10.2% in children and adolescents, and 4.4% in adults [5,6]. Children with ADHD may have the disorder persist into adulthood in approximately 50%–70% of cases [7–9].

Stimulants, methylphenidate (MPH) and amphetamine (AMP), have been used to treat ADHD for more than 60 years, with long-acting stimulant formulations currently recommended as first-line pharmacotherapy in children, adolescents, and adults with ADHD because of their greater efficacy compared to non-stimulant medications [2,9–15]. Both MPH and AMP have been shown to have very high effect sizes (>0.8) relative to non-stimulant medications (~0.6), with AMP having moderately greater effects than MPH [16–18]. While the majority of patients with ADHD respond to either MPH or AMP, with response rates of approximately 71% and 68%, respectively, the proportion of patients responding to either class of stimulant is even higher (91%) [17].

Immediate-release (IR) formulations of stimulants were first approved by the Food and Drug Administration (FDA)

for the treatment of ADHD. However, given their rapid absorption and metabolism, the therapeutic effects of IR stimulants typically wear off within a few hours, requiring twice- or thrice-daily dosing to achieve symptom control [19,20]. This presents a number of significant challenges for patients, including fluctuating peak and trough plasma concentrations that may increase the risk of adverse events or reduce efficacy; the inconvenience of multiple daily dosing, which may result in embarrassment, stigma, and lack of privacy, especially when administering therapy during a school or work day; reduced treatment compliance; and the potential for diversion of these Schedule II drugs [17,19–24]. Sustained-release (SR) formulations of MPH were initially developed to address these challenges. Unfortunately, they were not as effective as IR formulations and the reduced efficacy was attributed to acute tolerance due to a lack of a steep absorption phase and a flat (i.e. zero-order) drug delivery profile following peak levels [19,21,22]. Subsequently, an ascending (e.g. first-order) drug delivery profile was proposed to overcome or minimize this tachyphylaxis [21,22]. Based on this observation, several extended-release (ER) formulations of both MPH and AMP have since been developed with ascending plasma concentrations that mimic twice- or thrice-daily administration of IR stimulants.

Article highlights

- Stimulants, methylphenidate (MPH) and amphetamine (AMP), have been used to treat attention-deficit/hyperactivity disorder (ADHD) for more than 60 years, with long-acting stimulants currently recommended as first-line pharmacotherapy.
- Over the past 20 years, the ever-expanding armamentarium of long-acting stimulant formulations has evolved to include various drug delivery technologies, enantiomers and/or salts, and dosage forms.
- Despite having unique pharmacokinetic profiles and not being bioequivalent, all long-acting stimulant formulations are designed with the aim of producing an ascending (e.g. first-order) plasma concentration profile believed to be necessary for preventing acute tolerance and associated with the greatest therapeutic benefit.
- Several factors, including drug-specific factors, patient characteristics, lifestyle, environment, or genetics, may affect the pharmacokinetics of long-acting stimulant formulations, which may lead to increased variability, and thereby affect their resulting efficacy and safety.
- Since there are currently no reliable biomarkers that can predict individualized response to long-acting stimulants, a better understanding of the unique patterns of drug release produced by various formulations, their resulting pharmacokinetic profiles and pharmacokinetic-pharmacodynamic relationships, and how certain factors can affect their pharmacokinetics affords clinicians further prescribing flexibility to individualize and optimize ADHD therapy specifically based on their patient's clinical needs, characteristics, and dosing preferences.
- While there is an increasing awareness of the distinct pharmacokinetic properties of the various long-acting stimulant formulations, there is a dearth of well-designed head-to-head clinical trials evaluating differences in pharmacokinetic-pharmacodynamic response, particularly between newer long-acting stimulants.
- Less invasive and high-throughput quantification techniques and novel time-based scales are being developed to further advance research on the pharmacokinetic-pharmacodynamic relationships of long-acting stimulants and facilitate comparisons between various formulations through head-to-head studies across different age groups, settings, and temporal periods.
- Until these advances in ADHD research are validated and optimized, model-based pharmacokinetic-pharmacodynamic approaches can be applied to ensure that the development of novel stimulant formulations specifically target treatment gaps in ADHD and that existing drugs are used appropriately to individualize therapy.

This box summarizes key points contained in the article.

Over the past 20 years, the ever-expanding armamentarium of long-acting stimulant formulations has evolved to include varying drug release profiles, enantiomers and/or salts, dosage forms (e.g. capsules containing composite or mixed beads, disintegrating tablets, chewable tablets, patches, liquid suspensions), and prodrugs (summarized in Table 1 and discussed in Section 4) [19,20,24–26]. While this tremendous diversity of available long-acting stimulant formulations may be overwhelming and increase the complexity of selecting the most appropriate therapy, it also affords clinicians the opportunity to individualize therapy specifically based on their patient's characteristics, clinical needs, and dosing preferences. To do this rationally, a clinician needs to understand and consider the distinctive pharmacokinetic properties of these varying stimulant formulations, including but not limited to the shape of the pharmacokinetic profile, differences in the rate and extent of absorption, variability, dose proportionality, comparative bioavailability, food or alcohol effect, age or gender effect, and potential for accumulation with multiple dosing. The present review focuses on the pharmacokinetic differences among available long-acting stimulant formulations, as well

as those currently in development, and highlights the pharmacokinetic features that a clinician should consider in their rational selection of a stimulant formulation for individualizing therapy for their patients with ADHD.

2. Aim and methods

The objective of this review was to discuss the pharmacokinetic properties of approved and investigational long-acting MPH and AMP formulations for the treatment of ADHD, and highlight specific pharmacokinetic features that clinicians should consider when selecting a long-acting stimulant for their patients with ADHD. A comprehensive literature search and review were conducted using the PubMed database up to March 2019 using the following keywords: '*methylphenidate OR amphetamine AND stimulants AND pharmacokinetics AND 'long-acting OR extended-release'*'. This search yielded 122 references. Using similar keywords in Google Scholar, additional relevant articles were identified. Titles and abstracts were manually reviewed to identify original articles and relevant reviews. Full versions of these articles were obtained and references in these articles, as well as important articles known to the authors, were hand searched to identify any additional relevant studies and major reviews not found in the original search. The search was limited to human data and *in vitro* data, and animal studies were generally excluded. ClinicalTrials.gov and Drugs@FDA were also searched for formulation-specific information. While it was our initial intention to only cite and include data published in peer-reviewed periodicals, to include a more comprehensive coverage of all stimulant formulations, it was necessary to include data from scientific meeting abstracts and posters, product labels (i.e. prescribing information), and online documents available through the U.S. FDA. The review and summary tables of the pharmacokinetic properties of commercially available long-acting stimulant formulations only included information from studies using FDA-approved doses published in original articles, product labels, FDA *Clinical Pharmacology and Biopharmaceutics Review* documents, and scientific meeting abstracts and/or posters.

3. Pharmacology of stimulants

3.1. Mechanism of action

The main pharmacologic effect of stimulants is to increase synaptic extracellular levels of dopamine (DA) and norepinephrine (NE), and the resulting increase in these neurotransmitters is postulated to be the basis for their therapeutic effect [9,17,28]. This effect is mediated by overlapping, but also distinct mechanisms of action of MPH and AMP. Both MPH and AMP inhibit the reuptake of DA and NE from the synapse into the presynaptic neuron by blocking their respective monoamine transporters (i.e. DA transporters [DAT] and NE transporters [NET]) [9,17]. In contrast to MPH, AMP is also thought to induce an increased release of these monoamines from presynaptic terminals by: 1) blocking vesicular monoamine transporter 2 (VMAT-2), which in turn increases cytosolic levels of monoamines; 2) reversing the transport of cytosolic monoamines into the synapse via DAT and NET; and 3) preventing the breakdown of cytosolic monoamines by inhibiting

**Table 1.** Summary of long-acting methylphenidate and amphetamine formulations approved in U.S. for the treatment of ADHD (past 20 years).

Brand Name (Manufacturer Name)	Manufacturer (as of March 2019)	Approval Date	FDA- approved Age	Available Dosing Strengths	Dosage Form	Administration	Formulation	Drug Delivery Platform	IR/ER (%)	Enantiomer/ Salt
Methylphenidate formulations										
ADHANSA XR (PRC-063) [78]	Adlon Therapeutics (Purdue Pharma)	February 2019	≥6 years	25, 35, 45, 55, 70, and 85 mg	Capsule (composite beads)	Oral (whole or sprinkled)	MPH-MLR	Multilayered beads	IR 20%; ER 80%	d-/MPH
APTENSIO XR (RP-BP) [66]	Rhodes Pharmaceuticals	April 2015	≥6 years	10, 15, 20, 30, 40, 50, and 60 mg	Capsule (composite beads)	Oral (whole or sprinkled)	MPH-MLR	Multilayered beads	IR 40%; ER 60%	d-/MPH
CONCERTA [40]	Janssen Pharmaceuticals	August 2000	≥6 years	18, 27, 36, and 54 mg	Tablet	Oral (whole)	OROS-MPH	OROS [®]	IR 22%; ER 78%	d-/MPH
COTEMPLA XR-ODT (NT-0102) [19,72]	Neos Therapeutics	June 2017	≤65 years 6–17 years	8.6, 17.3, and 25.9 mg	Orally disintegrating tablet	Oral (whole)	MPH XR-ODT	Ion-exchange resin microparticles	IR 25%; ER 75%	d-/MPH
DAYTRANA (SPD485) [27,61]	Noven Therapeutics	April 2006	≥6 years	10 mg/9 hours (1.1 mg/h), 15 mg/9 hours (1.6 mg/h), 20 mg/9 hours (2.2 mg/h), 30 mg/9 hours (3.3 mg/h)	Transdermal patch	Topical (hip)	MTS	DOT Matrix [®] Transdermal	N/A	d-/MPH
FOCALIN XR [57]	Novartis Pharmaceuticals	May 2005	≥6 years	5, 10, 15, 20, 25, 30, 35, and 40 mg	Capsule (mixed beads)	Oral (whole or sprinkled)	d-MPH-ER	SODAS [®]	IR 50%; ER 50%	d-MPH
JORNAY PM (HLD200) [75]	Ironshore Pharmaceuticals	August 2018	≥6 years	20, 40, 60, 80, and 100 mg	Capsule (composite beads)	Oral (whole or sprinkled)	DR/ER-MPH	DELEXIS [®]	N/A	d-/MPH
METADATE CD [47]	UCB	April 2001	6–15 years	10, 20, 30, 40, and 50 mg	Capsule (mixed bead)	Oral (whole or sprinkled)	MPH-CD	Diffucaps [®]	IR 30%; ER 70%	d-/MPH
QUILLICHEW ER (NWP09) [70]	Tris Pharma	December 2015	≥6 years	20, 30, and 40 mg	Chewable tablet	Oral (chewed)	MPH-ERCT	Ion-exchange resin microparticles	IR 30%; ER 70%	d-/MPH
QUILLIVANT XR (NWP06) [62]	Tris Pharma	September 2012	≥6 years	5 mg/mL in bottles containing 300, 600, and 750 mg of powder (to prepare 60, 120, and 150 mL suspensions, respectively)	Liquid oral suspension	Oral	MEROS	LiquiXR [®]	IR 20%; ER 80%	d-/MPH
RITALIN LA [53]	Novartis Pharmaceuticals	June 2002	≥6 years	10, 20, 30, and 40 mg	Capsule (mixed beads)	Oral (whole or sprinkled)	MPH-LA	SODAS [®]	IR 50%; ER 50%	d-/MPH
Amphetamine formulations										
ADDERALL XR (SLI381) [37]	Shire	October 2001	≥6 years	5, 10, 15, 20, 25, and 30 mg	Capsule (mixed beads)	Oral (whole or sprinkled)	MAS-ER	SODAS [®]	IR 50%; ER 50%	Mixed salts of d- and l-AMP (ratio of 3:1)
ADZENY5 ER (NT-0201) [97]	Neos Therapeutics	September 2017	≥6 years	1.25 mg/mL in 450 mL bottles	Liquid oral suspension	Oral	AMP XR-OS	Ion-exchange resin microparticles	IR 50%; ER 50%	Mixed salts of d- and l-AMP (ratio of 3:1)
ADZENY5 XR-ODT (NT-0202) [94]	Neos Therapeutics	January 2016	≥6 years	3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg	Orally disintegrating tablet	Oral (whole)	AMP XR-ODT	Ion-exchange resin microparticles	IR 50%; ER 50%	Mixed salts of d- and l-AMP (ratio of 3:1)
DYANAVEL XR (TRI102) [91]	Tris Pharmaceuticals	October 2015	≥6 years	2.5 mg/mL in 464 mL bottles	Liquid oral suspension	Oral	AMP EROS	LiquiXR [®]	NR	Mixed salts of d- and l-AMP (ratio of 3.2:1)
MYDAYIS (SPD465; SHP465) [101]	Shire	June 2017	≥13 years	12.5, 25, 37.5, and 50 mg	Capsule (mixed beads)	Oral (whole or sprinkled)	Triple-bead MAS-ER	Triple-bead	NR	Mixed salts of d- and l-AMP (ratio of 3:1)
VYVANSE (SPD489; NRP104) [36]	Shire	February 2007	≥6 years	10, 20, 30, 40, 50, 60, and 70 mg	Capsule (powder)	Oral (whole or sprinkled)	LDX	Prodrug	N/A	d-AMP
		April 2017		10, 20, 30, 40, 50, and 60 mg	Chewable tablet	Oral (chewed)				

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; AMP EROS, amphetamine extended-release oral suspension; AMP XR-ODT, amphetamine extended-release orally disintegrating tablet; AMP XR-OS, amphetamine extended-release oral suspension; d-MPH-ER, d-methylphenidate extended-release; DR/ER-MPH, delayed-release and extended-release methylphenidate; ER, extended-release; FDA, Food and Drug Administration; IR, immediate-release; LDX, lisdexamfetamine; MAS-ER, mixed amphetamine salts extended-release; MEROS, methylphenidate extended-release oral suspension; MPH, methylphenidate; MPH-CD, methylphenidate controlled-delivery; MPH-ERCT, methylphenidate extended-release chewable tablets; MPH-LA, methylphenidate long-acting; MPH-MLR, methylphenidate multilayer extended-release; MPH XR-ODT, methylphenidate extended-release orally disintegrating tablet; MTS, methylphenidate transdermal system; N/A, not applicable; NR, not reported; OROS-MPH, osmotic-release oral system methylphenidate; SODAS, spheroidal oral drug absorption system; US, United States.

monoamine oxidase (MAO) activity [9,17,28]. Furthermore, MPH is believed to have differing effects to AMP on the redistribution VMAT-2 within nerve terminals [9,29]. While the moderately greater efficacy of AMP versus MPH in patients with ADHD may be related to their distinct mechanisms of action, there is no conclusive evidence or guidelines to support the use of one stimulant type over another in specific patient populations [9,16,17].

Therapeutic improvement with stimulants is dependent on how fast (ascending slope or rate of release), how long (length of time that the stimulant occupies DAT and NET), and how much (plasma concentration) stimulants occupy the DAT and NET [30]. The ideal drug release profile is one that provides a slow increasing rate of release, robust but subsaturating plasma levels of neurotransmitters, and a long duration of DAT and NET occupancy by the stimulant before declining and wearing off, such that the resulting effect is an increase in tonic signaling without an increase in phasic signaling [30]. This tonic drug delivery will ensure optimal efficacy without any euphoric effects that occur when DAT and NET are saturated in a phasic pulsatile manner [30].

3.2. Absorption

There are four stereoisomers of MPH (*d*-*l*-*threo* and *d*-*l*-*erythro*); however, central nervous system (CNS) activity is only found with the *threo* racemate. While most currently available formulations of MPH include a racemic (1:1) mixture of both *d*-*threo*-MPH (*d*-MPH) and *l*-*threo*-MPH (*l*-MPH), data suggest that *d*-MPH is the most pharmacologically active enantiomer [31]. MPH hydrochloride is used in all formulations, and its basic properties (pKa 8.9) make it highly soluble, enabling dissolution in the fluids of the gastrointestinal (GI) tract when administered orally. Little degradation is believed to occur in the stomach because the acidic environment suppresses the non-enzymatic hydrolysis of MPH [25]. Following oral administration, IR MPH is rapidly and completely absorbed. The time to peak plasma concentration (T_{max}) is between 1 to 3 hours; although, there is considerable interindividual variability [18,32,33].

AMP has a chiral center with two enantiomers, levo-AMP (*l*-AMP) and dextro-AMP (*d*-AMP) [20,28]. *d*-AMP has been shown to be more potent than *l*-AMP in promoting the release of DA, whereas *l*-AMP appears to be either equally or more potent to *d*-AMP in inducing NE release [20,28]. While AMP formulations were originally available as racemic *d,l*-AMP, they were first supplanted by the enantiopure *d*-AMP sulfate and then mixed amphetamine salt (MAS) formulations containing equal parts of racemic *d,l*-AMP sulfate, *d,l*-AMP aspartate monohydrate, and two enantiopure *d*-AMP salts (*d*-AMP sulfate and *d*-AMP saccharate), yielding a 3:1 ratio of *d*-AMP to *l*-AMP isomers and salts [20,28]. Accordingly, MAS have a relatively greater effect in inducing NE release than *d*-AMP, but still more of an effect on DA than NE release. Similar to MPH, IR AMP is readily absorbed with more than 90% of the dose absorbed in the GI tract. Whether administered as a racemic *d,l*-AMP, enantiopure *d*-AMP, or MAS, the rate and extent of absorption is similar and T_{max} ranges between 2 and 4 hours; albeit, substantial variability has been reported [20,28].

Following oral administration of lisdexamfetamine (LDX), the prodrug of *d*-AMP that is covalently bound to an *l*-lysine, LDX is rapidly taken up from the small intestine into the

bloodstream via carrier-mediated active transport (i.e. probably via peptide transporter 1 [PEPT1]) and reaches T_{max} more quickly (i.e. 1–2 hours) and with less variability than *d*-AMP [20,34–36]. Once LDX is converted into the pharmacologically active *d*-AMP, it crosses the blood brain barrier to access the CNS and elicit its effects. Due to the rate-limiting conversion of LDX, the T_{max} of *d*-AMP occurs ~1 hour later than an equivalent dose of *d*-AMP sulfate [35].

3.3. Distribution

Given its low degree of protein binding and high lipid solubility, MPH is rapidly distributed, with the two enantiomers exhibiting different tissue distributions [18,31,32]. Significant amounts of *d*-MPH cross the blood brain barrier into the CNS, whereas *l*-MPH does not get taken up into the CNS [18]. Once *d*-MPH travels to the synaptic cleft, it must bind to DAT to provide its inhibitory effect. This inhibitory effect will last as long as MPH is bound to DAT.

Similar to MPH, AMP has low protein binding (~16% to 20% is bound to plasma protein) and gets rapidly distributed throughout the body and readily penetrates the CNS [20]. While both *d*-AMP and *l*-AMP accumulate in the CNS, *d*-AMP appears to reach higher concentrations. Furthermore, despite LDX being rapidly taken up into the bloodstream, it does not readily cross the blood brain barrier until it is converted into the active *d*-AMP enantiomer [35].

3.4. Metabolism

MPH has an age-dependent half-life ($t_{1/2}$) of approximately 2.5 hours in children and 3.5 hours in adults [31,33]. The *d*- and *l*-*threo* enantiomers of MPH are predominantly and rapidly metabolized by endoplasmic reticulum human carboxylesterase 1 (CES1A1) into inactive metabolites *d*- and *l*-*threo*-ritalinic acid, respectively. However, CES1A1 has a 6-fold higher preference for *l*-MPH versus *d*-MPH, resulting in higher concentrations of *d*-MPH [31]. The enantioselective de-esterification of MPH results in limited bioavailability of MPH and contributes to variability. Indeed, the bioavailability of MPH has been shown to range from 11% to 53% in children [25,31]. Despite the low bioavailability and large interindividual variability, therapeutic levels of MPH are achieved through dose titration or individualization of therapy.

AMP undergoes stereoselective metabolism with *d*-AMP metabolized more rapidly than *l*-AMP, resulting in different exposures to each enantiomer [20,37]. This is reflected by *d*-AMP having a $t_{1/2}$ that is approximately 2–3 hours shorter than *l*-AMP (e.g. 9–11 h for *d*-AMP and 11–14 h for *l*-AMP) [37]. AMP is highly metabolized and subject to two primary oxidative pathways: hydroxylation catalyzed predominantly by CYP2D6 into two active metabolites (i.e. 4-hydroxyamphetamine and α -hydroxyamphetamine [norephedrine], both of which are subject to further metabolism) and oxidative deamination [20,37]. Furthermore, LDX in the bloodstream undergoes hydrolysis in the erythrocyte cytosol by an unknown aminopeptidase, yielding the pharmacologically active *d*-AMP that has the same metabolic fate as the *d*-AMP acquired from all other AMP formulations [35,36].

3.5. Elimination

Following 48 hours after oral administration of MPH, 60% to 80% of the dose is eliminated as its metabolite, ritalinic acid, predominantly in urine (90%) and to a smaller extent in feces (3.3%). Less than 1% is excreted as the unchanged parent compound [18,31].

While AMP is also eliminated primarily through the kidneys, its excretion is highly dependent on urinary pH and flow rates, with urinary recovery of AMP ranging from 1% to 75%, and the remainder undergoing hepatic metabolism [20,37]. At normal urinary pH levels, 30% to 40% of the dose is largely eliminated as the unchanged parent compound and approximately 50% of the dose is eliminated as alpha-hydroxyamphetamine or its downstream inactive metabolite, hippuric acid [20,37]. Because AMP is a weak base with a pKa of 9.9, it is rapidly excreted when urine is acidic (pH <6.0), and conversely, delayed when urine is alkaline (pH >7.5). Accordingly, the relative amounts of AMP and metabolites excreted differ depending on the urinary pH conditions. It has been reported that the $t_{1/2}$ of AMP increases by approximately 7 hours for every unit increase in urinary pH; however, large deviations from normal physiological levels are unlikely unless the patient ingests acidifying or alkalizing agents.

LDX is almost entirely excreted through urine (~96%), with 42% of the dose eliminated as AMP, 25% as hippuric acid, and 2% as intact LDX [36]. Unlike AMP, LDX is not as sensitive to urinary pH, and therefore, its elimination is not pH-dependent and its $t_{1/2}$ is typically less than 1 hour [20,35,36].

4. Pharmacokinetics of long-acting stimulant formulations

4.1. Approved extended-release methylphenidate formulations

Since 2000, there have been 11 ER MPH formulations approved by the FDA and marketed in the U.S. (Table 1). The pharmacokinetic properties of these ER MPH formulations are summarized in chronological order of approval in Table 2 and described in detail below.

4.1.1. Osmotic-release oral system methylphenidate (OROS-MPH; CONCERTA®)

The first ER MPH formulation developed for the treatment of ADHD utilized the OROS® drug delivery system, which resembles conventional tablets, but uses osmotic pressure to deliver MPH at a controlled rate [40]. OROS-MPH tablets comprise an overcoat containing 22% IR MPH and a semipermeable membrane surrounding an inner trilayer core containing two drug layers and an osmotically-active push layer that gradually expands as water permeates the membrane into the tablet and pushes out the remaining 78% of MPH through a laser-drilled hole on the drug layer end. Once MPH has been entirely released, the tablet remains intact and gets eliminated in the stool as a shell with the insoluble core components. Accordingly, the OROS-MPH tablet must be swallowed whole and cannot be opened, crushed, divided, or chewed. This may have some clinical implications for patients that who have difficulties swallowing or GI abnormalities, such as narrowing or obstruction, as well as in the event of lodging in the esophagus [18,25].

OROS-MPH is characterized by a pharmacokinetic profile with a smooth ascending absorption phase reaching an initial peak concentration at approximately 1 hour, followed by a continued gradual ascending increase in plasma levels until a maximum plasma concentration (C_{max}) is achieved between 6 and 10 hours [40–43]. The apparent $t_{1/2}$ of MPH in healthy adults administered OROS-MPH is approximately 3.3 to 4 hours [40,41,43–45]. Despite having a lower C_{max} , the relative bioavailability of OROS-MPH was comparable to IR MPH dosed thrice-daily every 4 hours [41].

In the presence of food (i.e. high-fat breakfast), the pharmacokinetic profile of OROS-MPH appears to have one peak, with C_{max} and total exposure (i.e. area under the curve [AUC]) increasing slightly (10% to 30%) and T_{max} occurring approximately 1 hour later than in the fasted state [44]. Accordingly, OROS-MPH may be administered in the fed or fasted state because food does not result in dose dumping nor does it impede absorption in a clinically meaningful manner. Furthermore, there was no evidence of clinically significant accumulation with repeated once-daily administration of OROS-MPH for 6 days (AUC was 13.7% higher with repeated vs. single dosing) [41]. OROS-MPH is available at once-daily doses of 18, 27, 36, and 54 mg, and has demonstrated linear dose proportionality for d-MPH between doses of 18 mg and 54 mg [40,45]. While C_{max} and AUC increase disproportionately for l-MPH, plasma concentrations for this inert enantiomer were 40-fold lower than those of d-MPH, with its AUC values being only ~1% of d-MPH.

Except for one study conducted in children with ADHD [42], all other pharmacokinetic studies of OROS-MPH were conducted in healthy adults and no formal analyses were conducted to determine whether there is an age effect [41,44,45]. Per the data collected in Table 2, it appears that children with ADHD have a ~1.5-fold higher C_{max} and a slightly higher AUC (~10%–25%) than adults. As with many other MPH formulations, it is expected that the rate and extent of exposure would be similar across age groups when normalized for dose and body weight.

4.1.2. Methylphenidate controlled-delivery (MPH-CD; METADATE CD®)

The first ER MPH formulation to use bead technology was MPH-CD, which uses the Diffucaps® technology [46,47]. MPH-CD gelatin capsules contain 30% IR beads and 70% ER beads that were designed to release MPH in a biphasic manner to mimic twice-daily administration of IR MPH.

The pharmacokinetic profile of MPH-CD in children with ADHD is characterized by a sharp, initial slope similar to IR MPH reaching the first peak at approximately 1.5 hours followed by continued absorption and then a second peak (C_{max}) occurring approximately 3 hours later [47–49]. Although the pharmacokinetic profile of MPH-CD is generally characterized by two peaks, approximately 25% to 35% of children with ADHD exhibited a profile with one peak in a multiple-dose pharmacokinetic study [47–49]. The apparent $t_{1/2}$ of MPH following administration of MPH-CD to healthy adults is approximately 5.6 to 6.4 hours [46–50]. Compared with twice-daily IR MPH dosed 4 hours apart, both C_{max} and AUC were slightly lower for once-daily MPH-CD at a similar total daily dose of 20 mg [47–49].

MPH-CD is available in six dosage strengths of 10, 20, 30, 40, 50, and 60 mg [47]. MPH-CD has demonstrated linear dose proportionality at 20 mg and 40 mg in children with ADHD,

Table 2. Summary of pharmacokinetic properties of long-acting methylphenidate formulations (FDA-approved doses only).

Drug	PK Profile	Population	Dose(s) tested (mg)	Single/multiple dosing	Fasted/fed/ sprinkled	Enantiomer	Pharmacokinetic Parameters ^a				
							AUC _{0-∞} ^b (ng·h/mL)	C _{max} (ng/mL)	Median (range) or Mean ± SD (CV%)	T _{max} (h)	t _{1/2} (h)
ADHANSIA XR	Two peaks	Healthy adults (n = 15) [77,78]	100 mg	Multiple (5 days)	Fasted	d-MPH	Mean ± SD (CV%) 227.17 ± 83.61 (36.81%) ^c	Mean ± SD (CV%) 15.73 ± 4.54 (28.86%) ^c	T _{max1} : 1.5 (1–2.5) T _{max2} : 11.5 (8.5–16)		~7
		Adolescents with ADHD (12–16 years) (n = 17) [77,78] Children with ADHD (6–12 years) [78] Healthy adults (n = 24–25) [66,67]	62.9 ± 19.8 mg (range: 25–85 mg)	Single	Fasted	d-MPH	205.80 ± 90.41 (43.93%) ^c	13.64 ± 6.21 (45.53%) ^c	T _{max1} : 2 (1–4) T _{max2} : 11.3 (8–14)		4.91 ± 3.04 (61.17%) ^c
APTENSIO XR ^d	Two peaks	Healthy adults (n = 21) [69]	NR	NR	NR	d,l-MPH	NR	NR	T _{max1} : 2 (1–4) T _{max2} : 10 (8–14)		4–7
		Healthy adults (6–12 years) [78]	80 mg	Single	Fasted	d,l-MPH	258.1 ± 94.2 (36.50%) ^c	23.47 ± 11.4 (48.57%) ^c	T _{max1} : 2 T _{max2} : 8		5.09 ± 1.6 (31.43%) ^c
		Healthy adults (n = 24–25) [66,67]			Sprinkled		258.0 ± 84.4 (32.71%) ^c	21.78 ± 9.5 (43.62%) ^c	T _{max1} : 2 T _{max2} : 8		5.43 ± 2.5 (46.04%) ^c
		Healthy adults (n = 21) [69]	80 mg	Single	Fed	MPH	289.9 ± 90.8 (31.32%) ^c	23.7 ± 6.4 (27.00%) ^c	3.0 (2.0–10.0)		6.0 ± 5.4 (90.00%) ^c
		Children with ADHD (6–12 years) (n = 14) [68]	38.6 ± 17.7 mg/d (range: 20–80 mg)	Multiple (4 days) Single	Fed (standard breakfast) Fed	MPH	305.4 ± 92.9 (30.42%) ^c 155.11 ± 71.16 (45.88%) ^c	28.1 ± 7.1 (25.27%) ^c 12.12 ± 5.76 (47.52%) ^c	2.0 (1.0–5.0) 3.97 ± 2.61 (65.74%) ^c		5.4 ± 2.0 (37.04%) ^c 5.07 ± 1.47 (28.99%) ^c
CONCERTA	Two peaks	Healthy adults (18–45 years) (n = 36) [40,41,43]	18 mg	Single	NR	MPH	41.8 ± 13.9 (36.47%) ^c	3.73 ± 1.01 (27.08%) ^c	T _{max1} : ~1 T _{max2} : 6.8 ± 1.8 (26.47%) ^c		3.5 ± 0.4 (11.43%) ^c
		Healthy adults (18–45 years) (n = 32) [41,43]	18 mg	Single	NR	MPH	32.9 ± 12 (33.25%) ^c	2.81 ± 0.96 (34.16%) ^c	7.4 ± 2.0 (27.03%) ^c		3.9 ± 0.71 (18.21%) ^c
		Healthy adults (18–45 years) (n = 32) [41,43]	18 mg	Multiple (6 days) Single	NR	MPH	AUC ₀₋₂₄ : 35.2 ± 12 (34.09%) ^c 37.6 ± 17.5 (46.54%) ^c	3.00 ± 1.1 (36.67%) ^c 3.3 ± 1.3 (39.39%) ^c	6.6 ± 2.3 (34.85%) ^c 6.1 ± 2.2 (36.07%) ^c		3.9 ± 0.76 (19.49%) ^c 4.0 ± 0.7 (17.50%) ^c
		Healthy adults (n = 24) [40,44]	18 mg	Single	Fasted	MPH	45.3 ± 20.8 (45.92%) ^c	4.4 ± 1.9 (43.18%) ^c	7.2 ± 1.3 (18.06%) ^c		3.8 ± 0.7 (18.42%) ^c
			36 mg (n = 31)	Single	Fasted		67.6 ± 23.7 (35.06%) ^c	6.20 ± 2.2 (35.48%) ^c	6.5 ± 1.0 (15.38%) ^c		3.5 ± 0.5 (14.29%) ^c
				Single	Fed		79.0 ± 26.8 (33.92%) ^c	6.87 ± 2.3 (33.48%) ^c	7.4 ± 1.3 (17.57%) ^c		3.3 ± 0.3 (9.09%) ^c
		Healthy adults (18–43 years) (n = 33) [43,45]	18 mg	Single	Fasted	d-MPH	41.1 ± 15.9 (38.69%) ^c	3.8 ± 1.8 (47.37%) ^c	7.9 ± 1.7 (21.52%) ^c		3.7 ± 0.9 (24.32%) ^c
			36 mg	Single	Fasted		80.9 ± 30.8 (38.07%) ^c	7.3 ± 2.8 (38.36%) ^c	7.5 ± 1.3 (17.33%) ^c		3.9 ± 0.7 (17.95%) ^c
			54 mg	Single	Fasted		118.9 ± 45.9 (38.60%) ^c	10.5 ± 3.4 (32.38%) ^c	7.2 ± 1.5 (20.83%) ^c		3.9 ± 0.7 (17.95%) ^c
		Children with ADHD (6–12 years) (n = 32) [42,43]	18 mg (n = 3) 36 mg (n = 7) 54 mg (n = 3) 18 mg (n = 3) 36 mg (n = 7) 54 mg (n = 3)	Single	Fasted	MPH	50.4 ± 7.8 (15.48%) ^c 87.7 ± 18.2 (20.75%) ^c 121.5 ± 37 (30.45%) ^c 57.1 ± 2.8 (4.90%) ^c 92.6 ± 30.4 (32.83%) ^c 118.9 ± 45 (37.85%) ^c	6.0 ± 1.3 (21.67%) ^c 11.3 ± 2.6 (23.01%) ^c 15.0 ± 3.8 (25.33%) ^c 7.2 ± 0.5 (6.94%) ^c 12.5 ± 3.8 (30.40%) ^c 16.1 ± 4.9 (30.43%) ^c	9.4 ± 0.02 (0.21%) ^c 8.1 ± 1.1 (13.58%) ^c 9.1 ± 2.5 (27.47%) ^c 9.6 ± 1.7 (17.71%) ^c 8.0 ± 2.8 (35.00%) ^c 10.3 ± 2.0 (19.42%) ^c		NR NR NR NR NR NR

(Continued)



Table 2. (Continued).

Drug	PK Profile	Population	Dose(s) tested (mg)	Single/multiple dosing	Fasted/fed/ sprinkled	Enantiomer	Pharmacokinetic Parameters ^a				
							AUC _{0-∞} ^b (ng·h/mL)		C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)
							Mean ± SD (CV%)	Mean ± SD (CV%)			
COTEMPLA XR-ODT	Single peak	Healthy adults (n = 38) [38,72]	51.8 mg	Single	Fasted	d-MPH	169.1 ± 57.13 (33.78%) ^c	20.8 ± 5.22 (25.10%) ^c	4.98 (2.5–6.5)		4.00 ± 0.73 (18.25%) ^c
		Adolescents with ADHD (13–17 years) (n = 8) [38,39,72]	51.8 mg	Single	Fasted	d-MPH	187.2 ± 62.05 (33.15%) ^c	20.2 ± 5.79 (28.66%) ^c	5.5 (3.5–8.0)		3.93 ± 0.33 (8.40%) ^c
		Children with ADHD (6–12 years) (n = 24) [38,39,72]	51.8 mg	Single	Fasted	d-MPH	328.9 ± 90.21 (27.43%) ^c	32.7 ± 9.83 (30.06%) ^c	4.5 (2.0–8.0)		4.43 ± 1.00 (22.57%) ^c
		Children with ADHD (6–12 years) (n = 24) [38,39,72]	12.5 cm ² /9 h (10 mg/9 h)	Single	N/A	d-MPH	99.2 ± 42.9 (43.25%) ^c	9.30 ± 3.60 (38.71%) ^c	10.0 (8.00–12.0)		5.01 ± 1.20 (23.95%) ^c
DAYTRANA [60,61]	Single peak	Adolescents with ADHD (13–17 years) (n = 11)					48.7 ± 21.9 (44.97%) ^c	4.15 ± 2.59 (62.41%) ^c	10.0 (6.00–12.0)		4.35 ± 0.788 (18.11%) ^c
		Children with ADHD (6–12 years) (n = 11; 12)	12.5 cm ² /9 h (10 mg/9 h)	Multiple (up to 28 days)	N/A	d-MPH	163 ± 101 (61.96%) ^c	15.7 ± 9.39 (59.81%) ^c	9.00 (8.00–10.0)		N/A
			37.5 cm ² /9 h (up to 30 mg/9 h)	Multiple (up to 28 days)	N/A	d-MPH	447 ± 230 (51.45%) ^c	42.9 ± 22.4 (52.21%) ^c	8.00 (8.00–12.00)		N/A
		Adolescents with ADHD (13–17 years) (n = 12; 10)	12.5 cm ² /9 h (10 mg/9 h)	Multiple (up to 28 days)	N/A	d-MPH	85.7 ± 50.0 (58.34%) ^c	8.32 ± 4.60 (55.29%) ^c	10.0 (6.00–24.0)		N/A
FOCALIN XR	Two peaks	Healthy adults (19–45 years) (n = 24) [55,57,58]	37.5 cm ² /9 h (up to 30 mg/9 h)	Multiple (up to 28 days)	N/A	d-MPH	167 ± 66.0 (39.52%) ^c	16.5 ± 6.94 (42.06%) ^c	9.00 (1.00–10.00)		N/A
			20 mg	Single	Fasted	d-MPH	119.1 ± 40.7 (34.1%)	C _{max1} : 13.7 ± 4.6 (34.0%) C _{max2} : 14.9 ± 4.0 (26.8%)	T _{max1} : 1.5 (1.0–2.0) T _{max2} : 6.5 (4.5–7.0)		3.26 ± 0.51 (15.81%)
		Healthy adults (19–45 years) (n = 21)	5 mg	Single	Fasted	d-MPH	24.3 (30.7%)	C _{max1} : 2.68 (37.1%) C _{max2} : 3.18 (27.5%)	T _{max1} : 2.0 (1.5–4.0) T _{max2} : 5.5 (4.1–7.1)		2.86 (21.6%)
		(n = 23)	10 mg				45.9 (30.2%)	C _{max1} : 5.00 (35.7%) C _{max2} : 5.84 (27.7%)	T _{max1} : 1.5 (1.1–4.0) T _{max2} : 6.0 (4.5–8.0)		2.93 (24.0%)
		(n = 23)	20 mg				96.4 (35.5%)	C _{max1} : 10.8 (41.9%) C _{max2} : 12.5 (31.7%)	T _{max1} : 2.0 (0.52–4.0) T _{max2} : 5.5 (4.5–7.0)		3.11 (22.2%)
		(n = 24)	30 mg				144 (33.3%)	C _{max1} : 15.7 (38.4%) C _{max2} : 17.7 (31.6%)	T _{max1} : 1.5 (1.0–4.0) T _{max2} : 6.0 (4.5–7.0)		3.03 (16.5%)
		(n = 23)	40 mg				195 (30.9%)	C _{max1} : 20.6 (40.9%) C _{max2} : 23.6 (29.0%)	T _{max1} : 1.5 (1.0–4.0) T _{max2} : 6.5 (4.5–8.0)		3.20 (23.3%)

(Continued)

Table 2. (Continued).

Pharmacokinetic Parameters ^a												
Drug	PK Profile	Population	Dose(s) tested (mg)	Single/multiple dosing	Fasted/fed/ sprinkled	Enantiomer	AUC _{0-∞} ^b (ng·h/mL)		T _{max} (h)		t _{1/2} (h)	Mean ± SD (CV %)
							Mean ± SD (CV%)	C _{max} (ng/mL)	Median (range) or Mean ± SD (CV%)			
JORNAY PM	Single peak	Healthy adults (n = 20) [74,75]	20 mg	Single	Fasted	MPH	AUC _{0-t} : 33.4 (38.9%) AUC _{0-∞} : 34.7 (40.5%) 176.7 (34.0%)	2.56 (34.4%)	14 (13–19) 14.25 (12.7%) 14 (13–20)	6.51 (32.3%)		
			100 mg	Single	Fasted	MPH	183.0 (44.3%)	12.31 (36.5%)	14.85 (12.0%)	6.40 (34.5%)		
		Healthy adults (n = 18) [74,75]	100 mg	Single	Fasted	MPH	178.7 (43.4%) 187.4 (40.0%)	14.17 (46.5%)	14.00 (11.50–18.05) 14.31 (11.9%)	5.90 (41.6%)		
					Fed (evening meal) Sprinkled		178.7 (43.4%) 187.4 (40.0%)	12.21 (41.3%) 13.71 (39.5%)	16.50 (13.00–20.00) 16.67 (11.3%) 14.00 (11.50–20.02) 14.64 (14.2%)	5.94 (23.5%) 6.25 (27.2%)		
METADATE CD ^c	Two peaks	Healthy adults (n = 12) [73,75]	54 mg	Single	Fasted	MPH	AUC _{0-t} : 83.4 (27.1%)	5.99 (24.0%)	16 (13–18) 15.6 (11.1%)		NR	
			54 mg	Single	Fasted	MPH	109.6 (30.8%)	7.17 (23.7%)	16.2 (13.9–22.1) 17.1 (14.5%)		NR	
		Children with ADHD (8–12 years) (n = 11) [73,75]	54 mg	Single	Fasted	MPH	210.1 (38.5%)	11.64 (36.3%)	18.2 (12.4–22) 17.7 (14.1%)		NR	
			20 mg (n = 12) 40 mg (n = 9)	Multiple	NR	MPH	AUC _{0-t} : 63.0 ± 16.8 (26.67%) ^c AUC _{0-∞} : 119.7 ± 39.6 (33.08%) ^c	C _{max1} : 8.6 ± 2.6 (30.23%) ^c C _{max2} : 10.9 ± 3.9 (35.78%) ^c C _{max1} : 16.8 ± 5.1 (30.36%) ^c C _{max2} : 15.1 ± 5.8 (38.41%) ^c	T _{max1} : 1.5 (2.2 ± 0.7) T _{max2} : 4.5 (5.1 ± 1.0) T _{max1} : 1.5 (1.9 ± 1.0) T _{max2} : 4.5 (5.2 ± 0.8)		NR	
QUILLICHEW ER	Single peak	Healthy adults (20–50 years) (n = 18) [47–49]	40 mg	Single	Fasted Fed	d-MPH	99.7 ± 41.3 (41.42%) ^c 116.5 ± 48.0 (41.20%) ^c	8.9 ± 3.0 (33.71%) ^c 11.7 ± 4.6 (39.32%) ^c	4.8 ± 1.2 (25.00%) ^c 5.7 ± 1.7 (29.82%) ^c		NR	
			20 mg	Single	Fasted	MPH	45.62 ± 20.05 (43.95%) ^c 47.15 ± 20.30 (43.05%) ^c	4.58 ± 1.97 (43.01%) ^c 4.78 ± 1.88 (39.33%) ^c	4.58 ± 1.17 (25.55%) ^c 4.39 ± 1.39 (31.66%) ^c	6.42 ± 1.43 (22.27%) ^c 6.27 ± 1.80 (28.71%) ^c		
		Healthy adults (21–40 years) (n = 26) [46,47]	10 mg	Single	Fasted	d,l-MPH	25.77 ± 10.77 (41.80%)	2.34 ± 0.99 (42.19%)	5.00 (1.00–6.00) 4.72 ± 1.16 (24.51%)	5.61 ± 0.85 (15.16%)		
			20 mg 30 mg	Single	Sprinkled Fasted		50.66 ± 21.98 (43.39%) 76.03 ± 31.62 (41.59%)	4.80 ± 2.23 (46.35%) 7.38 ± 3.14 (42.47%)	5.00 (1.00–6.00) 4.52 ± 1.30 (28.77%) 5.00 (3.00–6.00) 5.00 ± 0.60 (12.06%)	6.06 ± 1.42 (23.36%) 5.75 ± 0.79 (13.83%) 5.2 (15%)		
		Healthy adults (18–55 years) (n = 31) [70,71]	40 mg	Single	Fasted	MPH	118.1 (30%) 12.5 (29%)	4.2 (28%)				

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(Continued)

Table 2. (Continued).

Drug	PK Profile	Population	Dose(s) tested (mg)	Single/multiple dosing	Fasted/fed/ sprinkled	Enantiomer	Pharmacokinetic Parameters ^a				
							AUC _{0-∞} ^b (ng·h/mL)		C _{max} (ng/mL)		t _{1/2} (h)
							Mean ± SD (CV%)	Mean ± SD (CV%)	Mean ± SD (CV%)	Median (range) or Mean ± SD (CV%)	
QUILLIVANT XR	Single peak	Healthy adults (18–68 years) (n = 28) [62,64]	60 mg	Single	Fasted	d-MPH	143.65 (50.67%)	13.61 ± 5.8 (42.56%)	5.00 (1.67–6.00)		5.65 ± 0.848 (15.01%)
		Healthy adults (n = 27) [62,65]	60 mg	Single	Fed	d-MPH	163.2 ± 80.3 (49.20%) ^c	17.0 ± 7.7 (45.29%) ^c	4.00 (1.3–7.3)		5.24 ± 1.05 (20.04%) ^c
		Adolescents with ADHD (13–15 years) (n = 4) [62,65]	20 mg	Single	Fed	MPH	82.4 ± 4.76 (5.78%) ^c	9.22 ± 0.560 (6.07%) ^c	2.00 (1.98–4.00)		5.18 ± 0.227 (4.38%) ^c
		Children with ADHD (6–12 years) (n = 3) [62,65]	20 mg	Single	Fed	MPH	101 ± 4.23 (4.19%) ^c	11.5 ± 2.17 (18.87%) ^c	2.00 (1.98–4.00)		5.04 ± 0.214 (4.25%) ^c
		Healthy adult males (n = 8) [53]	20 mg	Single	NR	d,l-MPH	378 ± 175 (46.30%) ^c	34.4 ± 14.0 (40.70%) ^c	4.05 (3.98–6.00)		5.27 ± 0.665 (12.62%) ^c
RITALIN LA	Two peaks	Healthy adult males (n = 8) [53]	20 mg	Single	NR	d,l-MPH	45.8 ± 10.0 (21.83%) ^c	C _{max1} : 5.3 ± 0.9 (16.98%) ^c C _{max2} : 6.2 ± 1.6 (25.81%) ^c	T _{max1} : 2.0 ± 0.9 (45.00%) ^c T _{max2} : 5.5 ± 0.8 (14.55%) ^c		5.19 ± 0.0832 (1.60%) ^c
		Children with ADHD (7–12 years) (n = 18) [53]	20 mg	Single	NR	d,l-MPH	86.6 ± 64.0 (73.90%) ^c	C _{max1} : 10.3 ± 5.1 (49.51%) ^c C _{max2} : 10.2 ± 5.9 (57.84%) ^c	T _{max1} : 2.0 ± 0.8 (40.00%) ^c T _{max2} : 6.6 ± 1.5 (22.73%) ^c		3.3 ± 0.4 (12.12%) ^c
		Healthy adults [51]	40 mg	Single	Fasted (n = 18)	d,l-MPH	105.72 ± 22.42 (21.21%) ^c	C _{max1} : 12.47 ± 2.60 (20.85%) ^c C _{max2} : 14.84 ± 2.71 (18.26%) ^c	T _{max1} : 1.56 ± 0.74 (47.44%) ^c T _{max2} : 5.44 ± 0.62 (11.40%) ^c		NR
					Fed (n = 18)		111.33 ± 18.14 (16.24%) ^c	C _{max1} : 12.75 ± 4.38 (34.35%) ^c C _{max2} : 11.42 ± 3.52 (30.82%) ^c	T _{max1} : 2.42 ± 1.23 (50.83%) ^c T _{max2} : 5.33 ± 1.44 (27.02%) ^c		NR
					Sprinkled (n = 17)		101.97 ± 20.56 (20.16%) ^c	C _{max1} : 12.95 ± 3.56 (27.49%) ^c C _{max2} : 13.10 ± 2.84 (21.68%) ^c	T _{max1} : 1.26 ± 0.31 (24.60%) ^c T _{max2} : 5.76 ± 0.59 (10.24%) ^c		NR

Footnotes: ^aArithmetic mean ± SD (CV%) except for time to maximum observed plasma concentration (T_{max}), for which the median (range) is reported, unless specified otherwise; ^bAUC_{0-∞} unless specified otherwise; ^cCV was derived using the following formula: CV% = (SD/mean) * 100%; ^dWhile 80 mg is not an approved dose, the FDA's evaluation was based on these pharmacokinetic studies; ^eIn the multiple-dose pharmacokinetic study of METADATE CD evaluated in children with ADHD, approximately 25%–30% of participants had only one peak. The C_{max} data reported in the FDA Pharmacology Review differs from the label (i.e. at 20 mg, C_{max1} was 8.6 ± 2.6 and C_{max2} was 9.6 ± 3.8, and at 40 mg, C_{max1} was 15.4 ± 8.1 and C_{max2} was 17.0 ± 4.4). These data discrepancies may be due to differences in accounting for participants that did not have a second peak.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AUC_{0-∞}, area under the plasma concentration–time curve from zero to infinite time; AUC₀₋₉, area under the plasma concentration–time curve from zero to 9 hours; AUC₀₋₂₄, area under the plasma concentration–time curve from zero to 24 hours; AUC_{0-t}, area under the plasma concentration–time curve from zero to the time point with the last quantifiable concentration; C_{max}, peak plasma concentration; C_{max1}, first peak plasma concentration; C_{max2}, second peak plasma concentration; CV, coefficient of variation; FDA, Food and Drug Administration; MPH, methylphenidate; N/A, not applicable; NR, not reported; SD, standard deviation; t_{1/2}, half-life; T_{max1}, first time to peak plasma concentration; T_{max2}, second time to peak plasma concentration.

and between 10 mg and 60 mg in healthy adults [47,50]. MPH-CD capsules can either be swallowed whole or opened and sprinkled onto applesauce when patients have difficulty swallowing. The bioavailability of MPH was unaffected by sprinkling the MPH-CD capsule contents onto applesauce in healthy adults [46,47]. The presence of food delayed T_{\max} by 1 hour, and increased C_{\max} by 30% and AUC by 17% in adults with ADHD [47–49]. While the food effect observed is not considered to be clinically meaningful, it is recommended that MPH-CD be administered in the morning before breakfast [47].

4.1.3. Methylphenidate long-acting (MPH-LA; RITALIN LA®)

MPH-LA is another ER MPH formulation that produces a pharmacokinetic profile characterized by two peaks in both healthy adults and children with ADHD [51–54]. It is developed utilizing the spheroidal oral drug absorption system (SODAS®), with each MPH-LA capsule containing 50% IR beads that provide an initial rapid release of MPH peaking ($C_{\max 1}$) at approximately 2 hours and 50% enteric-coated ER beads that result in a second peak ($C_{\max 2}$) of MPH approximately 4 hours later [52,53]. The apparent $t_{1/2}$ of MPH-LA is approximately 2.4 hours in children with ADHD and 3.3 hours in healthy adult males, which is comparable to IR MPH [53]. Children with ADHD have a 2-fold higher C_{\max} than healthy adults receiving 20 mg of MPH-LA. This higher exposure is mostly due to the smaller body weight and volume of distribution in children, and it is expected that the rate and extent of exposure would be similar across age groups when normalized for dose and body weight [53].

The available dosage strengths of MPH-LA are 10, 20, 30, and 40 mg. While no clinically meaningful accumulation is expected, there is a slight upward trend in AUC and both $C_{\max 1}$ and $C_{\max 2}$ after administration of 20 and 40 mg to healthy adults [53]. As with other formulations that use bead technologies, MPH-LA capsules can either be swallowed whole or opened and sprinkled onto applesauce [53]. In healthy adults, administration of MPH-LA sprinkled onto a spoon of applesauce did not affect the pharmacokinetics compared with administration in the fasted state [51,53]. Furthermore, while AUC, $C_{\max 1}$, and $T_{\max 2}$ were mostly unaffected when MPH-LA was administered with a high-fat breakfast in healthy adults, $C_{\max 2}$ decreased by 23% and $T_{\max 1}$ was delayed by an hour [51].

4.1.4. d-Methylphenidate extended-release (d-MPH-ER; FOCALIN XR®)

The only ER MPH formulation to solely contain the pure d-MPH enantiomer is d-MPH-ER. Similar to MPH-LA, this formulation also uses SODAS® technology with 50% IR and 50% ER beads. In healthy adults, d-MPH-ER results in a pharmacokinetic profile characterized by an initial peak around 1.5 to 2 hours and a second higher peak at 5.5 to 6.5 hours, with a trough in plasma MPH concentrations between the two peaks [55–58]. The apparent $t_{1/2}$ is approximately 3 hours in healthy adults. The pharmacokinetics of d-MPH-ER have not been evaluated in children and adolescents (i.e. aged <18 years) [57].

Since only the pharmacologically active d-MPH enantiomer is included in the formulation, the total daily dose of d-MPH-ER is half of all other ER MPH formulations that contain both d- and l-MPH. Once-daily d-MPH-ER at 20 mg was

found to be bioequivalent to two doses of IR d-MPH at 10 mg given 4 hours apart and once-daily MPH-LA at 40 mg [55,57,59]. However, d-MPH-ER had a slightly lower second peak concentration ($C_{\max 2}$) and longer $T_{\max 2}$ than IR d-MPH, suggesting fewer peak and trough fluctuations with d-MPH-ER [55,57,59].

The eight available dosage strengths of d-MPH-ER are 5, 10, 15, 20, 25, 30, 35, and 40 mg. In healthy adults, d-MPH-ER was found to be dose proportional between 5 and 40 mg [56,58]. While the effect of food and sprinkling the capsule contents onto a small amount of applesauce on the pharmacokinetic profile of d-MPH-ER have not been studied, it is expected that d-MPH-ER would behave similarly to MPH-LA because they use the same drug delivery technology [57,59].

4.1.5. Methylphenidate transdermal system (MTS; DAYTRANA®)

MTS is the only ER MPH that delivers racemic MPH transdermally through a diffusion-based patch that uses DOT Matrix® transdermal technology [60,61]. The patch consists of a multipolymer adhesive layer containing MPH, which is applied to intact skin to continuously deliver MPH, and a polyester/ethylene acetate laminate film backing [61]. The dose of MPH delivered is dependent on the patch size and wear time. Additionally, since transdermal delivery reduces first-pass metabolism, plasma concentrations of the less potent l-MPH enantiomer tend to be higher with MTS (i.e. about half the exposure to d-MPH) than those seen with orally administered ER MPH formulations, which tend to be negligible [60,61].

MTS is available in four patch dosage strengths that can be worn up to 9 hours: 12.5 cm² (10 mg), 18.75 cm² (15 mg), 25 cm² (20 mg), and 37.5 cm² (30 mg). In children with ADHD, dose proportionality was observed for d-MPH between patch doses of 12.5 cm² (10 mg) and 37.5 cm² (30 mg) [61]. While C_{\max} of l-MPH was dose proportional, AUC was slightly greater than proportional to patch dose.

In children and adolescents with ADHD, a single application of a 12.5 cm² patch for 9 hours resulted in a pharmacokinetic profile characterized by a 2-hour delay in d-MPH absorption, with peak plasma concentrations achieved at 10 hours and a $t_{1/2}$ of about 4 to 5 hours [60,61]. Progressively increasing accumulation of d-MPH was evident with multiple 9-hour applications of MTS over a 28-day period using fixed dosing (i.e. 12.5 cm² patch) and escalating dosing (i.e. 12.5 cm² to 37.5 cm² patch) strategies, with steady state likely achieved by approximately 14 days [60,61]. After 28 days of repeated administration of MTS to children and adolescents with ADHD at a fixed dose of 12.5 cm² for 9 hours, AUC increased by 64% and 76%, respectively, and C_{\max} increased by 69% and 100%, respectively, relative to a single dose [61]. There also appeared to be a carryover effect, where low concentrations of MPH were observed earlier in the pharmacokinetic profile, thereby reducing the initial delay in MPH absorption seen with single dosing; accordingly, C_{\max} was reached between 8 to 10 hours. Due to its accumulation, systemic exposure to d-MPH was 1.4- to 1.6-fold higher for MTS compared with multiple escalating doses of OROS-MPH (18 to 54 mg) in children; however, it was similar in adolescents for both formulations [60].

4.1.6. *Methylphenidate extended-release oral suspension (MEROS; QUILLIVANT XR®)*

MEROS is the first liquid formulation of an ER MPH that is supplied in bottles with either 300, 600, or 750 mg of powder that, after reconstitution with water, becomes a suspension containing 5 mg/mL of MPH [62]. MEROS uses LiquiXR® technology consisting of two types of particles: solid particles with an ion-exchange resin that form a complex with MPH through ionic binding and similar particles that are coated with variable thicknesses of an aqueous, pH-independent polymer [62,63]. The uncoated particles deliver 20% of MPH as IR and the polymer-coated particles deliver 80% of MPH as ER.

MEROS exhibits a pharmacokinetic profile with a rapid initial rise in MPH concentrations followed by a gradual, extended period of release. In healthy adults administered a single dose of 60 mg under fasted conditions, the maximum concentration of d-MPH was reached after 5 hours and the $t_{1/2}$ was 5.65 hours [62,64]. Once-daily MEROS at 60 mg is bioequivalent to two 30-mg doses of an oral solution of IR MPH administered 6 hours apart, despite having a 30% lower C_{max} versus the second peak of the IR MPH [62,64]. Administration of MEROS with a high-fat breakfast shortened T_{max} by 1 hour and increased C_{max} by 28% and AUC by 19%; however, these changes are not considered clinically significant [62,64,65].

In children and adolescents with ADHD, peak plasma d-MPH concentrations were generally achieved between 2 and 4 hours after administering a single 20 mg or 60 mg dose of MEROS [62,65]. Although C_{max} was similar for children and adolescents at the 20 mg dose, it was significantly higher in children than adolescents at the 60-mg dose [65]. However, after adjusting for dose and body weight, C_{max} and AUC were similar, suggesting dose proportionality and a similar rate and extent of MPH absorption in both children and adolescents [65]. After a single 60 mg dose of MEROS, C_{max} was approximately 2-fold higher than adults, whereas C_{max} in adolescents was comparable to adults [62].

4.1.7. *Methylphenidate multilayer extended-release (MPH-MLR; APTENSIO XR®)*

MPH-MLR is the first ER MPH formulation to use composite multilayered beads that have an outer IR layer containing approximately 40% of MPH and an inner controlled-release layer providing extended release of the remaining 60% of MPH [66]. MPH-MLR capsules are available in seven once-daily dosage strengths of 10, 15, 20, 30, 40, 50, and 60 mg, and can be administered as whole capsules or sprinkled on applesauce [66].

MPH-MLR was designed to provide a rapid initial release of MPH that is comparable to that of IR MPH, followed by a small but noticeable drop in MPH release over the lunchtime period, and then a second controlled release of MPH throughout the rest of the day with MPH levels gradually decreasing through dinner and sleeping hours [67]. Consistent with the intended design, in healthy adults, MPH-MLR produced a distinct pharmacokinetic profile characterized by an initial phase of rapid MPH absorption peaking at approximately 2 hours postdose, followed by a moderate decline in plasma concentrations over the subsequent 4 to 6 hours, and then a gradual increase

culminating in an attenuated second peak at approximately 7 to 8 hours postdose [66,67]. The apparent $t_{1/2}$ of MPH following administration of MPH-MLR to healthy adults under fasted conditions is approximately 5 hours. The pharmacokinetic profile of MPH-MLR is qualitatively similar in children with ADHD aged 6 to 12 years and healthy adults, and bioequivalent when dose normalized [66,68].

Compared with thrice-daily IR MPH dosed 4 hours apart, the pharmacokinetic profile of once-daily MPH-MLR at a comparable total daily dose had one fewer peak and trough and marked differences in C_{max} . MPH-MLR demonstrated higher C_{max} values for its initial peak, whereas C_{max} progressively increased with each successive dose of IR MPH [67]. Accordingly, when taken whole as a capsule or sprinkled, acute systemic exposure with MPH-MLR was higher than that of IR MPH over the first 4 hours postdose; however, total systemic exposure or relative bioavailability was comparable [66,67].

Administration of MPH-MLR with a high-fat breakfast increased C_{max} and AUC by approximately 28% and 19%, respectively, and diminished or lowered the second peak [66]. In healthy adults, single-dose and steady-state pharmacokinetics were qualitatively and quantitatively similar in the fed state; however, coadministration of a single MPH-MLR dose with a high-fat breakfast delayed T_{max} by 1 hour versus coadministration of multiple MPH-MLR doses over 4 days with a standard breakfast [69].

4.1.8. *Methylphenidate extended-release chewable tablets (MPH-ERCT; QUILLICHEW ER®)*

MPH-ERCT is a cherry-flavored, chewable tablet formulated to deliver 30% IR MPH and 70% ER MPH [70]. MPH-ERCT is available in dosage strengths of 20, 30, and 40 mg; although, these dosage strengths are expressed as MPH hydrochloride equivalents. The composition of MPH-ERCT is approximately 15% of MPH as MPH hydrochloride salt and the remaining 85% of MPH ionically bound to the sulfonate groups of sodium polystyrene sulfonate particles.

MPH-ERCT produces a pharmacokinetic profile with peak concentrations reached at approximately 5 hours and a $t_{1/2}$ of 5.2 hours in healthy adults administered a single dose of 40 mg under fasted conditions [70,71]. The pharmacokinetics of MPH-ERCT have not been evaluated in children and adolescents with ADHD [70]. The relative bioavailability of a single 40 mg dose of MPH-ERCT is comparable to a twice-daily IR MPH chewable tablet administered in two 20 mg doses 6 hours apart; however, C_{max} was 20% lower for MPH-ERCT relative to the second peak of IR MPH [71]. A high-fat meal had no effect on T_{max} , and increased C_{max} and AUC by 20% and 4%, respectively, after a single 40 mg dose of MPH-ERCT [70].

4.1.9. *Methylphenidate extended-release orally disintegrating tablet (MPH XR-ODT; COTEMPLA XR-ODT®)*

MPH XR-ODT is the first ER MPH to be formulated as a once-daily orally disintegrating tablet (ODT) that contains 25% IR MPH and 75% ER MPH [10,72]. MPH XR-ODT utilizes an ion-exchange resin technology, where MPH is ionically-bound to the sulfonate of polystyrene sulfonate microparticles. To create MPH-loaded microparticles, MPH salts are dissociated in solution, and the positively charged MPH replaces the Na^+ of

the resin. These microparticles are either uncoated (IR) or coated (ER), and then compressed into ODTs. MPH XR-ODT is available in dosage strengths of 8.6, 17.3, and 25.9 mg, which are equivalent to 10, 20, and 30 mg of MPH hydrochloride [72].

In healthy adults dosed 51.8 mg of MPH XR-ODT in the fasted state, the pharmacokinetic profile of MPH XR-ODT is characterized by a broad peak that reaches its maximum 5 hours post-dose, followed by an apparent first-order elimination phase with a $t_{1/2}$ of 4 hours [72]. Administration of MPH XR-ODT with a high-fat meal resulted in a shortened T_{max} by half an hour, and a 24% lower C_{max} and 16% higher AUC [72]. A single 51.8 mg dose of MPH XR-ODT resulted in a 2-fold higher C_{max} in children versus adults, whereas there were no differences in C_{max} between adolescents and adults [10,72]. However, when adjusted for body weight, there were no differences across age groups.

4.1.10. Delayed-release and extended-release methylphenidate (DR/ER-MPH; JORNAY PM™)

DR/ER-MPH is the first evening-dosed ER MPH formulation that utilizes the DELEXIS® drug delivery platform containing uniform microbeads composed of two functional layers: an outer delayed-release (DR) layer and an inner ER layer, surrounding an IR MPH-loaded core. The outer DR layer comprises hydrophobic, hygroscopic, and pH-dependent polymers designed to provide a prolonged, predictable delay in the timing of initial MPH release, which is intended to offer a therapeutic effect upon awakening. The inner ER layer, composed of hydrophobic and soluble polymers, is designed to provide a controlled, extended release of MPH with the goal of maintaining efficacy throughout the rest of the day [73–75].

Evening-dosed DR/ER-MPH exhibits a single-peak pharmacokinetic profile with a consistent, predictable delay in the initial release of MPH until the early morning (i.e. ~8–10 hours after ingestion), followed by a period of extended, controlled release across the day [73–75]. Similar to other ER MPH formulations, the pharmacokinetic profiles of healthy adults and children and adolescents with ADHD are nearly superimposable after adjusting for dose and body weight [73,75]. In five separate single-dose pharmacokinetic studies of DR/ER-MPH, early drug exposure from 0 to 10 hours after evening dosing was <5% of total drug exposure in healthy adults and in adolescents and children with ADHD, confirming that there is no drug release while the patient sleeps [73–75]. After the delay in initial drug release, plasma MPH concentrations increased rapidly and peaked at 14 to 16 hours postdose in healthy adults and 16 to 18 hours postdose in children and adolescents with ADHD. This was followed by a slower decline in drug concentrations, with more than 50% of drug exposure occurring after peak concentrations were reached, suggesting that DR/ER-MPH has a prolonged absorption phase and thereby protracted elimination phase [73]. The apparent $t_{1/2}$ of DR/ER-MPH administered to healthy adults under fasted conditions is approximately 5.9 to 6.5 hours [73–75].

DR/ER-MPH is available in five dosage strengths of 20, 40, 60, 80, and 100 mg, and has demonstrated dose proportionality between the 20 and 100 mg doses [74,75]. Multiple-dose pharmacokinetics of DR/ER-MPH were simulated at doses of 20 and 100 mg and it was determined that there was no significant accumulation of MPH compared with single doses,

and that steady state is reached by the second dose [74]. The relative bioavailability of once-daily DR/ER-MPH compared with a similar dose of thrice-daily IR MPH in healthy adults was 73.9% [74,75]. DR/ER-MPH also exhibited a protracted elimination phase relative to IR MPH. The protracted elimination phase and lower bioavailability of DR/ER-MPH are likely due to its targeted delivery to the relatively less absorptive colon, resulting in prolonged absorption with some of the released MPH not ending up being absorbed and undergoing fecal elimination [73,74].

DR/ER-MPH capsules can either be swallowed whole or opened and sprinkled onto applesauce [75]. In healthy adults, administration of 100 mg of DR/ER-MPH sprinkled onto a spoon of applesauce did not affect the pharmacokinetics compared with administration in the fasted state [74,75]. Given that DR/ER-MPH is uniquely dosed in the evening, the effect of food on its single-dose pharmacokinetics at a dose of 100 mg was investigated with both evening administration and breakfast the following morning [74,75]. A high-fat meal in the evening did not affect total exposure (AUC) compared to the fasted and sprinkled states; however, C_{max} was slightly reduced by 11% to 14% and T_{max} was delayed by ~2.5 hours. For most patients, these effects are not expected to be clinically relevant, especially if DR/ER-MPH is administered consistently with or without food. As expected, after a single dose of DR/ER-MPH, the composition of a morning meal (i.e. low- vs. medium-fat breakfast) had no effect on its pharmacokinetics. This is likely because by this point the DR/ER-MPH microbeads have transited to the colon, and few food-induced physiological changes are expected to affect bioavailability of MPH.

Based on the properties of the multiple polymers in the DR and ER layers of DR/ER-MPH microbeads, the initial dissolution and subsequent absorption of MPH are not dependent on any single factor, such as a pH trigger, normal variations in gastrointestinal transit, or site of release [73,74]. A lack of a reliance on a single trigger for MPH release may contribute to minimizing interpatient and inpatient variability. Indeed, following a single-dose administration of DR/ER-MPH, intersubject variability, as measured by the coefficient of variation (CV), in the time to achieve a specific plasma MPH concentration (2–5 ng/mL) on the ascending concentration–time curve was low (i.e. <30% [76]) in both children (CV: 7.8%–12.1%) and adolescents (CV: 9.0%–12.8%) with ADHD and healthy adults (CV: 11.3%–17.7%) [73]. Similarly, low intersubject variability was observed in mean T_{max} (CV<14.5%) in all populations in five separate pharmacokinetic studies of DR/ER-MPH at varying doses [73,74]. Lastly, low intrasubject variability in C_{max} (CV: 20.1%) and AUC (CV: 12.4%) was observed in healthy adults administered DR/ER-MPH [74].

4.1.11. Methylphenidate multilayer extended-release (MPH-MLR; PRC-063; ADHANSIA XR®)

The most recent ER MPH formulation approved for the treatment of ADHD is PRC-063, which is similar to MPH-MLR in that it utilizes the same multilayered bead technology; however, the IR to ER ratio of MPH delivered is different because the outer IR layer contains approximately 20% of MPH and the inner controlled-release layer contains the remaining 80% of MPH [77,78].

Similar to MPH-MLR, PRC-063 has a pharmacokinetic profile with two very distinct peaks – the first peak occurring at about 1.5 hours and the second one at approximately 12 hours after multiple dosing under fasted conditions in healthy adults [77,78]. After adjusting for body weight, the pharmacokinetic profile in adults is comparable to that of children and adolescents with ADHD, with the first and second peak concentrations for d,l-MPH occurring at about 2 and 10 hours, respectively, in children and about 2 and 11 hours, respectively, in adolescents [78]. The apparent $t_{1/2}$ was approximately 7 hours in adults, 5 hours in adolescents, and 4 to 7 hours in children [78].

After administration of once-daily PRC-063 at 100 mg in healthy adults under fasted conditions for 5 days, steady state was reached from day 3 [77,78]. At steady state, the first C_{max} was 22% higher but the second C_{max} was similar for PRC-063 compared with IR MPH dosed at 20 mg thrice-daily 4 hours apart [77,78]. Also, the extent of exposure (AUC) was 50% higher for PRC-063 versus IR MPH. In adolescents with ADHD, a single dose of PRC-063 was bioequivalent to thrice-daily IR MPH when both were administered at an equivalent pre-study MPH dose; however, C_{max} was 33% lower with PRC-063 [77].

PRC-063 is available in six dosage strengths of 25, 35, 45, 55, 70, and 85 mg, and can be administered both as an intact capsule or sprinkled on applesauce without any effects to its pharmacokinetic profile [78]. Administration of PRC-063 with a high-fat meal did not affect C_{max} and AUC; however, both T_{max1} and T_{max2} were delayed by an hour compared to fasted conditions [78].

4.2. Approved extended-release amphetamine formulations

Prior to 2001, AMP formulations used in the treatment of ADHD included IR formulations of d-AMP salts, immediate- and modified-release formulations of enantiopure d-AMP sulfate, or IR formulations of mixed d- and l-AMP salts [20,28]. In the last two decades, there have been seven ER AMP formulations approved by the FDA and marketed in the U.S. that include compositions of mixed d- and l-AMP salts and a prodrug of d-AMP (Table 1). The pharmacokinetic properties of these ER AMP formulations are summarized in chronological order of approval in Table 3 and described below.

4.2.1. Mixed amphetamine salts extended-release (MAS-ER; ADDERALL XR®)

MAS-ER was the first once-daily ER AMP formulation developed to mimic the pharmacokinetics of twice-daily IR AMP [79]. MAS-ER contains a racemic mixture of d- to l-AMP isomers in a ratio of 3:1 and utilizes the SODAS® drug delivery platform with each capsule containing two types of beads: 50% IR beads and 50% ER beads [37,79].

As expected, MAS-ER produces a pharmacokinetic profile with a 3:1 ratio of d-AMP to l-AMP observed for AUC and C_{max} in studies of healthy adults, and children and adolescents with ADHD [37,79–83]. A single 20 mg dose of MAS-ER was found to be bioequivalent to IR MAS dosed at 10 mg twice-daily 4 hours apart in healthy adults, with comparable AUC and C_{max} values for both d- and l-AMP [79]. In healthy adults, a single 30 mg dose MAS-ER under fasting conditions attained mean peak plasma

concentrations for d-AMP and l-AMP at approximately 5.2 and 5.5 hours, respectively, with d-AMP having a shorter mean elimination $t_{1/2}$ than l-AMP (10.4 vs. 12.7 hours) [79,83]. At steady-state, T_{max} was 4.2 hours for d-AMP and 4.3 hours for l-AMP when 30 mg of MAS-ER was administered once-daily for 7 consecutive days under fasting conditions in healthy adults [80].

There are six dosage strengths available for MAS-ER: 5, 10, 15, 20, 25, and 30 mg [37]. MAS-ER has demonstrated linear pharmacokinetics across doses of 20 to 60 mg in adults and adolescents weighing more than 75 kg [80,82], 10 to 40 mg in adolescents weighing 75 kg and less [82], and 5 to 30 mg in children aged 6 to 12 years [37,81]. MAS-ER capsules can either be taken whole or sprinkled on a spoonful of applesauce if a patient has difficulty with swallowing [37]. The bioavailability of d- and l-AMP was unaffected when MAS-ER was administered whole or sprinkled onto applesauce in healthy adults dosed 30 mg under fasted conditions [37,79]. In the presences of a high-fat meal, a single 30 mg dose of MAS-ER had comparable bioequivalence to the same dose administered in the fasted state for both d- and l-AMP; however, T_{max} was prolonged by about 2.5 hours for d-AMP and 2.7 hours for l-AMP [37,79].

In children with ADHD administered a single 20 mg dose of MAS-ER, T_{max} was achieved at 6.8 hours for d-AMP and 6.9 hours for l-AMP, with $t_{1/2}$ of 9.5 and 10.9 hours for d- and l-AMP, respectively [81]. After administering 20 mg of MAS-ER once-daily for 7 consecutive days, the steady-state pharmacokinetics were generally comparable to those achieved with a single dose, where AUC decreased by 17% for d-AMP and 15% for l-AMP, C_{max} increased by 11% for d-AMP and 16% for l-AMP, and T_{max} was shorter by 1 hour for both d- and l-AMP (5.8 and 5.7 hours, respectively) [81]. Accordingly, no clinically significant accumulation is expected in children [37].

There was a body weight-dependent effect on the single-dose pharmacokinetics of MAS-ER in adolescents with ADHD under fasting conditions, where AUC and C_{max} decreased with increasing body weight for both d- and l-AMP; however, T_{max} remained consistent at 4 to 5 hours [82]. Comparisons of MAS-ER pharmacokinetics between children, adolescents, and adults confirmed that body weight is a primary determinant of the differences in C_{max} and AUC, where both decreased with increasing body weight [37,79,81,82]. After normalizing for dose and body weight, children had 30% lower systemic exposure than adults [37]. Additionally, systemic exposure to AMP was 20% to 30% higher in women than men; however, these differences were also diminished after adjusting for dose and body weight [37].

4.2.2. Lisdexamfetamine (LDX; VYVANSE®)

LDX is a long-acting prodrug of d-AMP and the first stimulant to release the active drug biochemically into the systemic circulation rather than the GI tract [35,36]. Following oral administration, the pharmacologically inactive LDX is rapidly absorbed from the small intestine into the bloodstream, where it gets converted to l-lysine and the pharmacologically active d-AMP [35,36]. Accordingly, the pharmacokinetic properties of LDX are characterized and described for both the inactive LDX and active d-AMP.

Table 3. Summary of pharmacokinetic properties of long-acting amphetamine formulations (FDA-approved doses only).

Pharmacokinetic Parameters ^a										
Drug	PK Profile	Population	Dose(s) Tested (mg)	Single/multiple dosing	Fasted/ fed/ sprinkled	Enantiomer/ entity	AUC _{0-∞} ^b (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)
							Mean ± SD (CV%)	Mean ± SD (CV%)	Median (range) or Mean ± SD (CV%)	
ADDERALL XR	Single peak	Healthy adults (n = 19) [37,79,83]	20 mg	Single	Fed	d-AMP	566.62 ± 114.30 (20%)	28.13 ± 8.84 (31%)	6.95 ± 2.35 (33.81%) ^c	11.83 ± 2.74 (23.16%) ^c
						l-AMP	203.12 ± 46.04 (23%)	8.67 ± 2.80 (32%)	8.15 ± 4.44 (54.48%) ^c	13.72 ± 2.83 (20.63%) ^c
			30 mg	Single	Fasted	d-AMP	851.17 ± 213.51 (25.04%) ^c	44.33 ± 11.10 (25.04%) ^c	5.20 ± 1.96 (37.69%) ^c	10.40 ± 2.31 (22.21%) ^c
						l-AMP	288.59 ± 79.17 (27.43%) ^c	13.32 ± 3.66 (27.48%) ^c	7 (NR)	12.71 ± 3.30 (25.96%) ^c
	Healthy adults (n = 19) [37,79,83]	Fed	d-AMP	822.56 ± 200.18 (24.34%) ^c	39.70 ± 8.84 (22.27%) ^c	7.67 ± 2.31 (30.12%) ^c	10.34 ± 1.98 (19.15%) ^c			
			l-AMP	273.56 ± 68.98 (25.22%) ^c	11.98 ± 2.89 (24.12%) ^c	8.33 ± 2.89 (34.69%) ^c	12.50 ± 2.56 (20.48%) ^c			
		Sprinkled	d-AMP	855.98 ± 179.68 (20.99%) ^c	43.51 ± 9.61 (22.09%) ^c	5.50 ± 1.76 (32.00%) ^c	10.39 ± 2.05 (19.73%) ^c			
			l-AMP	290.38 ± 64.49 (22.21%) ^c	13.04 ± 3.20 (24.54%) ^c	5.60 ± 1.73 (30.89%) ^c	12.73 ± 2.83 (22.23%) ^c			
	Healthy adults (n = 20) [37,80]	30 mg	Multiple	Fasted	d-AMP	1294.37 ± 290.45 (22.44%) ^c	66.88 ± 13.8 (20.63%) ^c	4.18 ± 1.18 (28.23%) ^c	11.28 ± 1.12 (9.93%) ^c	
					l-AMP	506.17 ± 125.05 (24.71%) ^c	21.72 ± 4.60 (21.18%) ^c	4.30 ± 1.12 (26.05%) ^c	13.77 ± 3.3 (23.97%) ^c	
		10 mg	Single	Fasted	d-AMP	351 ± 56.9 (16.21%) ^c	18.4 ± 2.96 (16.09%) ^c	3.93	10.8 ± 2.65 (24.54%) ^c	
					l-AMP	129 ± 28.6 (22.17%) ^c	5.80 ± 0.86 (14.83%) ^c	4.00	12.9 ± 4.54 (35.19%) ^c	
Adolescents with ADHD (13–17 years; ≤75 kg) [37,82]	20 mg	Single	Fasted	d-AMP	689 ± 128 (18.58%) ^c	34.1 ± 7.80 (22.87%) ^c	4.99	11.0 ± 2.28 (20.73%) ^c		
				l-AMP	267 ± 62.7 (23.48%) ^c	11.3 ± 2.45 (21.68%) ^c	5.01	13.5 ± 3.62 (26.81%) ^c		
	20 mg	Single	Fasted	d-AMP	589 ± 84.2 (14.30%) ^c	29.4 ± 2.70 (9.18%) ^c	5.00	12.4 ± 2.05 (16.53%) ^c		
				l-AMP	225 ± 39.1 (17.38%) ^c	9.60 ± 0.97 (10.10%) ^c	4.98	15.0 ± 2.78 (18.53%) ^c		
Adolescents with ADHD (13–17 years; >75 kg) [37,82]	20 mg	Single	NR	d-AMP	936.7 ± 319 (34.06%) ^c	48.8 ± 13.5 (27.66%) ^c	6.8 ± 3.2 (47.06%) ^c	9.5 ± 2.4 (25.26%) ^c		
				l-AMP	309.0 ± 115 (34.06%) ^c	14.8 ± 4.3 (29.05%) ^c	6.9 ± 3.3 (47.83%) ^c	10.9 ± 3.1 (28.44%) ^c		
	10 mg (n = 8) [37,81,83]	Multiple	NR	d-AMP	AUC ₀₋₂₄ : 431.9 ± 123 (28.48%) ^c	28.8 ± 6.2 (21.53%) ^c	6.4 ± 3.5 (54.69%) ^c	NR		
				l-AMP	AUC ₀₋₂₄ : 138.3 ± 40 (28.92%) ^c	8.8 ± 1.9 (21.59%) ^c	6.4 ± 3.5 (54.69%) ^c	NR		
Children with ADHD (6–12 years) [37,81,83]	20 mg (n = 9)	Multiple	NR	d-AMP	AUC ₀₋₂₄ : 777.2 ± 304 (39.11%) ^c	54.6 ± 18.8 (34.43%) ^c	5.8 ± 1.8 (31.03%) ^c	NR		
				l-AMP	AUC ₀₋₂₄ : 261.6 ± 120 (45.87%) ^c	17.2 ± 6.8 (39.53%) ^c	5.7 ± 2.2 (38.60%) ^c	NR		
	30 mg (n = 6)	Multiple	NR	d-AMP	AUC ₀₋₂₄ : 1364.3 ± 364 (26.68%) ^c	89.0 ± 15.6 (17.53%) ^c	5.5 ± 2.1 (38.18%) ^c	NR		
				l-AMP	AUC ₀₋₂₄ : 443.5 ± 134 (30.21%) ^c	28.1 ± 6.5 (23.13%) ^c	5.5 ± 2.1 (38.18%) ^c	NR		

(Continued)



Table 3. (Continued).

Drug	PK Profile	Population	Dose(s) Tested (mg)	Single/multiple dosing	Fasted/ fed/ sprinkled	Enantiomer/ entity	Pharmacokinetic Parameters ^a				
							AUC _{0-∞} ^b (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	Mean ± SD (CV%)	t _{1/2} (h)
ADZENYS ER	Single peak	Healthy adults (20–70 years) (n = 42) [97,99]	18.8 mg (15 mL)	Single	Fasted	d-AMP	Mean ± SD (CV%)	Mean ± SD (CV%)	Median (range) or Mean ± SD (CV%)	Mean ± SD (CV%)	
						d-AMP	925.2 ± 209.0 (22.59%)	47.2 ± 7.68 (16.26%)	5.00 (3.00–7.50)	11.41 ± 2.27 (19.92%)	
		Healthy adults (20–68 years) (n = 30) [97,98]	18.8 mg (15 mL)	Single	Fasted	I-AMP	350.2 ± 87.02 (24.85%)	14.9 ± 2.40 (16.09%)	5.00 (3.00–8.00)	14.11 ± 3.52 (24.95%)	
						d-AMP	996.3 ± 193.7 (19.44%) ^c	51.9 ± 9.02 (17.38%) ^c	5.00 (3.00–7.00)	11.82 ± 1.83 (15.48%) ^c	
						I-AMP	370.9 ± 83.23 (22.49%) ^c	16.4 ± 2.97 (18.11%) ^c	4.95 ± 0.99 (20.00%) ^c	14.47 ± 2.80 (19.35%) ^c	
						d-AMP	961.5 ± 176.8 (18.39%) ^c	45.9 ± 7.98 (17.39%) ^c	5.16 ± 1.02 (19.77%) ^c	12.12 ± 1.90 (15.68%) ^c	
						I-AMP	357.4 ± 76.22 (21.33%) ^c	14.6 ± 2.61 (17.88%) ^c	5.47 ± 1.91 (34.92%) ^c	14.84 ± 3.07 (20.69%) ^c	
						d-AMP	1599 ± 784.4 (49.05%)	68.0 ± 12.3 (18.06%)	5.88 ± 2.16 (36.73%) ^c	12.70 ± 6.36 (50.11%)	
						I-AMP	642.1 ± 576.7 (89.81%)	23.5 ± 4.10 (17.46%)	5.93 ± 1.97 (33.24%)	15.3 ± 14.44 (94.27%)	
						d-AMP	876.9 ± 182.4 (20.81%)	44.9 ± 8.94 (19.94%)	5 (3–12)	11.25 ± 2.02 (17.95%)	
						I-AMP	320.7 ± 69.96 (21.81%)	14.5 ± 3.00 (20.74%)	5.25 (3.00–12.00)	12.94 ± 2.72 (20.99%)	
						d-AMP	856.3 ± 166.1 (19.40%)	36.3 ± 6.85 (18.88%)	7 (3–16)	11.33 ± 2.00 (17.61%)	
ADZENYS XR-ODT	Single peak	Children with ADHD (6–12 years) (n = 29) [97,99]	18.8 mg (15 mL)	Single	Fasted	I-AMP	310.7 ± 62.11 (19.99%)	11.7 ± 2.27 (19.32%)	7.50 (3.05–16.00)	13.18 ± 2.67 (20.23%)	
						d-AMP	1486.0 ± 232.3 (15.63%) ^c	86.7 ± 19.5 (22.49%) ^c	5.6 ± 86.7 ^d	9.5 ± 1.7 (17.89%) ^c	
		Healthy adults (n = 29) [91,92]	18.8 mg	Single	Fasted	I-AMP	529.1 ± 95.9 (18.13%) ^c	27.0 ± 5.2 (19.26%) ^c	5.9 ± 2.1 (35.59%) ^c	11.0 ± 2.1 (19.09%) ^c	
						d-AMP	1197.321 (22%)	54.128 (19%)	4.00 (2.00–7.00)	12.36 ± 2.95 (23.87%) ^c	
						I-AMP	461.544 (23%)	17.286 (19%)	4.00 (2.00–7.00)	15.12 ± 4.40 (29.10%) ^c	
						d-AMP	1125.248 (20%)	55.031 (18%)	5.00 (3.00–8.00)	NR	
						I-AMP	425.849 (21%)	17.683 (19%)	5.00 (3.00–8.00)	NR	
						d-AMP	1061.199 ± 309.200 (29.14%)	54.879 ± 15.221 (27.74%)	3.43 (2.92–5.93)	10.59 ± 2.01 (19.01%)	
						I-AMP	380.533 ± 112.234 (29.49%)	17.148 ± 5.206 (30.36%)	4.04 ± 1.37 (33.84%)	12.46 ± 3.15 (25.31%)	
						d-AMP			4.85 ± 1.96 (40.52%)		
						I-AMP					
						d-AMP					

(Continued)

Table 3. (Continued).

Drug	PK Profile	Population	Dose(s) Tested (mg)	Single/multiple dosing	Fasted/ fed/ sprinkled	Enantiomer/ entity	Pharmacokinetic Parameters ^a				
							AUC _{0-∞} ^b (ng·h/mL)	C _{max} (ng/mL)	Median (range) or Mean ± SD (CV%)	T _{max} (h)	t _{1/2} (h)
MYDAYIS	Single peak	Healthy adults (19–51 years) (n = 20) [100–102]	37.5 mg	Single	Fasted	d-AMP	Mean ± SD (CV%) 1084.9 ± 196.2 (18.08%) ^c	Mean ± SD (CV%) 50.3 ± 7.5 (14.91%) ^c	Median (range) or Mean ± SD (CV%) 8.2 ± 2.0 (24.39%) ^c	8.0 (NR)	Mean ± SD (CV%) 10.1 ± 1.3 (12.87%) ^c
						l-AMP	372.8 ± 73.5 (19.72%) ^c	14.7 ± 2.2 (14.97%) ^c	8.0 (NR)		12.5 ± 1.7 (13.60%) ^c
						d-AMP	1589.5 ± 360.0 (22.65%) ^c	72.3 ± 13.7 (18.95%) ^c	8.4 ± 2.1 (25.00%) ^c		10.9 ± 2.6 (23.85%) ^c
						l-AMP	545.2 ± 147.9 (27.13%) ^c	21.1 ± 3.7 (17.54%) ^c	7.0 (6.0–10.0)		13.6 ± 3.7 (27.21%) ^c
VYVANSE (capsule)	Single peak	Healthy adults (18–55 years) (n = 18) [85,86]	50 mg	Single	Fasted (n = 14)	d-AMP	1433.8 ± 339.5 (23.68%) ^c	60.0 ± 7.1 (11.83%) ^c	12.0 (8.0–14.0)	7.5 (6.0–12.0)	10.5 ± 2.1 (20.00%) ^c
						l-AMP	481.7 ± 138.4 (28.73%) ^c	17.6 ± 2.2 (12.50%) ^c	12.0 (8.0–14.0)		12.8 ± 3.3 (25.78%) ^c
						d-AMP	1497.9 ± 300.8 (20.08%) ^c	67.3 ± 7.7 (11.44%) ^c	7.5 ± (5.0–9.0)		10.6 ± 2.2 (20.75%) ^c
						l-AMP	511.4 ± 127.1 (24.85%) ^c	20.0 ± 2.5 (12.50%) ^c	8.0 (5.0–12.0)		13.0 ± 3.2 (24.62%) ^c
		Adolescents with ADHD (13–17 years) (n = 14) [101,102]	25 mg	Single	Fasted	d-AMP	651.97 ± 174.282 (26.7%) ^c	40.57 ± 9.255 (22.8%) ^c	8.00 (6.00–10.00)		11.3666 ± 1.95137 (17.2%) ^c
						l-AMP	326.09 ± 92.866 (28.5%) ^c	12.88 ± 3.205 (24.9%) ^c	7.496 ± 1.4454 (19.3%) ^c		13.1525 ± 2.90674 (22.1%) ^c
						d-AMP	844.6 ± 116.7 (13.8%) ^c	53.2 ± 9.62 (18.1%) ^c	7.738 ± 1.7332 (22.4%) ^c		8.90 ± 1.33 (15.0%) ^c
						LDX	27.88 ± 9.29 (33.3%) ^c	21.9 ± 5.97 (27.3%) ^c	3.41 ± 1.09 (31.9%) ^c		0.50 ± 0.19 (37.9%) ^c
		Children with ADHD (6–12 years) (n = 17) [35,36,84,86]	30 mg	Single	Fasted	d-AMP	1510.0 ± 241.6 (16.0%) ^c	93.3 ± 18.2 (19.5%) ^c	0.97 ± 0.14 (14.4%) ^c		8.61 ± 1.04 (12.1%) ^c
						LDX	57.90 ± 21.03 (36.3%) ^c	46.0 ± 20.7 (44.9%) ^c	3.58 ± 1.18 (33.0%) ^c		0.60 ± 0.44 (72.8%) ^c
						d-AMP	2157.0 ± 383.3 (17.8%) ^c	134 ± 26.1 (19.4%) ^c	0.98 ± 0.06 (6.2%) ^c		8.64 ± 1.32 (15.3%) ^c
						LDX	108.90 ± 50.46 (46.3%) ^c	89.5 ± 38.5 (43.0%) ^c	3.46 ± 1.34 (38.6%) ^c		0.51 ± 0.19 (37.6%) ^c
VYVANSE (capsule)	Single peak	Healthy adults (18–55 years) (n = 18) [85,86]	70 mg	Single	Fasted	d-AMP	1110 ± 314.2 (28.31%) ^c	69.3 ± 14.3 (20.63%) ^c	3.78 ± 1.01 (26.72%) ^c	3.0 (1.5–7.0)	9.69 ± 1.96 (20.23%) ^c
						LDX	66.84 ± 23.61 (35.32%) ^c	48.0 ± 23.8 (49.58%) ^c	1.15 ± 0.28 (24.35%) ^c		0.41 ± 0.07 (17.07%) ^c
						d-AMP	1038 ± 238.6 (22.99%) ^c	65.3 ± 13.4 (20.52%) ^c	4.72 ± 1.07 (22.67%) ^c		9.59 ± 1.89 (19.71%) ^c
						LDX	58.81 ± 15.26 (25.95%) ^c	26.2 ± 11.9 (45.42%) ^c	2.08 ± 0.65 (31.25%) ^c		0.63 ± 0.20 (31.75%) ^c
						d-AMP	1074 ± 220.8 (20.56%) ^c	68.4 ± 14.6 (21.35%) ^c	3.33 ± 1.19 (35.74%) ^c		9.37 ± 2.06 (21.96%) ^c
						LDX	55.10 ± 16.97 (30.80%) ^c	45.6 ± 17.0 (37.28%) ^c	0.97 ± 0.27 (27.84%) ^c		0.44 ± 0.10 (22.73%) ^c
		Healthy adults (18–55 years) (n = 11) [85,86]	70 mg	Multiple (7 days)	Fasted	d-AMP	AUC _{0-∞} : 1453 ± 645.7 (44.44%) ^c	90.1 ± 29.6 (32.8%) ^c	3.0 (1.5–7.0)		NR
						LDX	AUC ₀₋₂₄ : 1110 ± 397 (35.7%) ^c		3.68 ± 1.42 (38.5%)		NR
						d-AMP	AUC _{0-∞} : 61.06 ± 20.63 (33.79%) ^c	47.9 ± 18.6 (38.8%)	1.0 (1.0–2.0)		NR
						LDX	AUC ₀₋₂₄ : 60.7 ± 21.0 (34.6%) ^c		1.14 ± 0.32 (28.5%)		NR

(Continued)



Table 3. (Continued).

Drug	PK Profile	Population	Dose(s) Tested (mg)	Single/multiple dosing	Fasted/ fed/ sprinkled	Enantiomer/ entity	Pharmacokinetic Parameters ^a				
							AUC _{0-∞} ^b (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	
VYVANSE (chewable)	Single peak	Healthy adults (n = 36) [36,89]	60 mg	Single	Fasted	d-AMP	Mean ± SD (CV%) 1168 ± 270 (23.12%) ^c	Mean ± SD (CV%) 56.9 ± 14.7 (25.83%) ^c	Median (range) or Mean ± SD (CV%) 4.4 ± 1.2 (27.27%) ^c	Mean ± SD (CV%) 12.7 ± 2.3 (18.11%) ^c	
						LDX	AUC _{0-t} : 35.7 ± 8.9 (24.93%) ^c	32.3 ± 8.3 (25.70%) ^c	1.0 ± 0.2 (20.00%) ^c		NR
		Healthy adults (n = 35) [36,89]	60 mg	Single	Fasted	d-AMP	1073 ± 201 (18.73%) ^c	54.9 ± 11.7 (21.31%) ^c	3.9 ± 1.0 (25.64%) ^c	12.3 ± 2.1 (17.07%) ^c	
						LDX	AUC _{0-t} : 33.9 ± 29.3 (86.43%) ^c	32.3 ± 30.2 (93.50%) ^c	0.97 ± 0.17 (17.53%) ^c		NR
				Fed		d-AMP	1025 ± 199 (19.41%) ^c	52.5 ± 10.3 (19.62%) ^c	4.9 ± 0.8 (16.33%) ^c	12.5 ± 2.9 (23.20%) ^c	
						LDX	AUC _{0-t} : 39.9 ± 11.1 (27.82%) ^c	20.7 ± 8.4 (40.58%) ^c	1.36 ± 0.36 (26.47%) ^c		NR

Footnotes: ^aArithmetic mean ± SD (CV%) except for time to maximum observed plasma concentration (T_{max}), for which the median (range) is reported, unless specified otherwise; ^bAUC_{0-∞}, unless specified otherwise; ^cCV was derived using the following formula: CV% = (SD/mean) * 100%; ^dThis standard deviation is likely a typo in the publication and there are no supporting documents to verify.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; AUC_{0-∞}, area under the plasma concentration–time curve from zero to infinite time; AUC₀₋₂₄, area under the plasma concentration–time curve from zero to 24 hours; AUC_{0-t}, area under the plasma concentration–time curve from zero to the time point with the last quantifiable concentration; C_{max}, peak plasma concentration; FDA, Food and Drug Administration; LDX, lisdexamfetamine; NR, not applicable; N/A, not reported; SD, standard deviation; t_{1/2}, half-life; T_{max}, time to peak plasma concentration.

LDX was originally available only as a capsule that could either be swallowed whole or opened and sprinkled as a powder onto yogurt, water, or orange juice [36]. In the past couple of years, LDX was also formulated into a chewable tablet, thereby providing a second alternative for patients who have difficulties with swallowing [36]. Both the capsule and chewable formulations are available in dosage strengths of 10, 20, 30, 40, 50, and 60 mg, with the capsule formulation having an additional dosage strength of 70 mg. LDX administered as a capsule was found to be dose proportional between doses of 30 and 70 mg in children with ADHD, and doses of 50 and 250 mg in healthy adults [35,84].

LDX exhibits a pharmacokinetic profile with a single peak for both LDX and d-AMP. In healthy adults administered a single 70 mg capsule of LDX under fasted conditions, T_{max} was reached at about an hour for LDX and 3.8 hours for d-AMP, and the elimination $t_{1/2}$ was about half an hour for LDX and 9.7 hours for d-AMP [85,86]. Additionally, following a single-dose administration of LDX to healthy adults at doses ranging from 30 to 70 mg, C_{max} and AUC, but not T_{max} , tend to exhibit low intersubject variability (i.e. CV <30%) [36,76]. Systemic exposure to d-AMP (both AUC and C_{max}) was found to be bioequivalent when the same dose was administered to healthy adults with or without food or sprinkled into a solution; however, T_{max} was prolonged by an hour with food (i.e. high-fat meal or yogurt) [85,86]. Steady state for d-AMP was reached by day 5 after multiple dosing of once-daily LDX at 70 mg for 7 consecutive days to healthy adults under fasted conditions [87]. There was no accumulation at steady state and 95% of d-AMP was eliminated within 48 hours after the final dose on day 7 [36,87].

In children with ADHD, T_{max} of LDX and d-AMP were reached at about an hour and 3.5 hours, respectively, after administering a single dose of LDX at capsule strengths of 30, 50, or 70 mg under fasted conditions [35,36,84,86]. The elimination $t_{1/2}$ was about half an hour for LDX and approximately 9 hours for d-AMP. While both C_{max} and AUC were higher in children with ADHD compared with healthy adults, there were no differences after normalizing for dose and body weight between single doses of 30 and 70 mg [36]. Compared with MAS-ER at a single dose of 30 mg, a single 70 mg capsule of LDX administered to children with ADHD resulted in higher rates and extent of exposure to d-AMP (C_{max} : 155 vs. 119 ng/mL; AUC 1326 vs. 1019 h·ng/mL), attained peak concentrations 1.5 hours faster (T_{max} : 4.5 vs. 6 hours), and had lower intersubject variability on these pharmacokinetic parameters (CV ≤21.6% vs. ≤52.8%) [88].

The pharmacokinetics of LDX formulated as a chewable tablet were evaluated in healthy adults only, and these data are only described in the prescribing information and FDA review documents [36,89]. After a single 60 mg dose of a LDX chewable tablet under fasted conditions, T_{max} was reached at about an hour for LDX and approximately 4 hours for d-AMP. Like the capsule formulation, administration with food prolongs the T_{max} for d-AMP by 1 hour. When the chewable tablet is compared with the capsule, C_{max} and AUC were approximately 15% lower for LDX at a dose of 60 mg, but similar for d-AMP [36].

4.2.3. Amphetamine extended-release oral suspension (AMP EROS; DYANAVEL XR®)

AMP EROS is the first liquid ER formulation of AMP containing a 3.2:1 ratio of mixed d- and l-AMP salts. Like MEROS, AMP EROS utilizes the LiquiRX® drug delivery platform; however, the proportion of both IR and ER particles has not yet been described [63,90,91]. AMP EROS does not need to be reconstituted and is supplied as a bubble gum flavored suspension in bottles of 464 mL at a concentration of 2.5 mg/mL of AMP base [91].

AMP EROS is characterized by a pharmacokinetic profile with a steep ascending portion that reaches peak plasma concentrations at approximately 4 hours for both d- and l-AMP, followed by a gradual, extended period of release with an elimination $t_{1/2}$ of 12.4 and 15.1 hours for d- and l-AMP, respectively, in healthy adults receiving a single 18.8 mg dose, and 10.6 hours and 12.5 hours for d- and l-AMP, respectively, in children with ADHD administered a single 10 mg dose [91,92]. Following a single dose of 18.8 mg in healthy adults under fasting conditions, AMP EROS demonstrated bioequivalence to an equal dose of MAS IR, where C_{max} for d- and l-AMP were 102% and 106% higher, respectively, and AUC for d- and l-AMP were 106% and 111% higher, respectively [91]. Administration with a high-fat meal did not affect the bioavailability of AMP EROS in healthy adults; however, T_{max} was prolonged by an hour [91].

4.2.4. Amphetamine extended-release orally disintegrating tablet (AMP XR-ODT; ADZENYS XR-ODT®)

AMP XR-ODT is the first ER AMP to be formulated as a once-daily ODT that contains a 3:1 ratio of mixed d- and l-AMP salts [93,94]. AMP XR-ODT utilizes a cation-exchange resin technology, where AMP salt is dissolved in the presence of an exchange resin and positively charged AMP replace the Na^+ of the resin to form stable AMP microparticles that are less than 200 μm in diameter [93,95,96]. These microparticles are either left uncoated or coated, and then both compressed into ODTs, with the uncoated microparticles delivering 50% IR AMP and the coated ones delivering 50% ER AMP. AMP XR-ODT is available in six dosage strengths of 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg [94].

The pharmacokinetic profile of AMP XR-ODT is characterized by a steep ascending portion of the curve achieving peak concentration of d- and l-AMP between 5 to 6 hours after a single 18.8 mg dose in both healthy adults and children with ADHD under fasted conditions [93,94]. Following peak AMP levels, there was a gradual decline in concentrations with an elimination $t_{1/2}$ of 11.3 and 9.5 hours for d-AMP and 12.9 and 11 hours for l-AMP, in adults and children, respectively.

In healthy adults, a single 18.8 mg dose of AMP XR-ODT was found to have a comparable pharmacokinetic profile to a single 30 mg dose of MAS-ER under fasted conditions, where bioequivalence was established for C_{max} and AUC; however, AMP XR-ODT had a slightly lower early exposure in the first 5 hours postdose (17% and 15% lower for d- and l-AMP, respectively) [94,96]. While T_{max} was prolonged by 2 hours for d-AMP and 2.5 hours for l-AMP, there was no clinically significant food effect on the rate and extent of exposure of d- and l-AMP, with a 19% reduction in C_{max} and only a 1-2% reduction in AUC compared to the fasted state [94,96]. Furthermore, although an *in vitro* study found that

there was a substantial increase in AMP release in the presence of 40% alcohol, there was neither dose dumping nor changes in the extent of exposure for d- and l-AMP *in vivo* when a single 18.8 mg dose of AMP XR-ODT was administered to healthy adults with varying concentrations of alcohol (between 4% and 40%) [94,95].

4.2.5. Amphetamine extended-release oral suspension (AMP XR-OS; ADZENYS ER®)

AMP XR-OS utilizes the same drug delivery technology as AMP XR-ODT, except the microparticles are suspended in an orange flavored solution supplied in bottles of 450 mL with a 1.25 mg/mL concentration of AMP [97]. Accordingly, as expected, the pharmacokinetic properties of AMP XR-OS are comparable with those of AMP XR-ODT. After a single 15 mL (18.8 mg) dose in both healthy adults and children with ADHD under fasted conditions, AMP XR-OS exhibits a pharmacokinetic profile with peak concentrations for d- and l-AMP reached between 5 to 6 hours and elimination $t_{1/2}$ of 11.4 and 12.7 hours for d-AMP and 14.1 and 15.3 hours for l-AMP, in adults and children, respectively [97–99]. A single 15 mL dose of AMP XR-OS was also found to be bioequivalent to 30 mg of MAS ER in healthy adults in the fasted state [97]. A high-fat breakfast did not significantly affect the rate and extent of exposure of d- and l-AMP, with an 11% reduction in C_{max} and only a 3% reduction in AUC compared to the fasted state; T_{max} was delayed by half an hour for d-AMP and an hour for l-AMP [97–99].

4.2.6. Triple-bead mixed amphetamine salts extended-release (triple-bead MAS-ER; MYDAYIS®)

The latest ER AMP to be approved for the treatment of ADHD is a triple-bead MAS-ER formulation that contains a 3:1 ratio of mixed d- and l-AMP salts [100,101]. As the name implies, triple-bead MAS-ER capsules contain three types of drug-releasing beads – immediate-release beads, delayed-release beads that release AMP at a pH of 5.5, and delayed-release beads that release AMP at a pH of 7.0. Of these three bead populations, the first two bead populations are similar to those of MAS-ER. Indeed, triple-bead MAS-ER dosed at 37.5 mg was bioequivalent to MAS-ER dosed at 25 mg followed by 12.5 mg of MAS-IR 8 hours later, with comparable rates and extent of exposure of d-AMP (ratios of 101% for C_{max} and 104.4% for AUC) and l-AMP (ratios of 90.9% for C_{max} and 95.3% for AUC) [100,101].

Although pharmacokinetic studies have been conducted in healthy adults and in adolescents and children with ADHD, triple-bead MAS-ER is only approved for patients 13 years and older [101]. In healthy adults and adolescents with ADHD under fasted conditions, the single-dose pharmacokinetic profile of triple-bead MAS-ER produces one peak with peak plasma concentrations of d- and l-AMP achieved at 7 to 8 hours, and an elimination $t_{1/2}$ of 10.1 to 11.4 hours for d-AMP and 12.5 to 13.6 hours for l-AMP [100–102]. After adjusting for dose, a single dose of triple-bead MAS-ER produced 21% to 31% higher C_{max} and AUC levels for both d- and l-AMP in adolescents versus adults, suggesting that body weight may be a primary determinant of these differences [101]. There were no differences in systemic exposure to d- and l-AMP in female versus male adults [101]. In healthy adults, steady state was achieved between days 7 and 8; however, multiple once-daily dosing with triple-bead MAS-ER appears to result in accumulation, with a mean accumulation ratio of 1.6 [101].

Triple-bead MAS-ER is available in four dosage strengths of 12.5, 25, 37.5, and 50 mg, and exhibited linear dose proportionality across this dose range in healthy adults [101]. Triple-bead MAS-ER can also be administered as a whole capsule or sprinkled on applesauce, as sprinkling the contents on applesauce has been shown to be bioequivalent to taking an intact capsule in the fasted state [101,102]. Furthermore, while a high fat meal does not have a clinically significant effect on the rate and extent of exposure to d- and l-AMP (11% to 13% increase in C_{max} ; ~20% increase in AUC), T_{max} was found to be prolonged by 5 hours compared to the fasted state, which is the longest delay reported by any long-acting stimulant [101,102]. *In vitro* testing revealed that there were increases in AMP release from triple-bead MAS-ER in the presence of 20% alcohol, and more noticeably, 40% alcohol; however, *in vivo* studies have not been conducted yet [101].

4.3. Investigational extended-release stimulant formulations

There are currently seven stimulant ER formulations in development; however, no published pharmacokinetic data are available. This section describes the pharmacokinetic properties of these formulations based on information available from conference abstracts and posters. The drug delivery technologies and pharmacokinetic properties of these investigational formulations are summarized in Table 4.

4.3.1. KP415: prodrug of d-MPH

KP415 is an investigational product containing IR d-MPH and a novel prodrug of d-MPH, serdexmethylphenidate (SDX), that utilizes a Ligand Activated Therapy (LAT™) platform technology [103]. It was designed to provide both a rapid onset of d-MPH followed by a sustained release of d-MPH throughout the day.

A single- and multiple-dose pharmacokinetic study evaluated oral KP415 solutions with three different ratios of IR d-MPH and prodrug compared with OROS-MPH in healthy adults [103]. It was determined that the optimal ratio is 30% IR d-MPH to 70% of SDX. The total d-MPH equivalent dose was 40 mg, with 12 mg of IR d-MPH and 56 mg of the prodrug. This ratio was selected for further clinical development. In this study, KP415 exhibited a pharmacokinetic profile with plasma d-MPH concentrations increasing rapidly and peaking at approximately 1.5 to 2 hours after a single dose and seven doses [103]. This was followed by a gradual decline in d-MPH concentrations over a 24-hour period. Similarly, exposure to the prodrug peaked at approximately 2 hours post-dose and was eliminated by 24 hours. KP415 achieved steady-state d-MPH concentrations after 3 days. While accumulation of d-MPH at steady-state (day 7) was variable for the three different KP415 ratios (ranging from 20%–33% and 24% for C_{max} , 18%–31% and 13% for C_{min} , and 25%–34% and 11% for AUC_{0-24}), accumulation of the product was low for the optimal KP415 ratio (24% for C_{max} , 13% for C_{min} , 11% for AUC_{0-24}). A caveat to these findings is that two of 12 subjects receiving the optimal ratio of 30% d-MPH/70% SDX appeared to be slow metabolizers and were excluded from the analysis, and the impact of removing these subjects on the accumulation findings are unknown.

Table 4. Investigational long-acting stimulant formulations in the pipeline for the treatment of ADHD.

Pharmacokinetic Properties							
Drug/ Company	Phase/ FDA Status	Formulation/Delivery System	Profile	AUC (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)
				Mean ± SD (CV%)	Mean ± SD (CV%)	Median (range)	Mean ± SD (CV%)
Methylphenidate formulations							
KP415/ KemPharm [103–105]	Phase III/INDA planned for Q1 2019	30% IR d-MPH and 70% serdexmethylphenidate (SDX), a d-MPH prodrug (utilizing a LAT TM [Ligand Activated Therapy] platform technology; capsule)	Single peak	Healthy adults: AUC _{0–24} : 207.6 ± 54.4 (steady state after 7 days on 56/12 mg) Adolescents with ADHD (13–17 years): AUC _{0–24} : 171.1 ± 19.4 (single dose of 56/12 mg) Children with ADHD (9–12 years): AUC _{0–24} : 294.1 ± 98.2 (single dose of 56/12 mg) NR	Healthy adults: 20.9 ± 3.1 (steady state after 7 days on 56/12 mg) Adolescents with ADHD (13–17 years): 14.0 ± 1.7 (single dose of 56/12 mg) Children with ADHD (9–12 years): 25.9 ± 9.7 (single dose of 56/12 mg) NR	Healthy adults: 1.8 ± 0.6 (steady state after 7 days on 56/12 mg) Adolescents with ADHD (13–17 years): 4 Children with ADHD (9–12 years): 4 Children with ADHD (9–12 years): NR	Healthy adults: 8.9 ± 2.2 (steady state after 7 days on 56/12 mg) Adolescents with ADHD (13–17 years): NR Children with ADHD (9–12 years): NR
KP484/ KemPharm	Unknown/IND filed in September 2017	‘Super’ extended-release d-MPH prodrug (utilizing a LAT TM platform technology; capsule)	Single peak	NR	NR	NR	NR
CTX-1301/ Cingulate [106, 107]	Phase I/II IND planned for EOY 2018	Triple-release, multicore formulation of d-MPH (utilizing Oralogik TM technology; tablet)	Three peaks	AUC _{8–24} : 29.2 and 31.6	C _{max} (0–4 h): 4.9 and 5.3 C _{max} (4–24 h): 6.6 and 6.9	T _{max} (0–4 h): 1.6 and 1.9	4.5 and 4.3
Amphetamine formulations							
HLD100/Ironshore Pharmaceuticals [109]	Phase II completed	Delayed-release and extended-release formulation of AMP (DR/ER-AMP; utilizing DELEXIS [®] technology; capsule)	Single peak following an 8-hour delay	Adolescents with ADHD: AUC _{0–∞} (15 mg): 536.6 (24.0%) AUC _{0–∞} (25 mg): 1195.7 (42.7%) AUC _{0–t} (15 mg): 476.2 (16.8%) AUC _{0–t} (25 mg): 1022.8 (42.7%) Children with ADHD: AUC _{0–∞} (15 mg): 1039.5 (18.7%) AUC _{0–∞} (25 mg): 1752.7 (26.2%) AUC _{0–t} (15 mg): 1034.7 (31.5%) AUC _{0–t} (25 mg): 1513.0 (27.3%) NR	Adolescents with ADHD: 15 mg: 22.0 (11.6%) 25 mg: 47.9 (36.5%) Children with ADHD: 15 mg: 44.18 (29.0%) 25 mg: 70.80 (19.3%)	~8-hour delayed release Adolescents with ADHD: 18 Children with ADHD: 18	NR
AMP ER TAB/Tris Pharma [110]	Unknown	Extended-release AMP chewable tablet containing a 3.2:1 ratio of mixed d- and l-AMP salts (utilizing LiquiXR [®] technology)	Single peak	NR	NR	NR	NR
CTX-1302/ Cingulate	Phase I/II IND planned for EOY 2018	Triple-release, multicore formulation of d-AMP	Three peaks	Not published	Not published	Not published	Not published
d-ATS/ Noven Pharmaceuticals [108]	Phase II completed/ Unknown	d-AMP patch	Not published	Not published	Not published	Not published	Not published

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; AUC, area under the plasma concentration–time curve; AUC_{0–∞}, area under the plasma concentration–time curve from zero to infinite time; AUC_{0–t}, area under the plasma concentration–time curve from zero to the time point with the last quantifiable concentration; AUC_{0–24}, area under the plasma concentration–time curve from zero to 24 hours; AUC_{0–24}, area under the plasma concentration–time curve from 8 to 24 hours C_{max}, peak plasma concentration; CV, coefficient of variation; EOY, end of year; IND, investigational new drug; IR, immediate-release; MPH, methylphenidate; NDA, new drug application; NR, not reported; Q1, first quarter; SD, standard deviation; SDX, serdexmethylphenidate; t_{1/2}, half-life; T_{max}, time to peak plasma concentration.

Dose proportionality and steady-state pharmacokinetics were also evaluated in healthy adults using three doses of KP415 at the optimal ratio of 30% IR d-MPH and 70% SDX [104]. KP415 demonstrated dose proportionality across the dose range evaluated (i.e. 6 mg of IR d-MPH and 28 mg of SDX [equimolar to 20 mg d-MPH], 9 mg of IR d-MPH and 42 mg of SDX [equimolar to 30 mg d-MPH], and 12 mg of IR d-MPH and 56 mg of SDX [equimolar to 40 mg d-MPH]). Median T_{\max} occurred at 2 hours for all three doses, and plasma d-MPH levels decreased gradually after C_{\max} , with appreciable concentrations still apparent at 13 hours post-dose (~3–6 ng/mL). Furthermore, steady-state concentrations of d-MPH were achieved between the second and third day of multiple once-daily dosing. After four doses of KP415 at the highest dose, C_{\max} , C_{\min} , and AUC_{0-24} were approximately 35%, 12%, and 36% higher, respectively, relative to a single dose.

In children and adolescents with ADHD, dose-normalized exposure to d-MPH following a single-dose administration of KP415 was higher in younger children; however, when normalized for body weight, there were no differences in C_{\max} (25.0–25.3 ng/mL/[mg/kg]), AUC_{0-24} (259.4–291.8 h·ng/mL/[mg/kg]), and median T_{\max} (4 hours) [105].

4.3.2. KP484: super extend-release prodrug of d-MPH

Similar to KP415, KP484 is an investigational product containing SDX, a novel prodrug of d-MPH that utilizes LATTM platform technology. It was designed with the objective of providing ‘super extended release’ of d-MPH for patients requiring a longer duration of coverage of their ADHD symptoms. To the best of our knowledge, the pharmacokinetic properties of KP484 have not yet been published or presented at any conferences.

4.3.3. CTx-1301: triple-release multicore formulation of d-MPH

CTx-1301 is a triple-release d-MPH tablet formulation that utilizes Precision Timed ReleaseTM (PTRTM) drug delivery platform technology (formerly OralgiKTM) [106]. The multicore tablet comprises an outer IR layer, followed by an ER layer with a 3- to 4-hour delay in release, and an inner IR core that also has a 3- to 4-hour delay in release [106,107].

In a pharmacoscintigraphic study of healthy male volunteers, the *in vivo* release and pharmacokinetics of CTx-1301 were characterized and compared with d-MPH-ER (10 mg) [106]. The onset of radiolabeled *in vivo* release from the ER layer and inner IR core of CTx-1301 occurred at 4.70 ± 1.31 hours and 10.28 ± 1.70 hours, respectively [106]. Compared with d-MPH-ER, which has a pharmacokinetic profile with two peaks, the intended pharmacokinetic profile of CTx-1301 was confirmed to be triphasic with a slower controlled descent of d-MPH. The initial T_{\max} between 0 and 4 hours post-dose ($T_{\max [0-4h]}$: 1.6 and 1.9 h vs. 2.3 h) and peak d-MPH plasma levels ($C_{\max [0-4 h]}$: 4.9 and 5.3 vs. 5.9 ng/mL) were comparable between CTx-1301 and d-MPH-ER [106,107]. The half-life was extended by more than an hour in CTx-1301 (4.5 and 4.3 hours) versus d-MPH-ER (3.0 hours) [107]. Additionally, between 8 and 24 hours post-dose, CTx-1301 maintained d-MPH levels of greater than 2 ng/mL longer than d-MPH-ER, and thereby exposure was significantly higher versus d-MPH-ER (AUC_{8-24} : 29.2 and 31.6 h·ng/mL vs. 17.1 h·ng/mL; $p < 0.005$) [106,107]. Phase I/II studies on CTx-1301 are planned for 2019.

4.3.4. HLD100: delayed-release and extended-release AMP (DR/ER-AMP)

DR/ER-AMP is the first evening-dosed, once-daily ER AMP formulation developed using the same DELEXIS[®] drug delivery platform as DR/ER-MPH [108]. The single-dose pharmacokinetics of DR/ER-AMP were evaluated over a 48-hour period in adolescents and children diagnosed with ADHD and previously treated with AMP [109]. DR/ER-AMP was administered in the evening (9 PM) at a dose of either 15 or 25 mg depending on the previous AMP dose of each participant. DR/ER-AMP exhibited a pharmacokinetic profile with a delay of approximately 8 hours in the initial release of AMP. This delay was followed by a period of extended, controlled release, where plasma AMP concentrations increased rapidly and peaked at approximately 18 hours postdose. As expected, exposure to AMP was higher in both children and adolescents administered 25 mg of DR/ER-AMP compared with those administered 15 mg. After adjusting for dose and body weight, the pharmacokinetics of children and adolescents were comparable (C_{\max} : 83.3 vs. 85.5 ng/mL/[mg/kg]; $AUC_{0-\infty}$: 2172.2 vs. 2104.4 h·ng/mL/[mg/kg]).

4.3.5. Amphetamine extended-release tablet (AMP ER TAB)

Similar to AMP EROS, AMP ER TAB is a tablet ER formulation of AMP containing a 3.2:1 ratio of mixed d- and l-AMP salts that utilizes the LiquiRX[®] drug delivery platform [63]. The tablet can either be swallowed whole or chewed. The comparative bioavailability of AMP ER TAB versus AMP EROS and the effect of food on the pharmacokinetics of AMP ER TAB were evaluated in healthy adults [110]. Following a single dose of 20 mg under fasting conditions, AMP ER TAB swallowed whole or chewed demonstrated bioequivalence to AMP EROS at a dose of 2.5 mg/mL for both d- and l-AMP. AMP ER TAB exhibited a similar pharmacokinetic profile to AMP EROS, with a steep ascending portion that reached peak plasma concentrations at approximately 5 hours for both d- and l-AMP, followed by a gradual, extended period of release. Administration with a high-fat meal did not affect the bioavailability of AMP ER TAB when it was administered chewed.

4.3.6. CTx-1302: triple-release multicore formulation of d-AMP

CTx-1302 is the AMP version of CTx-1301. To the best of our knowledge, the pharmacokinetic properties of CTx-1302 have not yet been published or presented at any conferences, and the manufacturer plans to conduct phase I/II studies in 2019.

4.3.7. d-ATS: d-AMP transdermal patch

d-ATS is the first transdermal patch containing d-AMP. It was found to be effective in a phase II, randomized, double-blind, placebo-controlled, crossover laboratory classroom study of youth with ADHD aged 6 to 17 years [108]. However, the pharmacokinetic properties of d-ATS are unknown, and to the best of our knowledge, no other studies have been published or presented at conferences.

5. Pharmacokinetic considerations in the use of long-acting stimulant formulations

5.1. Pharmacokinetic profile and the resulting pharmacokinetic-pharmacodynamic relationship

During the past 20 years, several long-acting stimulant formulations have been developed to overcome the challenges associated with multiple dosing of IR stimulants and prevent acute tolerance (i.e. tachyphylaxis) associated with a flat, zero-order release profile. To varying extents, most ER formulations exhibit dual drug release processes, whereby a particular proportion of the drug is released immediately, and the remainder is released over an extended period of time [19,23,111]. The initial rapid release of drug results in an ascending release profile, which is then followed by a subsequent, prolonged phase of drug delivery [21]. However, the distinct pharmacokinetic profiles of these ER formulations are heavily influenced by their varying drug delivery mechanisms, including the rate and timing of drug release throughout the day, and the magnitude of plasma concentrations achieved [19,23–25,33,112]. Furthermore, the onset and duration of action have been shown to closely mirror formulation-specific drug release mechanisms and their resulting pharmacokinetic profiles [19,24,33,112–114]. Despite these differences among long-acting stimulant formulations, currently there is very little guidance on how to select the most appropriate formulation for use in a particular clinical situation. A better understanding of the unique pharmacokinetic profiles produced by various formulations and the resulting pharmacokinetic-pharmacodynamic relationships afford clinicians further prescribing flexibility to individualize and optimize therapy in their patients with ADHD [19,24,25,33,112].

The shapes of pharmacokinetic profiles vary significantly from one formulation to another, and are dependent on the IR:ER ratios and/or the dissolution time course of the ER component (summarized in Tables 2 and 3 and described in Sections 4.1 and 4.2). Some formulations produce pharmacokinetic curves with two peaks (i.e. formulations having IR and ER properties with varying proportions of the dose released at different times), while others produce a smooth-rising pharmacokinetic curve with a single peak (i.e. formulations that have overlapping release of their IR and ER components or those utilizing unique drug delivery mechanisms, such as prodrugs or a combination of multiple polymers to produce DR and ER properties). Despite these differences, all long-acting stimulant formulations are designed with the aim of producing an ascending plasma concentration profile necessary for preventing acute tolerance.

On the basis that the greatest therapeutic improvement occurs during the absorption phase of the pharmacokinetic profile [22,115–117], clinicians should be aware of these unique patterns of absorption to best define the most appropriate stimulant formulation for their patients. There are several formulation-dependent characteristics and/or pharmacokinetic properties that can be used as predictors of pharmacodynamic response. These include: 1) the proportion of dose formulated as IR versus ER, which ultimately influences the onset and duration of action; 2) the proportion of early drug exposure during a particular timeframe that corresponds with patient-specific needs relative to the total exposure,

which can be used as a proxy of relative early pharmacological onset; and 3) T_{max} , which can be used as an indirect surrogate for gauging formulation-dependent durations of efficacy [24].

Many ER formulations have a certain proportion of the total dose that is formulated as IR, ranging anywhere from 20% to 50% (Table 1). Formulations with a higher proportion of dose formulated as IR or those that release their IR and ER components closer together tend to exhibit steeper slopes on the ascending portion of the pharmacokinetic curve, earlier peak plasma concentrations, and greater early drug exposures relative to total exposure, which in turn, is typically reflected by an earlier onset of action [19,24,25,33,118]. However, it is important to note that these formulations also tend to have less drug available for the rest of the day, and therefore, despite having an earlier onset of efficacy, tend to have a shorter duration of action [19,25,33,114,118]. Furthermore, there are some formulations that produce an ascending drug release profile, but do not have a specific IR component built into their formulation (i.e. MTS, LDX, DR/ER-MPH) (Table 1). Accordingly, rather than solely relying on IR:ER ratios, clinicians may want to consider comparing the proportions of partial exposure during a particular timeframe that correspond with the patient-specific needs compared to the total exposure [24,118]. In a recent review, early exposure was evaluated for several MPH formulations by calculating the percent of early exposure for the first 3 hours relative to total exposure [24]. Not surprisingly, it was determined that IR MPH formulations tend to provide greater early exposures over the first 3 hours after dosing (IR MPH: 33%; IR d-MPH: 39%) compared to ER MPH formulations (ranging from 13% to 30%). Additionally, ER MPH formulations with higher proportions of their dose formulated as IR tend to have greater early exposures than those with lower proportions (e.g. MPH-LA, which has 50% of the dose formulated as IR, has approximately twice [30% vs. <17%] the exposure to MPH during the first 3 hours compared to other formulations that have less than 25% of their dose formulated as IR) [24].

Comparisons of pharmacokinetic properties based on serial blood sampling of drug concentrations in one population (usually adults) with the pharmacodynamic profiles assessed using the Swanson, Kotkin, Atkins, M-Flynn, Pelham (SKAMP) rating scale in laboratory classroom studies of children with ADHD revealed that there is a close relationship between pharmacokinetic and pharmacodynamic properties of both IR and ER stimulants [19,25,33,112–114,118]. Specifically, it was found that pharmacodynamic patterns closely mirrored the expected pharmacokinetic profiles of various ER stimulant formulations, such that plasma drug levels measured over time across the day corresponded with their profile of efficacy. Additionally, clinical superiority at a particular time of the day was typically achieved by the formulation with the highest expected plasma drug concentration [19,24,25,33,112–114,118]. For example, results of the COMACS study demonstrated that when MPH-CD and OROS-MPH are administered in roughly equivalent daily doses, MPH-CD produced significantly better improvements in symptoms during the morning, efficacy was similar with both MPH-CD and OROS-MPH in the afternoon, and OROS-MPH was superior in the evening [113,114]. These findings closely reflected the expected differences in their

pharmacokinetic profiles, with MPH-CD achieving peak plasma MPH concentrations earlier in the day, and OROS-MPH producing peak plasma MPH concentrations later in the day. Accordingly, the duration of the absorption phase on the pharmacokinetic profile, which is best characterized by T_{max} , could serve as an indirect surrogate for predicting formulation-dependent duration of efficacy [24,113]. Indeed, previously published reviews summarizing and comparing the pharmacokinetic-pharmacodynamic properties of various formulations have concluded that formulations with longer T_{max} values tend to have longer durations of efficacy [19,24,33,118].

While it has been suggested that the magnitude of clinical effect is associated with plasma concentrations and that greater efficacy at any point in time is typically achieved by the formulation with the highest expected plasma drug concentration (i.e. higher C_{max}), direct comparisons between different formulations should not be made from absolute plasma concentrations for a few reasons, including: i) these concentrations are dose-dependent, ii) the extent of drug absorption necessary or the ultimate concentration responsible for the maximal clinical response is unknown, and iii) there is considerable interindividual variability in the pharmacokinetic profiles of many stimulants (discussed further in Section 5.2) [33,112–114,116,118,119]. Additionally, if not titrated appropriately, higher doses may increase the risk of adverse events. From a physiological perspective, it is well established that DAT occupancy is a key driver of clinical efficacy. Imaging studies in the human brain following oral administration of MPH have demonstrated that, to a certain extent, plasma concentrations are correlated with DAT occupancy, but once maximal DAT occupancy is achieved, increases in plasma MPH concentrations beyond the threshold plasma concentration resulted in DAT saturation, which presumably would preclude any additional clinical benefit [116,119]. It has also been suggested that the therapeutic effects of MPH are associated with slowly ascending plasma concentrations and presumably smooth rising dopamine levels that mimic those of tonic dopamine cell firing as opposed to rapid changes in plasma concentrations and presumably fast dopamine increases that mimic phasic firing, which are associated with the reinforcing effects of MPH [30,116]. Therefore, in addition to necessitating an ascending plasma concentration to prevent acute tolerance, it appears that there is an optimal rate of drug release that results in an ascending plasma concentration profile that produces an increase in tonic signaling without an increase in phasic signaling. Unfortunately, there is no single pharmacokinetic parameter that can describe this complex process. That said, recent pharmacokinetic-pharmacodynamic modeling using data for several ER MPH formulations has attempted to characterize the optimal drug release characteristics needed for optimal clinical benefit (discussed further in Section 7) [111,120].

In the case of formulations that produce pharmacokinetic profiles with two peaks, it is important to consider whether the initial peak plasma concentration is followed by continued absorption to a second higher peak or a trough prior to the second peak. It has been suggested that formulations that produce peaks and troughs in plasma concentrations may lead to ‘waxing and waning’ of therapeutic effects throughout the day and potentially rebound [21,22,121]. Conversely, it has also been argued that troughs coinciding

with mealtimes and bedtime may allow for normal appetite and sleep schedule, respectively [67,122].

Taken together, a clear understanding of the different pharmacokinetic profiles produced by various long-acting stimulant formulations, as well as an appreciation of their drug delivery characteristics, may be useful for clinicians in gauging the potential therapeutic advantages of each formulation and facilitating individualization of ADHD treatment. The choice of ER formulation and duration of daily drug exposure will depend on the profile of action required over time to target the specific periods of the day and meet the situational needs of each patient with ADHD (e.g. early morning routine, length of school or work day, homework or work load).

5.2. Variability

There is considerable variability in both the pharmacokinetics of stimulants across the day at an individual level, as well as in response [18,76,118,123]. Several factors potentially influence or contribute to the variability seen in individuals treated with stimulants, including drug specific factors (e.g. drug release mechanisms, route of administration, site of drug release), patient characteristics (e.g. age, gender), lifestyle/environment (e.g. diet, concomitant medications use, alcohol), or genetics (e.g. gene polymorphisms in enzymes responsible for drug metabolism) (discussed in further detail in subsequent sections) [76]. Additionally, imaging studies have demonstrated that there is large variability between individuals in MPH-induced changes in dopamine that are likely due to differences in dopamine cell activity (dopamine release) between individuals, suggesting that variability is also dependent, in part, on the state of the dopamine system [116].

A common way of estimating the level pharmacokinetic variability between individuals receiving the same dose at the population level (interpatient variability) and within the same individual with repeated drug administration (intrapatient variability) is to determine the coefficient of variation (CV) [35,76]. The percent CV is calculated by determining the degree of variance around the mean (i.e. standard deviation/mean \times 100%), with CVs of 30% or greater often considered highly variable [76]. An important limitation of determining the level of variability using this calculation is that the percent CV will be heavily dependent on the denominator. Furthermore, direct comparisons of CVs between studies cannot be made because of differences in study designs, patient populations, methodologies used for quantification of plasma concentrations, and doses administered [76]. Nevertheless, given that CVs are not reported in all pharmacokinetic studies, we used this calculation to determine the percent CVs for all available pharmacokinetic data reported in Tables 2 and 3 as means of providing context to the reader. As expected, it is apparent that there are differences in the degree of interindividual variability not only between ER formulations, but also between studies of the same formulation. Among MPH formulations, the CVs ranged widely from 4.2% to 73.9% for AUC, 6.1% to 62.4% for C_{max} , and 0.2% to 65.7% for T_{max} ; however, for all pharmacokinetic parameters, except $t_{1/2}$, CVs were typically near and above the 30% threshold for high variability

(Table 2). Among ER AMP formulation, the CVs for d-AMP ranged from 13.8% to 49.1% for AUC, 9.2% to 34.4% for C_{\max} , and 19.3% to 54.7% for T_{\max} , and the CVs for l-AMP ranged from 17.4% to 89.8% for AUC, 10.1% to 39.5% for C_{\max} , and 19.8% to 54.7% for T_{\max} (Table 3). Despite this, across all AMP formulations, most pharmacokinetic parameters had achieved CVs that were near or below the 30% threshold for high variability. Interestingly, pharmacokinetic parameters for LDX had CVs that were generally above the 30% threshold for high variability, even though the resulting d-AMP pharmacokinetics were typically below this threshold.

Both ER MPH and AMP formulations with similar $t_{1/2}$ to IR MPH (~2.5 to 3.5 hours) or IR AMP (d-AMP: 9 to 11 hours; l-AMP: 11 to 14 hours) tended to have less variability in their $t_{1/2}$ than those with higher $t_{1/2}$. Accordingly, a higher $t_{1/2}$ likely reflects an elimination phase that does not consist of pure elimination, but rather the sum of continued absorption and elimination resulting in a prolonged absorption window. To the best of our knowledge, only one pharmacokinetic study to date has evaluated variability in the average time to achieve various plasma MPH concentrations along the ascending portion of the pharmacokinetic curve (see Section 4.1.10) [73]. Similar evaluations with all other formulations would provide meaningful information about their variability on the portion of the pharmacokinetic profile associated with the greatest therapeutic improvement.

Given the significant variability in the pharmacokinetics and response to stimulants, it can be concluded that there is no one treatment that is superior for all patients and underscores the importance of individualizing treatment by titrating the dose of each formulation for optimal effects in each patient while minimizing adverse events [18,76,118,123].

5.3. Comparative bioavailability

From a regulatory perspective, bioavailability is defined by the extent and rate of absorption, where the extent of absorption is determined by total exposure (AUC), and the rate of absorption is typically described by the surrogate parameter, C_{\max} , because no single parameter can characterize this complex process [25]. While many ER MPH and AMP formulations generally have comparable relative bioavailability in the extent of absorption to either an IR formulation administered twice- or thrice-daily or an appropriate reference drug, they are not considered bioequivalent, particularly when comparing partial AUCs and C_{\max} , due to differences in absorption rates related to their varying drug release patterns throughout the day (Table 5) [24,25]. However, there are a few notable exceptions to this trend. Some ER formulations were specifically designed to be bioequivalent to a particular reference standard (e.g. AMP XR-ODT and AMP XR-OS were designed to be bioequivalent to MAS-ER) [93,99,124], and some ER formulations have different sites of drug release compared to most ER formulations, which typically target the upper GI tract. For example, it is well known that the MTS dermal patches circumvent first-pass metabolism, resulting in more MPH being bioavailable [10,26], as well as much higher l-MPH levels versus orally administered MPH formulations [61]. Furthermore, DR/ER-MPH has been shown to have a lower relative bioavailability

in both the extent and rate of absorption to a similar dose of thrice-daily IR MPH, which is likely due to its targeted delivery to the less absorptive colon, resulting in not only prolonged absorption, but also fecal elimination of unabsorbed MPH [73–75]. Accordingly, healthcare professionals need to be aware that most ER MPH and AMP formulations are not bioequivalent in both the extent and rate of absorption. To avoid therapeutic failure, ER formulations should not be used interchangeably, and caution should be taken when switching patients from one formulation to another by considering their unique patterns of drug release and their resulting pharmacokinetic profiles.

5.4. Dose proportionality

Generally, the pharmacokinetics of MPH and AMP are unaffected by increasing dose. Pharmacokinetic studies conducted with ER formulations revealed that plasma concentrations of MPH or AMP tend to be linear within the approved range of doses and that the extent and rate of absorption are dose proportional (Table 5). It should be noted that, unlike d-MPH, l-MPH levels have been shown to increase disproportionately in pharmacokinetic evaluations of some ER MPH formulations (e.g. OROS-MPH and MTS) [40,45,61]. The effects of this, however, are not likely to be clinically significant because plasma concentrations of l-MPH are significantly lower than d-MPH when administered orally (e.g. 40-fold lower with OROS-MPH [45]) and d-MPH is the more pharmacologically active enantiomer [31].

5.5. Accumulation

Most product labels of stimulant ER formulations report that accumulation is not expected at steady state, and that steady state is typically achieved within approximately a few days to a week (Table 5). However, there are a couple of notable exceptions worth mentioning. Among ER MPH formulations, MTS patches tend to reach steady state by approximately 14 days, and significant accumulation with repeated fixed dosing was observed with prolonged treatment [60,61]. In children and adolescents with ADHD administered a 12.5 cm² MTS patch for 9 hours per day for 7 days, steady-state AUC for d-MPH increased by 13% and 14%, respectively, relative to those anticipated with single-dose pharmacokinetics [61]. After 28 days of administration, further accumulation was evident in both children and adolescents, with steady-state AUC increasing by 64% and 76%, respectively, and C_{\max} increasing by approximately 69% and 100%, respectively. This accumulation could not be explained by accumulation predicted from single-dose pharmacokinetic; there was no evidence that clearance or rate of elimination changed between single and repeat dosing; and there were no differences in dosing patterns between treatments, age, race or gender [61]. Accordingly, these findings suggest that transdermal absorption of MPH may increase with repeated dosing of MTS and that further accumulation of d-MPH with MTS is related to continuance of dosing [60,61]. Among ER AMP formulations, triple-bead MAS achieved steady state between 7 and 8 days with a mean accumulation ratio of 1.6 [101].



Table 5. Dose proportionality, comparative bioavailability, multiple dose pharmacokinetics, and the effect of food, alcohol, age, and gender on the pharmacokinetic properties of long-acting stimulants.

Brand Name	Dose proportionality	Comparative bioavailability	Food effect		Alcohol effect	Age effect	Gender effect	Multiple dose
			High-fat meal	Sprinkled				
Methylphenidate formulations								
ADHANSIA XR [77,78]	NR	At steady state, increased C_{max1} by 22% and no difference in C_{max2} , increased AUC_{0-24} by 50%, and increased C_{min} by 288% at 100 mg qd vs. IR MPH at 20 mg tid	AUC: No effect C_{max1}/C_{max2} : No effect T_{max1}/T_{max2} : Delayed by 1 h	No effect on absorption or exposure (100 mg dose)	<i>In vitro</i> : No increase in release at 5%, 20%, and 40% in the first hour and at 5% and 20% in the second hour. At 40% alcohol, 71% and 61% of MPH release in the second hour at 70 mg and 100 mg doses, respectively. <i>In vivo</i> : At 40% alcohol, 1.4-fold increase in C_{max} and 1.3-fold increase in AUC at 70-mg dose.	When adjusted for body weight, PK profile of children (6–12 years) is comparable to adolescents (13–17 years) and adults	Insufficient experience to detect gender variations	Steady state after 3 days
APTENSIO XR [66,67,69,125]	Not studied	Comparable relative bioavailability to IR MPH tid (80 mg qd vs. 25 mg tid)	Decreased C_{max2} , but increased average C_{max} by 28% and AUC by 19%	No effect on C_{max} , AUC, and T_{max} (80 mg dose)	At 40% alcohol, 96% of MPH was released within 2 hours	PK profile qualitatively similar in children with ADHD (6–12 years) and healthy adults	Insufficient experience to detect gender variations	Steady state on day 4 After 4 days, C_{max} increased by 16% ^a and AUC increased by 5% ^a in healthy adults dosed 80 mg
CONCERTA [40,41,44,45]	Dose proportional C_{max} and $AUC_{0-\infty}$ of d-MPH at doses of 18, 36, and 54 mg; however, C_{max} and $AUC_{0-\infty}$ of l-MPH increased disproportionately (plasma concentrations of l-MPH were 1/40 to d-MPH)	Comparable relative bioavailability to IR MPH tid (18 mg qd vs. 5 mg tid)	C_{max} : Increased by 12% to 30% AUC: Increased by 20% T_{max} : Delayed by 1 hour	N/A	<i>In vitro</i> : At 40% alcohol, no increased release of MPH in the first hour at 18 mg dose	Increase in age resulted in increased apparent oral clearance (58% increase in adolescents vs. children), which could be explained by body weight differences	No difference in mean dose-adjusted $AUC_{0-\infty}$ between men and women (36.7 vs. 37.1 ng·h/mL)	No accumulation: No differences in PK, including AUC and $t_{1/2}$, after single- and multiple-dose administration of doses between 18 and 144 mg

(Continued)

Table 5. (Continued).

Brand Name	Dose proportionality	Comparative bioavailability	Food effect			Alcohol effect	Age effect	Gender effect	Multiple dose
			High-fat meal	Sprinkled					
COTEMPLA XR-ODT [38,72]	NR	C_{max} and AUC were 26% and 6% higher, respectively, at 51.8 mg qd vs. 60 mg qd of MPH-CD	AUC _{0-∞} : Increased by 16% C_{max} : Decreased by 24% T_{max} : Shortened by 0.5 h	N/A	<i>In vitro</i> : Dose dumping potential at 40% alcohol	C_{max} : Higher in children vs. adults (57% ^a higher), but similar between adolescents vs. adults AUC: Higher in children vs. adults (95% ^a higher), but similar between adolescents vs. adults Clearance: When body weight normalized, similar in children, adolescents, and adults	Insufficient experience to detect gender variations	NR	
DAYTRANA [27,60,61]	Dose proportional C_{max} and AUC of d-MPH, and C_{max} of l-MPH at doses of 10 mg/9 h to 30 mg/9 h. AUC of l-MPH was slightly greater than proportional to patch dose.	Children with ADHD (6–12 years) : C_{max} and AUC were 19% ^a and 5% ^a higher for d-MPH, respectively, at 10 mg/9 h vs. 18 mg of OROS-MPH. Adolescents with ADHD (13–17 years) : C_{max} and AUC were 16% ^a and 19% ^a lower for d-MPH, respectively, at 10 mg/9 h vs. 18 mg/9 h. Similar AUC (102%) and C_{max1} (106%), lower C_{max2} (82%), and fewer peak and trough fluctuations at 20 mg qd vs. 10 mg of IR d-MPH bid.	N/A	N/A	N/A	C_{max} : 124% ^a higher in children vs. adolescents at 10 mg/9 h AUC _{0-∞} : 104% ^a higher in children vs. adolescents at 10 mg/9 h	No difference after adjusting for body weight differences	Steady state likely after 14 days. After 28 days, C_{max} increased by 69% and 100%, and AUC increased by 64% and 76% in children and adolescents with ADHD, respectively, dosed 10 mg/9 h.	
FOCALIN XR [55–58]	Healthy adults : Dose proportional at 5, 10, 20, 30, and 40 mg		Not studied	Not studied	Not studied	Not studied in children <18 years	C_{max1} was 45% higher and C_{max2} was slightly, but not significantly, higher in women; these patterns remained even after adjusting for body weight.	Not studied	
JORNAY PM [73–75,126]	Dose proportional C_{max} (104%) and AUC (96%) between 20 and 100 mg	Relative bioavailability of 73.9% at similar dose of IR MPH given tid	AUC: No effect (decreased 3%) C_{max} : Decreased 14% T_{max} : Delayed by 2.5 h	No effect on C_{max} (decreased 2%), AUC (increased 3%), and T_{max} at 100 mg dose	<i>In vitro</i> : At 40% alcohol, 97% of MPH released in 2 hours. No increase in MPH release observed in the presence of 5% to 20% alcohol.	When adjusted for body weight and dose, PK profile is comparable in children (8–12 years), adolescents (13–17 years), and adults.	Not studied	Simulated steady state after 2 days	
METADATE CD [46–48,50]	Children with ADHD : dose proportional at doses of 20 and 40 mg Healthy adults : dose proportional between 10 and 60 mg	C_{max} and AUC were slightly lower at 20 mg qd vs. IR MPH at 10 mg bid dosed at 0 and 4 h	AUC: Increased 16.8% C_{max} : Increased 32.3% T_{max} : Delayed by 1 h	No effect on C_{max} (increased 6%) and AUC (increased 4%)	<i>In vitro</i> : At 40% alcohol, 84% of MPH released in the first hour at 60 mg dose.	NR	Single-dose PK was similar in adult men and women.	Studied in children; did not report on accumulation or steady state	

(Continued)

Table 5. (Continued).

Brand Name	Dose proportionality	Comparative bioavailability	Food effect			Alcohol effect	Age effect	Gender effect	Multiple dose
			High-fat meal	Sprinkled					
QUILLICHEW ER [70,71,127]	NR	Healthy adults: C_{max} and AUC were 20% and 11% lower, respectively, at 40 mg qd vs. IR MPH (chewable) at 20 mg bid dosed 6 h apart	AUC: Increased 4% C_{max} : Increased 20% T_{max} : No effect	N/A		At 40% alcohol, 90% of MPH released in the first 30 minutes at 40 mg dose.	Not studied in children <18 years	Insufficient experience to detect gender variations	NR
QUILLIVANT XR [62,64,128]	NR	Relative bioavailability of 95% at 60 mg qd vs. IR MPH (oral solution) at 30 mg bid dosed 6 h apart	AUC: Increase 19% C_{max} : Increase 28% T_{max} : Shortened by 1 h	N/A		<i>In vitro:</i> At 20% alcohol, 20% increase in MPH exposure. No effect at 5% and 10% alcohol.	C_{max} : ~2-fold higher in children (9–12 years) vs. adults, but similar in adolescents (13–15 years) vs. adults	Insufficient experience to detect gender variations	NR
RITALIN LA [51,53,54]	Healthy adults: Slight upward trend in AUC and C_{max1} and C_{max2} at 20 mg to 40 mg	Comparable to same total dose of IR-MPH given in 2 doses 4 hours apart	AUC: No effect C_{max} : No effect on C_{max1} and C_{max2} Decreased C_{max2} by 25% T_{max} : Variable delay in T_{max1} and T_{max2}	No effect		<i>In vitro:</i> At 40% alcohol, 98% of MPH released in the first hour at 40 mg dose.	C_{max} : 2-fold higher in children (7–12 years) vs. adults (18–35 years) at 20 mg dose	No apparent PK difference between healthy male and female adults	No accumulation is expected
Amphetamine formulations									
ADDERALL XR [37,79–83]	Linear PKs between 20 and 60 mg in adults and adolescents (>75 kg), between 10 and 40 mg in adolescents (≤ 75 kg), and between 5 and 30 mg in children (6–12 years)	Comparable PK profiles of both d-AMP and l-AMP at 20 mg qd vs. IR AMP 10 mg bid dosed 4 hours apart	AUC: No effect (3% ^a and 5% ^a decrease in d-AMP and l-AMP, respectively) C_{max} : 10% ^a decrease in both d-AMP and l-AMP T_{max} : Prolongs by 2.5 h for d-AMP and 2.7 h for l-AMP at 30 mg dose	No effect		NR	When adjusted for body weight and dose, children had 30% less exposure vs. adults	20%–30% greater exposure in women vs. men; however, no difference after adjusting for body weight	Accumulation not expected at steady state in children
ADZENYS ER [97–99]	NR	Comparable bioavailability to MAS ER (18.8 mg qd vs. 30 mg qd)	AUC: No effect (96.78% and 96.60% for d- and l-AMP) C_{max} : 11% reduction (88.68% and 89.63% for d- and l-AMP, respectively) T_{max} : 5 vs. 5.5 h for d-AMP and 5 vs. 6 h for l-AMP	N/A		<i>In vitro:</i> Substantial increase in AMP release at 40% alcohol, but not 5%, 10%, and 20%.	Based on PK of MAS-ER (ADDERALL XR)	Based on PK of MAS-ER (ADDERALL XR)	NR
ADZENYS XR-ODT [94–96,124]	Not studied	Comparable bioavailability (AUC: 99% and 103% for d-AMP and l-AMP, respectively; C_{max} : 97% and 99% for d-AMP and l-AMP, respectively) to MAS-ER (18.8 mg qd vs. 30 mg qd)	AUC: No effect (99% and 98% for d- and l-AMP, respectively) C_{max} : 19% reduction (81% and 82% for d- and l-AMP, respectively) T_{max} : Prolonged by 2 h for d-AMP and 2.25 h for l-AMP	N/A		<i>In vitro:</i> Substantial increase in AMP release at 40% alcohol, but not 5%, 10%, and 20%. <i>In vivo:</i> No dose dumping or change in the extent of absorption at 4%, 20%, or 40% alcohol.	Based on PK of MAS-ER (ADDERALL XR)	Based on PK of MAS-ER (ADDERALL XR)	Not studied

(Continued)

Table 5. (Continued).

Brand Name	Dose proportionality	Comparative bioavailability	Food effect			Alcohol effect	Age effect	Gender effect	Multiple dose
			High-fat meal	Sprinkled					
DYANAVEL XR [91,92]	NR	Relative bioavailability of 106% and 111% for d-AMP and d-AMP, respectively, at an equal dose of IR MAS	AUC: Decreased by 5.7% for d-AMP and 7.4% for l-AMP C_{max} : 2% increase in both d- AMP and l-AMP T_{max} : Delayed by 1 h for both d-AMP and l-AMP	N/A	<i>In vitro</i> : Increased induced dose dumping at 40% alcohol, but not observed at lower concentrations.	NR	NR	Steady state achieved on day 4	
MYDAYIS [100–102]	Linear dose proportionality between 12.5 and 50 mg	Comparable PK profiles of both d-AMP (C_{max} 101.0%; AUC 104.4%) and l-AMP (C_{max} 90.9%; AUC 95.3%) at 37.5 mg vs. MAS-ER at 25 mg qd plus 12.5 mg IR MAS given 8 h later	AUC: no effect (91.1% and 88.7% for d-AMP and l-AMP, respectively) C_{max} : decreased by 15% (85.3% and 85.2% for d-AMP and l-AMP, respectively) T_{max} : prolonged by 5 h for d-AMP and 4.5 h for l-AMP	No effect on AUC (95.8% and 94.8% for d-AMP and l-AMP, respectively) or C_{max} (95.8% and 96.9% for d-AMP and l-AMP, respectively)	<i>In vitro</i> : Increased AMP release at 20% alcohol, and more noticeably, at 40% alcohol.	C_{max} and AUC were 21%–31% higher for d-AMP and l-AMP in adolescents (13–17 years) vs. adults (19–51 years)	Similar exposure to d-AMP and l-AMP in women (n = 41) and men (n = 61)	Steady state achieved between 7–8 days, with a mean accumulation ratio of 1.6	
VYVANSE (capsule) [34,36,84,85,88]	Linear PK between 30 and 70 mg in children (6–12 years) and between 50 and 250 mg in adults.	30% ^a higher AUC and C_{max} for d-AMP at 70 mg LDX vs 30 mg MAS-ER	AUC: no effect (95.93% for d-AMP) C_{max} : no effect (94.26% for d-AMP) T_{max} : prolonged by 1 h for d-AMP [Note: no effect of yogurt or orange juice on AUC and C_{max} of d-AMP]	No effect on AUC (99.40% for d-AMP) or C_{max} (98.57% for d-AMP)	NR	When adjusted for body weight and dose, AUC and C_{max} were similar in children with ADHD (6–12 years) as adults (single doses of 30 to 70 mg)	AUC and C_{max} for d-AMP and LDX higher in women; however, similar when adjusted for dose and body weight	Steady state achieved by day 5 No accumulation at steady state	
VYVANSE (chewable) [36,89]	Not studied in children	LDX: C_{max} and AUC 15% lower at 60 mg qd of VYVANSE chewable vs. capsule d-AMP: C_{max} and AUC similar between the VYVANSE chewable and capsule	Exposure (AUC and C_{max}) 5% to 7% lower for d-AMP T_{max} : prolonged by 1 h	N/A	NR	Not studied	Not studied	Not studied	

Footnotes: ^aDerived using the following formula: % increase or decrease = (treatment/reference) * 100%.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMP, amphetamine; AUC, area under the plasma concentration–time curve from zero to infinite time; AUC_{0-12} , area under the plasma concentration–time curve from zero to the time point with the last quantifiable concentration; AUC_{0-24} , area under the plasma concentration–time curve from zero to 24 hours; bid, twice daily; C_{max} , peak plasma concentration; C_{max1} , first peak plasma concentration; C_{max2} , second peak plasma concentration; ER, extended-release; IR, immediate-release; LDX, lisdexamfetamine; MAS, mixed amphetamine salts; MAS-ER, mixed amphetamine salts extended-release; MPH, methylphenidate; MPH-CD, methylphenidate controlled-delivery; N/A, not applicable; NR, not reported; OROS-MPH, osmotic-release oral system methylphenidate; PK, pharmacokinetic; qd, once daily; $t_{1/2}$, half-life; tid, thrice daily; T_{max} , time to peak plasma concentration; T_{max1} , first time to peak plasma concentration; T_{max2} , second time to peak plasma concentration.

Whether this accumulation is unique to triple-bead MAS is unknown because, with the exception of LDX, accumulation with other ER AMP formulations was either not studied or reported in their respective product labels (Table 5).

5.6. Food effect

The potential effects of food or a high-fat meal on the absorption of MPH and AMP from long-acting stimulant formulations have been studied and specifically discussed above for each formulation in Sections 4.1 and 4.2. Overall, the effect of food on the pharmacokinetics of orally administered long-acting stimulants is generally minimal and not considered clinically relevant (Table 5). Following a high-fat meal, there is the potential for T_{\max} to be either prolonged or shortened and the rate and extent of absorption (C_{\max} and AUC) to be either slightly decreased or increased compared to the fasted state [20,25]. Among the approved orally administered ER MPH formulations, T_{\max} was generally delayed by 1 to 2.5 hours, except for MPH XR-ODT and MEROS, which had T_{\max} shortened by 0.5 and 1 hour, respectively. The extent of absorption was either unchanged or increased by up to 20%, and peak concentrations were generally increased by 12% to 32%, except for PRC-063, which had C_{\max} unchanged, and DR/ER-MPH and MPH-LA, which had C_{\max} reduced by 14% and 25%, respectively. Of the approved ER AMP formulations, there was minimal food effect on the extent and rate of absorption, with C_{\max} typically reduced by up to 19% and AUC either unchanged or reduced by up to 11%; however, there was a delay in T_{\max} of 0.5 to 5 hours, with triple-bead MAS-ER having the most prolonged T_{\max} . For the most part, these food effects on the pharmacokinetics of MPH and AMP are minimal, not considered clinically meaningful, and do not warrant prohibition of administering stimulant medications with meals, provided that they are taken consistently with or without food during titration and treatment [18].

For dosage forms that can be sprinkled on soft foods (e.g. applesauce, yogurt) or liquids (e.g. orange juice), there were no changes in the bioavailability observed compared to the fasted state (Table 5). Accordingly, these formulations can be sprinkled without any concerns, provided that the contents are consumed immediately after sprinkling and not chewed.

5.7. Administration

All long-acting stimulants are formulated to offer the convenience of once-daily dosing; however, certain dosing forms (e.g. tablets and capsules) may present an issue for some patients who have difficulties with swallowing [24,26]. Fortunately, there are many dosage form options available that ameliorate the issue of swallowing. For example, as mentioned before, many capsules containing beads have been found to be bioequivalent when they are opened and sprinkled onto soft foods or liquids to facilitate administration. If patients are using the sprinkling method, clinicians need to ensure that they do not chew the contents and administer the contents immediately. Otherwise, improper administration using the sprinkling method may affect the intended drug release properties, result in dose dumping (i.e. premature

drug release from the dosage form), or not allow for a reliable delivery of the full dose [10,26]. Some of these challenges can also be overcome by using other formulations, such as transdermal patches, liquid suspensions, chewable tablets, and orally disintegrating tablets. However, these also have limitations of their own. Transdermal patches require patients to wear the patch for a specific period of time (i.e. up to 9 hours), and some patients have reported skin irritations at the patch site [10,61,129]. Transdermal patches also circumvent first-pass metabolism, and therefore, result in different pharmacokinetics (e.g. plasma d- and l-MPH levels are higher with MTS versus orally administered MPH formulations) [10,26]. Furthermore, liquid suspensions rely on patients to accurately measure and administer the dose, and in some cases, require reconstitution with water (e.g. MEROS), which may result in human error [62,91,97]. Lastly, with the exception of DR/ER-MPH, which is administered in the evening, all long-acting stimulants are administered in the morning. Depending on patient preferences and lifestyle, there may be a benefit to dosing in either in the evening or morning (e.g. hectic morning routines may result in patients forgetting to take their medication).

5.8. Gastrointestinal tract

Given that most formulations are administered orally, it is important that clinicians consider their patient's history of GI disorders, concomitant medications, or dietary factors that may affect certain GI properties along with their choice of therapy. This is because variations in GI properties (e.g. pH, transit, anatomy) may affect drug release and site of absorption, and thereby, the pharmacokinetic profile. For instance, drug release from formulations that rely solely on one particular built-in trigger in their drug release technology, such as the pH-dependent polymers in triple-bead MAS-ER, may be affected in individuals who have variability in pH throughout the GI tract [76]. Additionally, product labels for AMP formulations caution that GI acidifying agents (e.g. guanethidine, reserpine, glutamic acid HCl, ascorbic acid) may lower AMP absorption, whereas GI alkalinizing agents (e.g. sodium bicarbonate; proton pump inhibitors [e.g. omeprazole]) may increase absorption [36,37,91,94,97,101]; however, coadministration with these pH-altering agents has not been thoroughly investigated [20]. Some formulations may also be affected by the physical characteristics of a patient's GI tract. For example, the OROS-MPH tablet can only be swallowed whole and remains intact throughout the GI until it gets excreted in the stool. This may have clinical implications for patients who have GI abnormalities, such as narrowing or obstruction [18,25]. Then again, certain oral formulations are unlikely to be affected by variations in GI properties because they are designed with multiple polymers that ensure drug release and subsequent absorption are not dependent on any single factor, such as a pH trigger or normal variations in gastrointestinal transit (e.g. DR/ER-MPH), or they are formulated as prodrugs that are metabolically converted into the active drug once absorbed into the systemic circulation (e.g. LDX) [35,73,74,76].

5.9. Age and body weight

The ability to prescribe certain long-acting stimulant formulations depends on the approved indication. While most available ER formulations are indicated for patients aged 6 years and older, there are a couple of exceptions. MPH-CD is limited to youth aged 6 to 15 years [47], MPH XR-ODT is limited to children and adolescents aged 6 to 17 years [72], and triple-bead MAS-ER is limited to adolescents and adults aged 13 years and older [101]. Currently, there are no stimulant ER formulations indicated for preschool children.

Among the pharmacokinetic studies of stimulant ER formulations conducted across age groups (i.e. in children, adolescents, and adults), the majority demonstrated that children in general have higher plasma levels and overall exposures to MPH and AMP than adults (Table 5). However, when normalized for dose and body weight, the rate and extent of exposure were found to be generally similar across age groups with both ER MPH and AMP formulations. This observation suggests that body weight is a primary determinant of the differences in observed plasma concentrations across the lifespan [20]. That said, a small pharmacokinetic study comparing the pharmacokinetics of IR MPH in preschool and school-aged children with ADHD found that preschool children had significantly greater C_{max} and slower clearance than school-aged children to the same weight-adjusted dose, suggesting that age may significantly affect absorption and metabolism of MPH in very young patients [130]. The slower clearance of MPH could be attributed to not only the smaller size but also the less fully developed metabolic enzymes in preschool children compared to school-aged children.

Lastly, clinicians may have a preference to use one stimulant type versus another across different age groups. Indeed, based on both efficacy and safety data evaluated in a recent meta-analysis of 133 double-blind randomized controlled trials of medications for ADHD, it was concluded that the preferred first-choice medication for the short-term treatment of ADHD was MPH in children and adolescents, and AMP in adults [26].

5.10. Gender differences

There is a dearth of clinical studies specifically designed to evaluate gender differences in the pharmacokinetics of stimulants [20,122]. Furthermore, the number of male participants in ADHD studies typically exceeds that of female participants making it difficult to conduct appropriate subgroup comparisons. Accordingly, most product labels state that there is insufficient evidence to detect gender variations or that these differences were not studied (Table 5). Among the product labels that do report on gender differences, it appears that females in general tend to have higher exposures to MPH and AMP than males; however, these differences disappear after adjusting for dose and body weight, suggesting that they are primarily a function of body weight rather than gender [36,37,40,47,53,61,101].

5.11. Genetic factors and drug-drug interactions

Genetic variability and potential drug interactions with the major enzymes involved in the metabolism of stimulants may lead to clinically significant alterations in their pharmacokinetics [20,31].

Polymorphisms in the *CES1* gene that result in diminished CES1A1 enzyme activity, and thereby reduced MPH metabolism, have been previously described [31,131]. However, the frequency of these variants is low (<5%), and the impact at the population level is unknown [131]. Conversely, genetic variability in AMP metabolism may be clinically relevant because the gene responsible for CYP2D6 activity is highly polymorphic [20]. In theory, poor metabolizers would require lower doses of AMP and ultrarapid metabolizers would require higher doses of AMP. However, the impact of CYP2D6 polymorphisms on AMP metabolism are yet to be elucidated, and the presence of alternate pathways involved in the metabolism of AMP may mitigate the impact of such genetic variations. Accordingly, despite pharmacogenetic testing becoming more affordable and the presence of testing panels for ADHD medications, testing for genes involved in the metabolism of stimulants it is not recommended.

In regard to drug-drug interactions, certain drugs (e.g. aripiprazole, perphenazine, thioridazine, fluoxetine) have been shown to be potent CES1A1 inhibitors that increase plasma concentrations of MPH when administered concomitantly [31]. Surprisingly, despite the long history of clinical use, there are few documented reports of drug-drug interactions that either inhibit or induce AMP metabolism. Nevertheless, clinicians need to be aware of all medications that their patients are taking and adjust stimulant doses when drug interactions are likely to affect their metabolism.

5.12. Alcohol

Approximately 30% of adolescents and young adults with ADHD take their stimulant medications concomitantly with alcohol and other drugs [95]. Alcohol may alter the pharmacokinetic profile of long-acting stimulant formulations either through an interaction with the metabolism of the active drug or by compromising the drug release mechanisms of the formulation [24,95,132]. Therefore, the potential for alcohol-induced increases in plasma concentrations or dose dumping of stimulants is very relevant to clinicians treating ADHD because there is a strong link between ADHD and alcohol abuse.

While there have been few studies characterizing the effects of alcohol on the metabolism of MPH and AMP, it appears that the metabolism of both stimulants is to some extent inhibited by alcohol [24,95]. As mentioned previously (see Section 3.4), MPH is primarily metabolized by hepatic CES1A1, with CES1A1 having a 6-fold higher preference for l-MPH versus d-MPH, resulting in higher concentrations of the more pharmacologically active d-MPH enantiomer [31]. When MPH is co-administered with alcohol, it inhibits CES1A1-mediated MPH hydrolysis by catalyzing the enantioselective transesterification of MPH into the metabolite ethylphenidate [24]. The presence of ethylphenidate has been shown to be accompanied by significantly higher plasma d-MPH concentrations and potentiated euphoric effects in humans [24]. In the case of AMP, a limited number of pharmacokinetic studies in rodents reported that AMP metabolism is inhibited by alcohol; however, these effects have not been characterized in humans [95].

Alcohol may also affect the pharmacokinetics of stimulants by altering the dissolution of the active drug from their formulations [24,95]. ER formulations typically contain more

active drug than IR formulations, and if their drug release mechanisms are compromised by alcohol, there may be a concern for dose dumping. Accordingly, the FDA requires that all ER medications undergo *in vitro* dissolution testing with varying concentrations of alcohol of up to 40%. According to product labeling, *in vitro* dissolution studies have shown that the majority of available long-acting stimulant formulations have a substantial increase in active drug release in the presence of 40% alcohol, but not at lower concentrations (Table 5). However, it has been suggested that *in vitro* dissolution data may not always predict the likelihood of dose dumping *in vivo* [95]. Additionally, the compositions of various ER formulations differ and may not be affected by alcohol in the same manner.

Unfortunately, to date, there have been only two studies funded by manufacturers that evaluate the *in vivo* effects of alcohol on the pharmacokinetics of long-acting stimulants – one with PRC-063 and the other with AMP XR-ODT [78,95]. In the case of PRC-063, there was a 1.4-fold increase in C_{max} and 1.3-fold increase in AUC when a 70 mg dose was co-administered in the presence of 40% alcohol [78]. Conversely, alcohol concentration ranging from 4% to 40% had no impact on the pharmacokinetic profile of AMP XR-ODT, providing some reassurance that its pharmacokinetics are not altered in the presence of alcohol [95]. Whether differences in the metabolism of the active drug, composition of the formulation, or both are responsible for the differences in the way alcohol affects the *in vivo* pharmacokinetics of these stimulant formulations is unknown. A recent study in healthy human volunteers attempted to answer this question by administering alcohol 4 hours after dosing either MPH-LA or d-MPH-ER, both of which contain a 50:50 IR to ER MPH ratio with the ER portion released 4 hours after administration [132]. Despite allowing the necessary time for gastric dissolution of the IR portion of the dose and the gastric emptying of the ER portion, alcohol had still potentiated the euphoric effects of MPH, thereby suggesting that the MPH-alcohol interaction is related to a more general inhibition of CES1A1 by alcohol rather than based on the formulation dissolution effects of alcohol. Nevertheless, future *in vivo* studies of long-acting stimulant formulations and alcohol coadministration are needed to provide further insights into the safe use of the plethora of stimulants available for the treatment of ADHD, particularly among adolescents and young adults. For the time being, clinicians may consider using ethylphenidate as a biomarker for comorbid alcohol abuse disorder in patients with ADHD taking MPH formulations [24].

5.13. MPH versus AMP

There are currently no reliable predictors of response to a particular stimulant [123]. While stimulants have long been recommended as first-line pharmacotherapy for ADHD, there are inconsistencies in the treatment recommendations in current guidelines [133]. Most guidelines and consensus statements recommend stimulants without identifying an agent of first choice nor offer any distinctions between MPH and AMP [2,11,13,14], whereas some recommend MPH over AMP for children [15,133]. Because AMP is thought to work through a different mechanism of action than MPH, a lack of response

to one class of psychostimulant does not preclude response to another class [122,123]. Therefore, when the initial choice of stimulant fails to deliver an optimal response or exhibits intolerance, then the patient becomes a candidate for an alternate stimulant (i.e. formulation and/or class of stimulant). Interestingly, a recent systematic review and network meta-analysis on the comparative efficacy and tolerability of medications used for managing ADHD in children, adolescents and adults concluded that the preferred first pharmacological choice for the treatment of ADHD in children and adolescents is MPH, whereas AMP is preferred in adults [133]. Lastly, since isometric mixtures are not bioequivalent, pharmacological differences in the ratios of enantiomers may also contribute to clinical differences [123].

6. Safety

Despite differences in formulations, the tolerability and safety profile of stimulants are generally comparable. The most commonly reported adverse events in children, adolescents, and adults with ADHD treated with MPH and AMP are decreased appetite and sleep problems [18,19,123,134–138]. Other common adverse events of stimulants include abdominal pain, weight loss, anxiety, dizziness, irritability, headache, mood swings (affect lability), tics, nausea, and vomiting [19,23,123,134–138]. These are rarely serious, often transient, and usually managed by dose titration or changing formulations [123].

In a Cochrane review of 185 clinical trials of children and adolescents with ADHD treated with MPH, it was found that the most common non-serious adverse events were appetite suppression (risk ratio [RR] of 3.66, 95% confidence interval [CI] 2.56–5.23) and sleep problems (RR 1.60, 95% CI 1.15–2.23), and that there is no evidence that MPH increases the risk of serious adverse events [136,137]. In a separate Cochrane review of 23 clinical trials of children and adolescents with ADHD treated with AMP, it was reported that AMP was associated with a higher proportion of participants experiencing decreased appetite (RR 6.31; 95% CI 2.58–15.46), insomnia (RR 3.80; 95% CI 2.12–6.83), and abdominal pain (RR 1.44; 95% CI 1.03–2.00) [138].

Furthermore, all stimulants are controlled substances and their FDA-approved product labels carry a black box warning for abuse and dependence. Stimulants have the potential for abuse; however, current data suggest that ER formulations are less likely to be misused than IR formulations [134,135]. That said, some ER formulations have the potential to dose dump when taken with high concentrations of alcohol. Accordingly, prior to being prescribed a stimulant, all patients should be evaluated for a risk or history of substance abuse and monitored for signs of abuse and dependence while on therapy.

Lastly, all stimulants have several warnings and precautions listed in their product labels including cardiovascular events, increases in heart rate and blood pressure, psychiatric or manic symptoms, priapism, peripheral vasculopathy (e.g. Reynaud's phenomenon), and growth suppression [135].

7. Conclusion

In the past two decades, efforts to achieve an earlier onset and/or extended duration of drug release, enhanced safety, and dosing

convenience have led to the development of multiple ER MPH and AMP formulations utilizing various drug delivery technologies (e.g. osmotic release systems, microbeads with increasingly more complicated functional coatings, varying proportions of IR and ER components, ion-exchange mechanisms, prodrugs), enantiomers and/or salts, and dosage forms (e.g. capsules containing composite or mixed beads, disintegrating tablets, chewable tablets, patches, liquid suspensions). Accordingly, each formulation is characterized by a distinct drug release profile resulting in a unique pharmacokinetic profile, which in turn, translates into varied patterns of therapeutic effect throughout the day. Some formulations produce pharmacokinetic curves with two peaks, while others produce a smooth-rising pharmacokinetic curve with a single peak. Some formulations produce unique pharmacokinetic profiles (e.g. LDX, DR/ER MPH), while others have similar pharmacokinetic profiles to previously approved stimulants but offer a more convenient dosage form for patients who have difficulties with swallowing (e.g. AMP XR-ODT and AMP OS-ER to MAS-ER). Nevertheless, all long-acting stimulant formulations are designed with the aim of producing an ascending plasma concentration profile to prevent acute tolerance and on the basis that the greatest therapeutic improvement occurs during the absorption phase of the pharmacokinetic profile.

While this tremendous diversity of available long-acting stimulant formulations may be overwhelming and increase the complexity of selecting the most appropriate therapy, it also affords clinicians further prescribing flexibility to individualize and optimize therapy specifically based on their patient's clinical needs, characteristics, and dosing preferences. To do this rationally, a clinician needs to appreciate and consider the distinctive pharmacokinetic properties of these varying stimulant formulations, including but not limited to the shape of the pharmacokinetic profile, differences in the rate and extent of absorption, variability, dose proportionality, comparative bioavailability, and potential for accumulation with multiple dosing. Additionally, clinicians need to understand that several factors can affect the pharmacokinetics of MPH and AMP, lead to increased variability, and thereby affect their resulting efficacy and safety. Some factors are dependent on the formulation and active drug (e.g. drug release mechanisms, route of administration, metabolism, site of drug release), while others are influenced by patient characteristics (e.g. age, gender, body weight), lifestyle/environment (e.g. diet, concomitant medications use, alcohol), or genetics (e.g. gene polymorphisms in enzymes responsible for drug metabolism). Given that many factors can affect the pharmacokinetics of long-acting stimulants and that there are currently no reliable biomarkers that can predict individualized response to long-acting stimulants, ADHD therapy should be individualized to the clinical needs of the patient and guided by titration until a suitable maintenance dose is achieved.

8. Expert opinion

Based on the available pharmacokinetic-pharmacodynamic evidence suggesting that the absorption phase better correlates with therapeutic benefit than the elimination phase, the development of novel long-acting stimulant formulations has

focused primarily on optimizing and prolonging the absorption phase of the pharmacokinetic curve [22,116,117]. However, this concept should not be considered conclusive given the limitations in the evidence base [25]. Furthermore, while there is an increasing awareness of the distinct pharmacokinetic properties of the various long-acting stimulant formulations, there is a dearth of well-designed head-to-head clinical trials evaluating the differences in pharmacodynamic response, particularly between newer long-acting stimulant formulations [19,25]. Accordingly, the clinical implications of any pharmacokinetic differences remain speculative and need to be confirmed and quantified using novel methodologies that allow for more direct and appropriate pharmacokinetic-pharmacodynamic comparisons.

The concept of acute tolerance remains theoretical and is mostly based on studies that made the correlation between pharmacokinetics and pharmacodynamics using serial blood sampling of MPH concentrations in one group (i.e. typically in healthy adults, but sometimes in children and adolescents with ADHD) and the evaluation of response in another group (i.e. typically in laboratory classroom studies of children with ADHD) [25]. To date, these findings have not been replicated in a pharmacokinetic-pharmacodynamic study largely due to the logistical and ethical limitations of designing such complex clinical trials in pediatric patients. Serial intravenous blood sampling necessary for defining the pharmacokinetics in children is limited by sampling volumes, the number of samples that can be taken safely, and number of participants who can be assessed [25,139]. Additionally, serial blood sampling may interfere with the behavior of children and collection of multiple response variables during a laboratory classroom assessment, potentially affecting clinical outcomes [25,139]. Recent efforts have been made to develop and successfully validate a minimally invasive sampling technique for high-throughput quantification of MPH using dried blood sampling (DBS) from finger pricks combined with liquid chromatography with tandem mass spectrometry (LC-MS-MS) in accordance with the FDA's *Guidance for Bioanalytical Method Validation* [139]. Novel and rapid sampling techniques, such as DBS, may facilitate future research on the pharmacokinetic-pharmacokinetic relationship of MPH, particularly in pediatric patients with ADHD, by allowing more frequent sampling in larger study populations with less effort and interference with pharmacodynamic assessments.

Furthermore, pharmacokinetic-pharmacodynamic comparisons have been limited to using time-dependent pharmacodynamic data collected from children in a laboratory classroom setting. This is because SKAMP and Permanent Product Measure of Performance (PERMP) are the only assessment tools capable of measuring hourly changes in the impairment of laboratory classroom-observed behaviors and performance, respectively, which allow for determining the onset and duration of action, as well as performing correlations with time-based pharmacokinetic data [25,118]. While studies conducted in a laboratory school setting control for context and timing of these assessments, they are usually inclusive of the school day only, limited to youth with ADHD, and lack many features of the natural environment of home, school, and extracurricular activities [113]. It is also uncertain whether the same patterns of efficacy would be observed in

a typical school setting where the child with ADHD would be predominantly surrounded by other students not affected by this disorder [113]. Therefore, additional studies evaluating the time-dependent effects of long-acting stimulants across the entire day (i.e. not just the school day), in other age groups (e.g. adults and preschoolers), and in more naturalistic settings are warranted. The development of novel, age-appropriate, time-based scales that assess symptoms and functional impairments related to ADHD would facilitate the research community in conducting such naturalistic studies and allow for better pharmacokinetic-pharmacodynamic comparisons between various formulations.

Pharmacokinetic-pharmacodynamic modeling is increasingly being utilized in drug development, clinical trial design, and for regulatory and therapeutic decisions to predict the time course of drug exposure and clinical response, identify factors that influence efficacy and safety, and individualize treatment in patients [111]. Given the plethora of long-acting stimulant formulations already available and additional investigational products in development, it is prudent to define and implement a rational modeling framework that accurately evaluates drug release characteristics and distinct pharmacokinetic profiles of different formulations in relation to an optimal clinical response [111,140]. Indeed, a recent study funded by the FDA used a model-based approach with literature data to link MPH exposure and clinical response characteristics of multiple ER MPH formulations with the aim of identifying the optimal *in vivo* drug release properties appropriate for maximizing the clinical benefit in the treatment of ADHD [111]. With OROS-MPH used as a reference drug, this modeling work by Gomeni and colleagues revealed that the optimal MPH release pattern for formulations exhibiting dual release characteristics is as follows: 1) approximately 20% of the dose released in the first process followed by the remainder of the dose in the second process; 2) a shorter time for delivering the initial fraction of the dose and a prolonged time for delivering the second fraction; and 3) a slower rate of release during both processes. Furthermore, an extension of this work proposed a convolution-based modeling approach to facilitate the development of drug formulations with optimal *in vivo* release properties by using *in vivo-in vitro* correlation (IVIVC) as a tool for maximizing the benefit-risk ratio of a treatment [120]. Specifically, a surface response analysis was used to identify the drug-related properties that could affect the clinical benefit of a treatment by connecting *in vitro* and *in vivo* drug release, *in vivo* drug release with pharmacokinetics, and pharmacokinetics with pharmacodynamics.

Modeling can also be used with existing long-acting stimulant formulations to inform the dose titration process or make predictions about the relative clinical benefit of formulations that have not been studied in head-to-head trials. Currently, when starting or switching to a new long-acting stimulant, clinicians advise patients to initiate therapy on a low dose and then titrate the dose up until symptom control is achieved without affecting tolerability [141]. However, dose titration can be a time-consuming process that leaves patients at subtherapeutic levels until an optimal dose is determined. Additionally, when switching from one formulation to another, clinicians are faced with the challenge of determining how to provide comparable coverage quickly without a lapse in response

[123]. To date, two separate studies sought to develop the population pharmacokinetic-pharmacodynamic models for MLR-MPH and MPH XR-ODT to simulate pharmacodynamic responses for a range of body weights and doses, with the goal of facilitating the dose titration process by predicting an optimal dose for these formulations based on patient body weight [141,142]. Furthermore, another study sought to develop a pharmacokinetic-pharmacodynamic model for DR/ER-MPH and compare its clinical benefit to four other ER MPH formulations using the previously described model developed by Gomeni and colleagues for formulations with dual release characteristics [143]. The model revealed that DR/ER-MPH produces a clinical response that occurs earlier in the morning, remains constant with less fluctuation throughout the day, and has a dose-dependent duration of effect lasting into the evening versus OROS-MPH, MPH-CD, MEROS, and d-MPH-ER.

Taken together, less invasive and high-throughput quantification techniques and novel time-based scales are being developed to further advance our understanding of the pharmacokinetic-pharmacodynamic relationships of long-acting stimulants and facilitate better comparisons between various formulations through head-to-head clinical trials across different age groups, settings, and temporal periods. Until these advances in ADHD research are validated and optimized, model-based approaches can be applied such that more well-informed and cost-effective decisions can be made to ensure that the development of novel stimulant formulations is optimized to specifically target treatment gaps in ADHD and that existing drugs are used appropriately to individualize therapy.

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M Komolova is an employee of Highland Therapeutics Inc., Toronto, ON, Canada.

FR Sallee is an employee of Ironshore Pharmaceuticals Inc., Durham, NC, USA and serves on the advisory board/board of directors of P2D Bioscience

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