The Pharmacokinetics and Pharmacogenomics of Psychostimulants

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KEYWORDS

• Psychostimulants • Amphetamine • Methylphenidate • Pharmacokinetics
• Pharmacodynamics • Pharmacogenomics

KEY POINTS

- Both stimulants are rapidly absorbed with short half-lives leading to the development of multiple extended-release dosage forms. There is significant interindividual variability in the pharmacokinetic disposition of both medications.
- Amphetamine (AMP) undergoes a high degree of oxidative metabolism forming multiple inactive metabolites while methylphenidate (MPH) is primarily metabolized by hydrolysis forming one major inactive metabolite.
- At present, pharmacogenomic testing to guide the treatment of attention-deficit/hyperactivity disorder (ADHD) cannot be routinely recommended.
- Although frequently used in combination with a variety of other medications there is little evidence that psychostimulants participate in pharmacokinetic drug interactions as a "victim" or "perpetrator."

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder beginning in childhood and often persisting into adulthood with an estimated worldwide prevalence in children and adolescents between 3% and 10%.[1–3] Symptoms of ADHD typically begin during early childhood or adolescence, persist over time, are pervasive across situations and can lead to significant impairments. Childhood ADHD symptoms may persist into adulthood in 60% or more of cases.[4,5] A variety of guidelines and algorithms are available recommending treatment approaches to ADHD with both medical and nonmedical approaches typically advocated.

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Nonpharmacological treatments include interventions such as behavioral modification and social skills training.[6,7]

With regard to neuropharmacology, converging evidence points to abnormalities of the monoamines dopamine (DA) and norepinephrine (NE) involving their synthesis, metabolism, and transport.[3,8,9] Further, the catecholaminergic systems and their associated transporters, and receptors which serve as the primary neural targets of both DA and NE can be subject to influence by any number of genetic variants which may alter these proteins and compromise overall function. Likewise, the function and expression of intra- and extracellular enzymes involved in both the biosynthesis and degradation of monoamines can be subject to the influences of genetic variation. Although DA and NE have been studied and conceptualized as two separate systems, they are increasingly appreciated to overlap in numerous ways including their biosynthetic pathway, corelease from noradrenergic neurons, innervation of similar and shared intracellular signaling pathways.[10]

Psychostimulant agents used in the treatment of ADHD are believed to optimize catecholamine signaling in the prefrontal cortex and neuropsychological and neuroimaging studies have implicated the fronto-subcortical networks of the brain as being of particular significance in the underlying dysfunction in ADHD.[11–13] Perturbations in DA and NE metabolism and turnover, as well as alterations in associated transporters and receptors, are theorized as major contributors to the pathophysiology of ADHD.

The medications with the greatest efficacy in ADHD are the psychostimulants amphetamine (AMP) and methylphenidate (MPH) which primarily target central DA and NE transporters (NET). With approximately 30 distinct psychostimulant formulations available for clinical use in the US, it is noteworthy that the primary differences between these products are the dosage forms (eg, capsules, transdermal systems, oral suspensions) and the pharmaceutical technologies they use (eg, osmotic-release systems, coated beads, etc.) to disperse drug at programmed times and doses. Otherwise, notwithstanding some differences in isomer composition (ie, racemic vs scalemic [non-50:50 ratio, eg, mixed AMP salts] mixtures vs enantiopure formulations) all of these products contain either MPH or AMP. Indeed, the only psychostimulant that was FDA approved for the treatment of ADHD since MPH (Ritalin) approval in 1955 which represented a novel chemical entity was the drug pemoline (Cylert) approved in 1975. Pemoline was later associated with hepatotoxicity and subsequently withdrawn from the market in 2005. Thus, almost half a century has passed since the last psychostimulant was approved for use for ADHD in the US.

AMP and MPH have been in continuous clinical use for well more than 60 years–longer than any other agents in clinical psychopharmacology. They are also some of the most effective medications available in terms of effect size and their ability to rapidly relieve core target symptoms of the disorder. Despite this extensive track record, up to 35% of patients may not respond adequately to a given psychostimulant and may discontinue treatment or otherwise switch to nonstimulant ADHD medications.[14,15] Poor treatment response and adverse effects are the most frequently cited reasons for discontinuation. Side effects and tolerability remain an issue for many patients and common adverse “class effects” associated with psychostimulants are often dose-related and include abdominal pain, decreased appetite, headache, and insomnia.[16] Other, less common yet more concerning and serious adverse drug reactions (ADRs) can include the exacerbation of tic disorders, substantial changes in blood pressure (BP), tachycardia, and dyskinetic movements and in rare instances, psychotic symptoms. An analysis of 49 clinical trials as well as postmarketing ADR data related reports linked visual hallucinations and other psychotic symptoms while taking psychostimulants, which suggested an association.[17] It was noted in this

analysis that these serious but relatively infrequent ADRs involving psychotic symptoms and significant BP elevations are more consistent with manifestations of stimulant overdose or toxicity, and suggest that the individuals experiencing these effects may have been manifesting the clinical signs of substantially elevated stimulant blood concentrations.[17] As monitoring of psychostimulant medication levels is not clinically useful nor generally performed, the detection of abnormally elevated (or lowered) systemic concentrations or identification of genetically aberrant metabolizers has had a low likelihood of being documented in the course of clinical practice. Thus, despite the extensive clinical experience with psychostimulants, there remains an unmet need to fully understand the basis for significant inter-individual differences in drug disposition, adverse events, and therapeutic response. Moreover, initial dosing and titration of psychostimulants continue to be approached on an empirical basis.

This article will briefly review the pharmacology and pharmacodynamics of the psychostimulants, discuss candidate gene association studies relevant to pharmacodynamics and mechanism of action. Next, the fundamental pharmacokinetic characteristics of the psychostimulants will be discussed, issues with MPH and AMP will be discussed as well as pharmacogenomic studies relevant to drug dispositional issues involving these agents. Potential drug–drug interaction (DDIs) liabilities will also be discussed.

PHARMACODYNAMICS

Although AMP and MPH are two of the most thoroughly studied drugs in all of the biomedicine, their theoretic mechanism(s) of action continue to be refined. Overall, the net pharmacologic effect of each of these agents is to increase the availability of both DA and NE in the neurosynapse. The molecular structures of both MPH and AMP share a phenethylamine moiety (**Fig. 1**) which superimposes on its putative neural substrates, DA and NE, which in theory provides the basis of their requisite receptor interactions. Nevertheless, there are significant differences between how these medications exert these pharmacologic effects, which will be reviewed briefly.

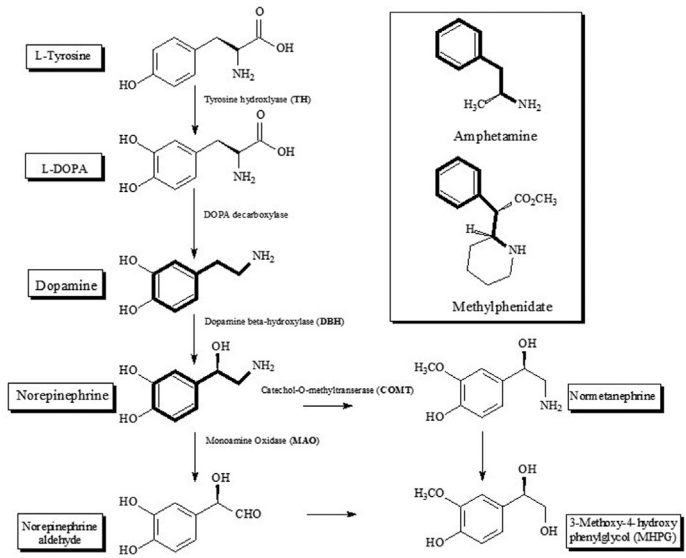

Fig. 1. General biosynthesis and degradation pathway of dopamine and norepinephrine.

Amphetamine

The preponderance of mechanistic evidence underlying the psychostimulant effects of AMP supports an AMP-induced increase in extracellular DA and NE mediated by efflux of the cytoplasmic monoamines through the DA transporter (DAT; SLC6A3) and NET (SLC6A2), respectively. AMP dramatically increases the concentrations of extraneuronal monoamines within their associated synapses through a reversal of the functional role of DAT and NET, and to a much lesser degree, serotonin (5-hydroxytryptamine [5-HT]) reuptake transporter. AMP seems to compete with endogenous monoamines for transport into the nerve terminals via DAT and NET. AMP binds to these respective transporter proteins localized on their presynaptic terminals, leading to a conformational change that moves the bound AMP to the interior of the neuron, and subsequently reverses the vesicular monoamine transporter (VMAT). This process has been described as "reverse transport" or "retro-transport," and the primary mechanism of action of AMP is that of a catecholaminergic releasing agent.[18,19] Although animal studies indicate that both *d*- and *l*-AMP release DA in the striatum and nucleus accumbens, the *d*-isomer seems to exhibit the greatest potency. It is known, however, that both isomers exert therapeutic effects. These intraneuronal dynamics subsequently produce a large efflux of displaced stores of monoamines into the synaptic cleft as the transporter releases the catecholamine on returning to its resting conformation.[20] There is also evidence that AMP has the additional action of inhibiting MAO and thereby inhibiting the degradation of cytosolic monoamines, potentially contributing to the molecule's therapeutic effects. In summary, recent studies suggest that AMP must be actively transported by DAT, NET as well as VMAT in tandem to induce its psychostimulant/therapeutic effects.[21]

Methylphenidate

MPH elicits its primary pharmacodynamic effects by blocking the reuptake of DA and NE into the presynaptic neuron through the inhibition of the DAT (SLC6A3) and NET (SLC6A2) thus resulting in increases in extracellular synaptic concentrations of DA and NE which may in turn bind to their respective transporters (ie, the DAT or NET) or to DA or NE receptors.[6,15] These hypothesized pharmacologic actions are supported by reductions in ligand binding observed in PET and SPECT studies. A redistribution of vesicular monoamine transporter 2 (VMAT-2) has also been reported. The pharmacologic activity of *dl*-MPH seems to reside almost entirely within the *d*-isomer.[22,23] There is some binding of *d*- MPH as an agonist at the 5-HT1A receptor but the significance of this observation is unclear.[24] Thus, while AMP and MPH are distinct in their pharmacologic mechanisms of action, they are primary if not unifying pharmacologic effect is to provide increased extracellular DA and NE in the neurosynapse.

Pharmacogenomic considerations related to psychostimulant pharmacodynamics

Genetics are widely believed to play a role in the etiology of ADHD and at least a partial role in treatment response to psychopharmacological agents including psychostimulants.[25] Genetic factors may likewise contribute to the potential adverse effects associated with treatments. Yet in spite of significant efforts over the last decade candidate gene studies have revealed very few variants that are consistently associated with enhanced (or diminished) responses to stimulants or to otherwise influence treatment outcomes in ADHD. As AMP and MPH both largely target the monoamine neurotransmitters DA and NE, most of the candidate gene association studies have been conducted evaluating specific variants of genes that encode for key catalytic enzymes involved in both the biosynthesis of DA and NE (which occurs intracellularly) as well

as those enzymes responsible for neurotransmitter degradation (see Fig. 1). For example, tyrosine hydroxylase (TH), the gene encoding for the enzyme required to catalyze the conversion of the amino acid tyrosine to the DA precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), and DA β-hydroxylase (DBH) responsible for the bioconversion of DA to NE have been investigated in a number of studies.[26] Likewise, functional polymorphisms of genes encoding for prominent catalytic enzymes responsible for the degradation of monoamines (catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) in the extracellular space have also been targets of pharmacogenomic studies (see Fig. 1).[26,27] Moving beyond the processes of the biosynthesis and degradation of DA and NE, other "catecholaminergic gene" variants associated with transporters of monoamines, as well as both pre and postsynaptic target receptors for DA and NE have likewise been targeted for study. Some of the more well-studied of these candidate genes include the DA receptor D4 (*DRD4*) gene, DA receptor D5 (*DRD5*) gene, the DA transporter gene (*DAT1* or *SLC6A3*), the most prevalent NE receptor type in the prefrontal cortex, α-2A adrenergic receptor (*ADRA2A*), the NET gene (*NET1*; *SLC6A2*) and others.[27] To date, however, findings from these studies have not been proved consistent nor have they been reliably replicated and do not adequately explain variability in response to psychostimulants. Additionally, it has been noted that most of these candidate gene variants fail to replicate in genome-wide association studies (GWAS).[25,27] GWAS examine the entire genome to detect common DNA variants (>1% of the population) having very specific effects; however, GWAS studies require large number of subjects to reliably map a genetic association. A limited number of GWAS studies have been conducted directed at the etiology of ADHD as well as its treatment.[28] An extensive discussion and analysis of ADHD GWAS studies is beyond the scope of the present review but specific and recent reviews are available.[28,29] At present, no single gene variant, gene variant combination, or currently available pharmacogenomics testing panel based upon monoamine synthesis, degradation or drug pharmacodynamics can be recommended to guide the selection of stimulant or stimulant dose in the treatment of ADHD.

PHARMACOKINETICS

Amphetamine metabolism and disposition

Following the oral administration of immediate-release (IR) racemic AMP, both isomers are well absorbed, but bioavailability is relatively low at an estimated 25%. Distribution is rapid and similar for both isomers and protein binding is approximately 15% to 40%. The steady-state volume of distribution (Vd) is estimated at 3 to 4 L/kg. AMP is highly metabolized in the liver with two primary oxidative pathways recognized (Fig. 2). Aromatic hydroxylation occurs to the para position to form small amounts of the pharmacologically active metabolite 4-hydroxyamphetamine through a reaction reportedly catalyzed by the cytochrome P450 (CYP) 2D6 pathway.[30] 4-hydroxyamphetamine is then converted into *p*-hydroxynorephedrine by DA -β-hydroxylase and further hydroxylation of *d*-AMP forms norephedrine (phenylpropanolamine) in small amounts. Oxidative deamination via *N*- or α-hydroxylation is the other primary oxidative route.[31–33] Another Phase I monooxygenase, flavin-containing monooxygenase form 3 (FMO3) was reported to contribute to the *N*-oxygenation of *d*- and *l*-AMP.[34] AMP is also oxidized to inactive metabolites phenylacetone which is subsequently oxidized to benzoic acid, which is conjugated to glycine and excreted as hippuric acid.[31,32] AMP deamination seems to be catalyzed by CYP450 isoenzymes of the CYP2C subfamily which also proceeds in a stereoselective manner.[35] Dextroamphetamine is metabolized more efficiently than *l*-AMP leading

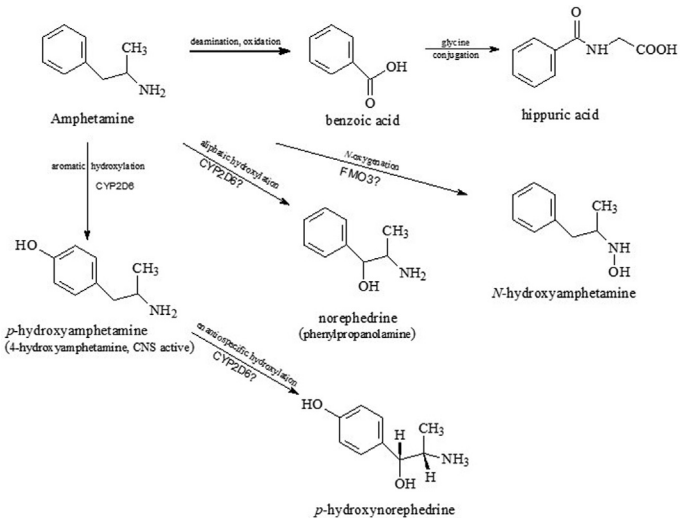

Fig. 2. Metabolism of amphetamine in humans.

to unequal amounts of isomers excreted in the urine following the administration of the racemic mixture. AMP does not seem to be a substrate or inhibitor of the P-glycoprotein (P-gp) transporter.[36]

In summary, in humans, AMP is highly metabolized by multiple enzymes to primarily inactive compounds found in relatively small amounts. The major enzymes involved in AMP's metabolism remain unclear. Anywhere from 5% to 30% of an administered dose is excreted unchanged in the urine, with the majority eliminated as benzoic acid and its corresponding glycine conjugate known as hippuric acid.

Potential sources of variability

Although there are some age-related differences in some pharmacokinetic parameters (eg, C_{max}, AUC) reported with different AMP formulations, in general, after adjustments are made for body weight and dosage there are no major differences in overall pharmacokinetics and exposure between children and adults. The influence of food and high-fat meals has been evaluated for all AMP formulations. Although there are some differences between different formulations, the following general observations can be made. With regard to IR dosage forms, little overall effects on the bioavailability or exposure to *d*-AMP from either an IR formulation or an initial sustained release formulation, Dexedrine Spansule, was noted.[37,38] More modern modified-release dosage forms are those which have a more specified pattern of drug release formulated to achieve a desired therapeutic objective or improved patient compliance. However, the consumption of food or a high-fat meal may significantly lengthen the time to reach T_{max} (ie, time to reach maximum plasma concentration [C_{max}]) of both the *d*- and *l*-isomers in many modified-release AMP dosage forms.[39] These delays in T_{max} vary widely among different product formulations, but may range between 2 and 4.5 hrs while not ultimately altering the overall exposure (observed area under the plasma concentration–time curve [AUC]) to most formulations.[40] To summarize, high-fat meals did not typically have significant effects on the exposure (AUC and C_{max}) to AMP formulations but tend to delay T_{max} to variable degrees. The plasma half-life ($t_{1/2}$) of IR racemic AMP is ~ 10 to 13 hrs in adults and shorter in children (~8 hrs) (**Table 1**). Studies in healthy volunteers receiving racemic AMP typically reveal a

Table 1
Comparison of enantiospecific pharmacokinetic parameters of immediate-release psychostimulants

Psychostimulant	~T_{max} (h)	~$t_{1/2}$ (h)	~Vd (L/kg)	~*F* (%)
dl-methylphenidate	*d*-isomer: 2 *l*-isomer: 2	*d*-isomer: 2–3 *l*-isomer: 0.5–1	*d*-isomer: 2.7 *l*-isomer: 1.8	*d*-isomer: 23 *l*-isomer: 5
dl-amphetamine	*d*-isomer: 2.5 *l*-isomer: 2.5	*d*-isomer: 10–11 *l*-isomer: 12–13	*d*-isomer: 3–4 *l*-isomer: 3–4	*d*-isomer: 25 *l*-isomer: 25

difference in the disposition of the AMP enantiomers with *d*-AMP having an elimination $t_{1/2}$ 1 to 2 hours shorter than *l*-AMP.[40,41] Multiple AMP dosage forms are now available, most of which permit once daily dosing (**Table 2**). Regarding the *d*-AMP prodrug lisdexamfetamine (LDX), it is a rapidly absorbed L-lysine conjugate that generally reaches its C_{max} approximately 1 hour (T_{max}) postdosing. It's elimination $t_{1/2}$ is typically less than 1 hr. Interestingly, LDX is not metabolized by human microsomes or in human hepatocytes and the primary site of hydrolytic metabolism to *d*-AMP is the red blood cell in a reaction believed to be catalyzed by unidentified peptidases.[42] The LDX capsule is not specifically formulated as an extended- or modified-release technology as the duration of activity is driven by the gradual hydrolysis releasing *d*-AMP over the day.

In general, for all AMP formulations, the AUC and the C_{max} are generally proportional to the dose. With regard to gender differences in pharmacokinetics, in general, it seems that women may have a 20%–40% higher exposure to a given dose of most of the AMP formulations than men, but these differences in overall drug exposure tend to disappear when the dose is normalized to subject weight.[40]

Amphetamine metabolism and the potential influence of genetic polymorphisms

As mentioned above, what is known about AMP metabolism is that there are multiple pathways and metabolites yet relatively few *in vitro* studies have been replicated which firmly identify major enzymes involved in its biotransformation. Although most AMP full prescribing information mentions CYP2D6 as having a role in the metabolism of AMP and CYP2D6 is mentioned in multiple FDA New Drug Applications for AMP products, no pharmaceutical company to our knowledge has submitted any original data supporting this contention to the FDA. However, as at least one report indicates that AMP serves as at least a partial substrate of the highly polymorphic enzyme/gene *CYP2D6,* the potential for genetic variability in metabolism, therapeutic response, and tolerability would seem to make it a prime candidate for pharmacogenomic testing, and indeed, this is a practice incorporated by some clinicians and commercial testing is readily available.[30,43] However, it must be borne in mind that the evidence for the involvement of CYP2D6 to date remains thin and seems to rest primarily on a single *in vitro* study.[30] Furthermore, if there is such a role *in vivo*, the degree of its involvement in the overall metabolism and clearance of AMP is unknown. We are unaware of any clinical study conducted or published demonstrating alterations in AMP disposition in individuals who are carriers of genetic variants of *CYP2D6* (eg, poor metabolizers or ultra-rapid metabolizers) versus extensive metabolizers. Likewise, there are no clinical studies assessing the influence of known CYP2D6 metabolic inhibitors (eg, paroxetine) on AMP metabolism and disposition in humans. With regard to FMO3 and its role in AMP metabolism, while a number of genetic variants have been identified that seem to influence the degree of drug oxidation by FMO3, as mentioned above, there are conflicting reports regarding the actual contribution of this oxidative enzyme

Table 2
Available amphetamine dosage forms

Composition	Proprietary Name	FDA Approval Year	Pharmaceutical Formulation/ Dosage Form	Daily Dosing Frequency	T_{max} (hr)	$t_{1/2}$ (hr)	Dosage Strengths	Sprinkle/Dividing
mixed salts of *d*- & *l* -amphetamine; 3:1	Adderall®	1996	Tablet, IR	2	~7	10–12	5, 7.5, 10, 12.5, 15, 20, 30 mg	Can split/crush
D-amphetamine	Dexedrine Spansule®	1996	Capsule, SR	1–2	~8	12	5, 10, 15 mg	Can be opened/sprinkled
mixed salts of *d*- & *l*-amphetamine; 3:1	Adderall XR®	2001	Capsule, ER	Once	7–8	11–13	5, 10, 15, 20, 25, 30 mg	Can be opened/sprinkled
Lisdexamfetamine prodrug of *d*-amphetamine	Vyvanse®	2007	Capsule	Once	~4	~11	10, 20, 30, 40, 50, 60, 70 mg	Can be opened/sprinkled
d-amphetamine	ProCentra®	2008	Oral Solution, IR	1–2	3–4	~12	5mg/mL	N/A
dl-amphetamine	Evekeo®	2012	Tablet, IR	1–2	~2.5	10–12	5, 10 mg	Can split/crush
d-amphetamine	Zenzedi® equiv to discontinued Dexedrine® tablets	2013	Tablet, IR	1–2	~3	~12	2.5, 5, 7.5, 10, 15, 20, 30 mg	Can split/crush
mixed salts of *d*- & *l*-amphetamine ratio of 3.2:1	Dyanavel® XR	2015	Suspension, ER	Once	4	12–15	2.5 mg/mL	N/A
mixed salts of *d*- & *l*-amphetamine ratio of 3:1	Adzenys XR-ODT®	2016	Orally disintegrating tablet, ER	Once	~5	11–13	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg	No
mixed salts of *d*- & *l*-amphetamine in the ratio of 3:1	Mydayis®	2017	Capsule, ER	Once	8	10–12	12.5, 25, 37.5, 50 mg	Can be opened/sprinkled

mixed salts of *d*- & *l*-amphetamine ratio of 3:1	Adzenys® ER	2017	Suspension, ER	Once	~5	~11	1.25 mg/mL	N/A
Lisdexamfetamine prodrug of *d*-amphetamine	Vyvanse®	2017	Chewable tablet	Once	~4	~11	10, 20, 30, 40, 50, 60 mg	No
dl-amphetamine	Evekeo® ODT	2019	Orally disintegrating tablet, IR	1–2	~3	10–12	5, 10, 15, 20 mg	No

Abbreviations: ER, extended release; IR, immediate release.

to AMP metabolism and disposition.[44] In summary, there have been no gene variants conclusively linked to decreased (or increased) AMP metabolism and we conclude there are insufficient data to recommend pharmacogenomic testing of any gene variant related to AMP pharmacokinetics as a means to personalize/optimize AMP pharmacotherapy.

Methylphenidate metabolism and disposition

With the exception of the enantiopure (*d*)-MPH products (threo-[+]-MPH, dexmethylphenidate) Focalin and Focalin XR and the recently introduced combination formulation containing the prodrug serdexmethylphenidate and *d*-MPH (Azstarys), all marketed MPH formulations contain a racemic (50:50) mixture of threo-RR-*d*- and threo-S,S-*l*-MPH isomers (**Table 3**). The hydrochloride salt of MPH is quite soluble in gastrointestinal fluids and it is rapidly absorbed from the small intestine to the colon. Distribution is also quite rapid and protein binding is low at 15%. The overall bioavailability of IR MPH is quite low (approximately 23% for the *d*-isomer vs 5% for the *l*-isomer) which is believed to be due to extensive and stereoselective first-pass metabolism.[45] The steady-state Vd is estimated at 2 L/kg with some differences noted between isomers (see **Table 1**). Unlike AMP, *dl*-MPH undergoes little oxidative metabolism and is instead subject to rapid stereoselective de-esterification (hydrolysis) to the major inactive metabolite, ritalinic acid (**Fig. 3**). Circulating concentrations of ritalinic acid greatly exceed those of the parent compound and it accounts for 60% to 80% of a dose recovered in urine. This deactivating/detoxifying process seems to be exclusively by the major hepatic esterase carboxylesterase 1 (CES1).[46]

A variety of modified-release oral dosage forms designs were introduced beginning in 2000 (see **Table 2**) and included pulsatile release and biphasic extended release, which provided intended fluctuations of plasma levels. More extensive reviews of these technologies can be found elsewhere.[45,47] The plasma half-life ($t_{1/2}$) of IR *d*-MPH is ~ 2 to 3 hrs (see **Table 1**). Whether an IR tablet or one of the modified-release oral dosage formulations, the C_{max} and AUC of MPH are generally proportional to the dose. CES1 mediated hydrolysis is highly stereoselective, with the catalytic efficiency of CES1 estimated to be 6- to 7-fold higher for the inactive *l*-isomer relative to *d*–MPH.[48] As a result, the plasma $t_{1/2}$ of *d*-MPH is markedly longer than that of *l*-MPH which has been reported to be ~0.5–1 hr (see **Table 1**).[22] In fact, this stereoselective metabolism is so significant, that *l*-MPH concentrations may fall below the analytical limits of detection within 1 to 2 hours of oral administration of racemic MPH. For example, in one enantiospecific pharmacokinetic evaluation of the OROS formulation of racemic MPH, the AUC values of *l*-MPH only attained only 1% of that of *d*-MPH.[49] In contrast to observations with racemic oral formulations is the transdermal patch formulation of racemic MPH which results in approximately equal amounts of *d*- and *l*-MPH isomers in the systemic circulation throughout the wear period.[50] This occurs presumably due to its continuous delivery through the skin which avoids the significant first-pass effect and stereoselective hepatic metabolism which influence orally administered drug. Only minor oxidative metabolism by other enzymes/pathways is known to occur including aromatic hydroxylation to form *p*-hydroxymethylphenidate, a metabolite with CNS activity but found in only minor amounts (~1%). A de-esterified lactam and a number of glucuronides are also formed.[51] Less than 1% of an MPH dose is excreted unchanged in the urine.

Potential sources of variability

As with AMP formulations, there are some age-related differences in some pharmacokinetic parameters (eg, C_{max}, AUC) reported with MPH. Likewise, in general, after

Table 3
Available methylphenidate dosage forms

Composition	Proprietary Name	FDA Approval Year	Pharmaceutical Formulation/ Dosage Form	Daily Dosing	T_{max} (hr)	t ½ (hr)	Dosage Strengths	Sprinkle/ Dividing
DL-methylphenidate	Ritalin®	1955	Tablet, IR	2–3	2	2.5–3	5, 10, 20 mg	Can split/crush
DL-methylphenidate	Methylin ER®	2000	Tablet, dissolution polymer ER, equiv to discontinued Ritalin SR®	Once	4–5	~3.5	10, 20 mg	No
DL-methylphenidate	Quillichew ER®	2015	Chewable tablet 30% IR MPH; 70% ER MPH	Once	5	5	20, 30, 40 mg	No
DL-methylphenidate	Concerta®	2000	Nondeformable tablet, osmotic release, OROS™	Once	~7	3.5	18, 27, 36, 54 mg	No
D-methylphenidate (dexmethylphenidate)	Focalin®	2001	Tablet, IR	Twice	1.5	2	2.5, 5, 10 mg	Can split/crush
DL-methylphenidate	Metadate CD®	2001	Capsule, beaded delivery 30% IR, 70% ER	Once	1.5	~7	10, 20, 30, 40, 50, 60 mg	Can be sprinkled
DL-methylphenidate	Ritalin LA®	2002	Capsule, biphasic beaded delivery, 50% IR, 50% ER	Once	2 (1st peak)	2–3	10, 20, 30, 40, 60 mg	Can be sprinkled
D-methylphenidate (dexmethylphenidate)	Focalin XR®	2005	Capsule, biphasic beaded delivery, 50% IR, 50% ER	Once	1.5 (1st peak)	3	5, 10, 15, 20, 25, 30, 35, 40 mg	Can be sprinkled

(*continued on next page*)

Table 3
(*continued*)

Composition	Proprietary Name	FDA Approval Year	Pharmaceutical Formulation/ Dosage Form	Daily Dosing	T_{max} (hr)	$t_{½}$ (hr)	Dosage Strengths	Sprinkle/ Dividing
dl-methylphenidate	Daytrana®	2006	Transdermal patch	Once	Depends on removal time	4–5 (*d*-MPH)	10, 15, 20, 30 mg	N/A
dl-methylphenidate	Quillivant XR®	2012	Suspension, reconstituted powder contains 20% IR, 80% ER	Once	4	5	10 mg/2 mL, 20 mg/4 mL 30 mg/6 mL, 40 mg/8 mL 50 mg/10 mL, 60 mg/12 mL	N/A
dl-methylphenidate	Aptensio XR®	2015	Capsule, outer IR layer 40% and inner CR layer 60%	Once	2	5	10, 15, 20, 30, 40, 50, 60 mg	Can be sprinkled
dl-methylphenidate	Cotempla® XR-ODT	2017	Orally disintegrating tablet, 25% IR, 75% ER MPH	Once	~5	4	8.6, 17.3, 25.9 mg	No
dl-methylphenidate	Jornay PM®	2018	Capsule, microbeads outer delayed-release layer, inner ER layer, and an IR core	Once (evening)	14	6	20, 40, 60, 80, 100 mg	Can be sprinkled

dl-methylphenidate	Adhansia XR®	2019	Capsule, multilayer release beads, 20% IR and 80% ER	Once	1.5 (1st peak)	7	25, 35, 45, 55 70, 85 mg	Can be sprinkled
d-methylphenidate & serdexmethylphenidate	Azstarys®	2021	Capsule contains IR *d*-MPH & prodrug of *d*-MPH, serdexme thylphenidate	Once	2	6: *d*-MPH 12: Serdex	Serdex: *d*-MPH ratio; 26.1 mg/5.2 mg 39.2 mg/7.8 mg 52.3 mg/10.4 mg	Can be sprinkled

Abbreviations: CR, controlled release; ER, extended release; IR, immediate release.

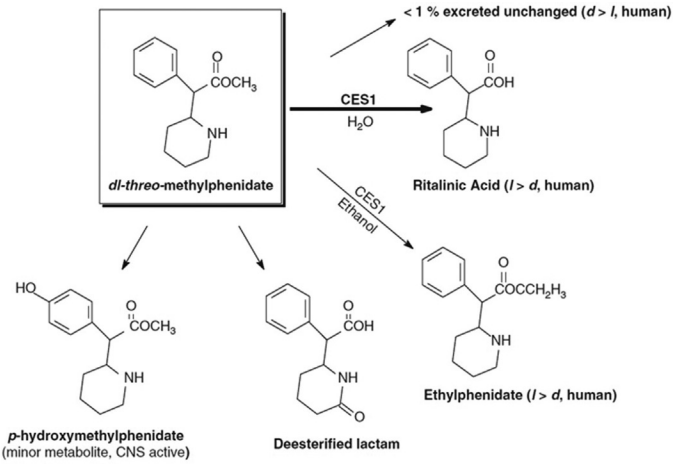

Fig. 3. Metabolism of methylphenidate in humans.

adjustments are made for body weight and dosage there are no significant differences in overall pharmacokinetics and exposure between children and adults. Regarding the fed versus fasted state, the extent of absorption of MPH from all oral dosage forms is similar when dosed in the fasting state. However, following the consumption of a high-fat meal, there is a potential for a delay in the time of peak concentrations (T_{max}), which is theorized to result from a delay in gastric emptying.[45] There are some differences between studies and formulations with some reported increased or decreased C_{max}, but in general, overall exposures as assessed by AUC are unchanged. There are several studies suggesting that there may be gender differences regarding MPH metabolism and disposition. At least two bioavailability studies which included male and female volunteers indicated that when the doses are normalized to the body weight of the subject, women have lower systemic exposure based on a mg/kg dose.[46] It has been speculated that more extensive first-pass metabolism of MPH may occur in women. The potential clinical significance of these observations is that women might require larger mg/kg doses to achieve the same MPH plasma concentration as their male counterparts. The apparent sex dimorphism in MPH bioavailability requires further study.[45]

Numerous clinical studies have demonstrated a significant *interindividual* in the metabolism and disposition in patients receiving typical doses of MPH. Interindividual variability in MPH pharmacokinetics may be particularly prominent when comparing the profiles of individual subjects after dosing with one of the long-acting formulations. This variability is well illustrated in **Fig. 4**. In this figure, "spaghetti" plots are presented depicting individual AUCs from 19 adult subjects (10 M, 9 F) participating in a healthy volunteer cross-over pharmacokinetic study comparing the two long-acting formulations Ritalin LA (*pane A*) and Concerta (*pane B*).[52] The mean values of these individual plots presented in *pane C* is quite representative of the typical profiles depicted in the two formulation's full prescribing information and promotional materials. What can be appreciated is that few of the individual subjects display a profile matching the mean profiles and some differ substantially, yet most of the prescribers assume their patients will have a profile very much mirroring the mean profiles (*pane C*) that is, that which appears in the prescribing materials. It should be noted that this type of interindividual variability in pharmacokinetic profiles is not unique to the Ritalin LA and

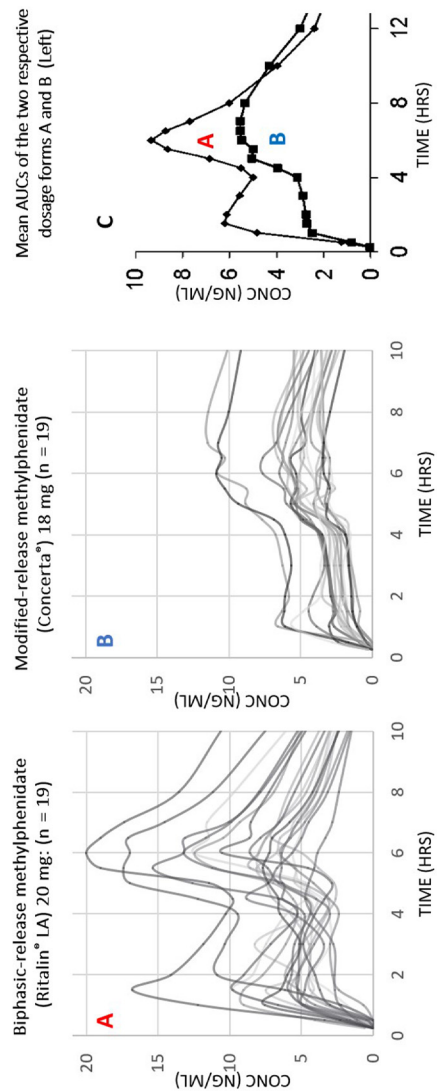

Fig. 4. Interindividual variability in long-acting methylphenidate formulations.

Concerta dosage forms, and although not routinely published it is quite typical of essentially all modified-release formulations of MPH.[53,54] With regard to *intra-subject* variability in MPH pharmacokinetics, it is generally believed to be of a smaller magnitude than that observed between subjects (ie, interindividual variability) but the issue has undergone little formal study.

In summary, MPH pharmacokinetics are generally linear and dose proportional. Absorption is rapid and oral bioavailability is low. Metabolism is almost entirely mediated by CES1, stereoselective, and forms the major inactive metabolite ritalinic acid. Clearance is rapid with little to no accumulation of the drug, even with the long-acting modified-release formulations and thus, true steady-state conditions are never really attained.

Methylphenidate metabolism and the potential influence of genetic polymorphisms

As described previously, the primary metabolic fate of MPH is to be de-esterified (hydrolyzed) into the major inactive metabolite ritalinic acid in a reaction catalyzed by CES1. There is otherwise little metabolism relevant to MPH disposition and clearance. CES1 has undergone little study relative to other drug-metabolizing enzymes such as members of the CYP450 superfamily and there is generally little clinician familiarity with the enzyme. It is, however, the most abundant drug-metabolizing enzyme (of any type) in the human liver and is responsible for an estimated 80%–95% of total hydrolytic activity in the liver. The enzyme is key in catalyzing the metabolism of an array of medications, drugs of abuse, environmental toxins, and endogenous substances.[55] Significant interindividual variability in the expression and activity of CES1 has been consistently observed and reported in the biomedical literature and this variability is likely attributable to both genetic and environmental factors, and in theory such variability could potentially result in treatment failure and/or unexpected adverse effects from a CES1 substrate medication. A single-nucleotide polymorphism (SNP) in the human *CES1* gene encoding for CES1 has been discovered which results in dysfunctional enzymatic activity, and may be one contributing factor to inter-individual variability in MPH exposure and response.[55,56] The first clinically significant *CES1* variant, the loss-of-function mutant G143E also referred to as 428G.A (rs71647871), was discovered serendipitously during the course of a healthy volunteer MPH pharmacokinetic study.[56] This variant led to gross impairments in MPH metabolism. Subsequently, this variant has been unequivocally shown *in vitro* and in clinical studies to lead to significantly impaired metabolism of MPH and other known CES1 substrates.[55–57] In a single-dose pharmacokinetic assessment, Stage and associates (2017) evaluated the influence of specific *CES1* genotypes on the pharmacokinetics of *d*-MPH in healthy subjects (n = 44).[57] G143E carriers were found to have an approximately 150% increase in MPH AUC relative to control subjects lacking the variant ($P < .0001$). It was further noted that individuals with 4 copies of *CES1* had 45% ($P = .011$) and 61% ($P = .028$) increased AUCs of *d*-MPH relative to control participants or those with fewer copies of *CES1*. Nemoda and coworkers reported the G143E variant to be associated with significantly lower MPH dosage requirements for symptom reduction in patients with ADHD.[58] In this prospective study (n = 122) children with ADHD were titrated to a dose of MPH between 10 and 30 mg in 2 doses to achieve adequate medication response. Subjects were then classified as responders or nonresponders using the ADHD Rating Scale (ADHD-RS). While there was no significant difference in response rate when comparing individuals with the variant to those without among those responding, those with the G143E variant (n = 5) required significantly lower doses (0.41 mg/kg/d vs 0.57 mg/kg/d; $P = .022$) versus those who did not carry the variant (n = 85).[58] This finding is consistent with impaired CES1 activity in G143E carriers.[59]

Thus, it seems that genetically deficient "poor metabolizers" of MPH do in fact exist and are associated with the G143E variant. The minor allele frequency (MAF) of the G143E variant is only 3% to 4% in the general population and estimated at approximately 3.7%, 4.3%, and 2%, in White, Hispanic, and African American populations, respectively, and the variant seems to be rare in Asian populations.[56]

As to whether it is clinically useful to genotype for *CES1* variants presently is open to debate. Although CES1 is recognized as the primary catalytic enzyme responsible for the metabolism of MPH, earlier nonpharmacogenomic studies evaluating plasma levels of the drug did not provide useful guidance for dosing and management of patients. There are well more than 7000 *CES1* SNPs registered in the National Center for Biotechnology Information database, the vast majority of which have not been evaluated for activity.[55] At present the field of CES1 pharmacogenomics is in its relative infancy and we would anticipate further functional variants will be discovered. At present, however, the universal genotyping for the presence of the *CES1* G143E variant (or others) cannot be recommended for all patients treated with MPH.

Drug–drug interactions

DDIs are a major source of concern in all medical disciplines and subspecialties due to their association with adverse effects, potential toxicity and increased morbidity and mortality. Additionally, DDIs resulting in ADRs and interactions are frequently a source of litigation. Because of the frequent existence of comorbid disorders in patients with ADHD which are amenable to treatment with medications and as ADHD often continues to be treated into adulthood, the concurrent use of ADHD medications with other therapeutic agents on a chronic or acute basis is often unavoidable.[60] An accumulating number of research reports, survey data, as well as analyses of health maintenance organization and prescription drug databases indicate a decade's long and continuing trend for children and adolescents diagnosed with ADHD to be concurrently treated with a psychostimulant and one or more other psychotropic medication. Among the more commonly coprescribed agents are α-2 agonists, SSRIs, second-generation antipsychotics, and anticonvulsants.[61,62]

DDIs may occur due to a number of reasons including clinician unfamiliarity with drug combinations known to be potentially problematic, the prescribing of medications by multiple clinicians–each unaware of prescribed treatments by the other, the use of over-the-counter medications or dietary supplements by the patient, and the prescribing of drug combinations which have never been assessed in a systematic fashion using modern *in vitro* screening techniques presently required by the US FDA before drug approval. This latter situation is certainly far more common for drugs that were initially approved for use many years ago such as MPH and AMP. In regard to DDIs with the psychostimulants, current full prescribing information (ie, package inserts) describe relatively few DDIs of clinical concern. In the recent past, drug prescribing materials contained a variety of cautions related to the use of stimulants with TCAs, anticonvulsants, and others. These cautions have been largely based on questionable case reports rather than formal study. Thorough reviews and assessments of most of these early stimulant DDI reports are available elsewhere.[63,64] There are in fact, relatively few published reports rigorously documenting pharmacokinetic DDIs for which the stimulants are the "victim" drugs. It should also be noted that as psychostimulant drug concentrations are seldom obtained in the clinical management of patients, this may well decrease the likelihood of discovering DDIs suspected or otherwise. Furthermore, over the extensive clinical lifetime of the psychostimulants it is only relatively recently that the respective metabolic pathways and requisite catalytic enzymes and drug transporters have been identified for MPH and AMP, and as

described above for AMP and CYP2D6, there remain deficits in our understanding of the complete picture of AMP clearance.

DDIs are generally characterized as either pharmacodynamic or pharmacokinetic in nature. *Pharmacodynamic drug interactions* may be antagonistic, additive, or potentially synergistic. Since pharmacodynamic interactions are not associated with an alteration in any tissue concentration of drug they are typically suspected on the basis of diminished, exaggerated, or even toxic effects in a patient previously maintained satisfactorily on an existing medication regimen. Evidence of a pharmacodynamic interaction primarily relies on clinical observations and objective measures of drug pharmacologic effects including changes in a drug's previous effectiveness in controlling target symptoms, changes in a patient mental status or otherwise unexplained changes in one or more vital signs. *Pharmacokinetic drug interactions,* which are a focus of this article, are those that affect one or more of the ADME parameters (ie, absorption, distribution, metabolism, elimination). Relative to pharmacodynamic DDIs, pharmacokinetic interactions are more easily detected and/or confirmed through the measurement of systemic blood concentrations of the suspected agents, ideally both prior to and after a suspected perpetrator agent is added to an existing drug regimen.

Amphetamine and drug–drug interactions

As discussed previously, the metabolism of AMP is complex with no single metabolic pathway or catalytic enzyme dominating. However, both *in vitro* and available healthy volunteer studies suggest that neither *d*-AMP nor intact LDX significantly impede the activity of any of the major CYP450 enzymes. In *in vitro* models, AMP does not seem to be an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human hepatic microsomal microsomes. Furthermore, in vitro assessments conducted in cultured human hepatocytes indicated that AMP was not an inducer of CYP1A2, CYP2B6, or CYP3A4/5.[65] In a healthy volunteer study using a probe drug cocktail approach, neither LDX nor *d*-AMP produced any significant effects on the substrate markers in the "Cooperstown Cocktail" (caffeine CYP1A2 substrate, dextromethorphan CYP2D6 substrate, omeprazole CYP2C19 substrate, midazolam CYP3A4 substrate), nor did these substrates seem to have any significant influence on LDX or *d*-AMP exposure.[66,67] On the other hand, one of the DDIs known to most profoundly alter the disposition of AMP is the coadministration of medications or other substance which can significantly alter urinary pH to one extreme or the other. Acidifying urine is known to greatly enhance the excretion of the parent compound while alkaline conditions have the opposite influence and significantly prolong drug half-life.[68,69] However, fortunately, there are relatively few agents which produce substantial effects on urinary pH. Citric acid and large doses of ascorbic acid can acidify urine while acetazolamide and sodium bicarbonate are examples of urinary alkalinizers. These combinations of agents seem relatively unlikely to occur, but some awareness of the potential is worthwhile. As there is some information regarding the metabolism of AMP implicating CYP2D6 it is possible that agents known to potently inhibit CYP2D6 (eg, paroxetine, quinidine) could impede the metabolism of AMP if used concurrently. In summary, there are few currently recognized pharmacokinetic interactions between AMP and CYP450 or other enzyme inhibitors.

Methylphenidate and drug–drug interactions

With respect to MPH, it is almost exclusively metabolized by the hepatic enzyme CES1 in a stereoselective manner to the major inactive metabolite, ritalinic acid. Thus, if any medications which might inhibit CES1 are coadministered with MPH on an acute or

chronic basis, a decrease in MPH clearance (and potentially increased side effects or toxicity) would be anticipated for the duration of concomitant use. Although systematic DDI studies conducted in healthy human subjects are considered the gold standard for DDI confirmation, *in vitro* studies are invaluable in identifying potential DDIs. Although the exploration of CES1-mediated DDIs is in its relative infancy compared with other drug-metabolizing enzyme systems such as the CYP450, *in vitro* studies have identified several compounds from an array of therapeutic classes which can significantly inhibit CES1 activity. Such drugs are by no means contraindicated with MPH but can be regarded as suspected perpetrators because of their confirmed inhibitory effects on CES1 *in vitro*. However, we do know that *in vitro* effects are often not borne out *in vivo* for a host of reasons. For example, an *in vitro* CES1 inhibitor like montelukast which has very low dosage levels (eg, 4–5 mg/d in children) may simply be insufficient to produce significant metabolic inhibition of an abundant enzyme. We do know that neither *dl*-MPH nor ritalinic acid themselves can inhibit CES1 activity *in vitro*. On the other hand, agents which may be used concurrently with MPH which have been screened by *in vitro* methods and *not* found to significantly inhibit CES1 include; the nonstimulant ADHD medications atomoxetine, clonidine, and guanfacine, the antipsychotics clozapine, olanzapine, risperidone, paliperidone, aripiprazole, ziprasidone, quetiapine and haloperidol, the TCA imipramine, the antibiotics amoxicillin, erythromycin, and ciprofloxacin, and antihistamine diphenhydramine and decongestant phenylephrine.[70]

The concurrent use of MPH with ethanol is associated with at least two metabolic phenomena. First, consumption of ethanol (0.6 g/kg) 30 min before or after the administration of modified-release racemic MPH (Ritalin LA) as well as dexmethylphenidate (Focalin XR) resulted in significantly increased the plasma C_{max} of the second pulse of MPH by 35% ($P < .01$) and the partial $(AUC)_{4\text{-}8h}$ by 25%.[71] Secondly, in a somewhat unusual trans-esterification reaction likewise catalyzed by hepatic CES1, the methyl-group on the MPH molecule is replaced by an ethyl-group from consumed ethanol forming the metabolite ethylphenidate.[72] This too is a highly stereoselective process favoring *l*-ethylphenidate formation. Although ethylphenidate does have potent CNS activity as a psychostimulant, the amounts formed from this reaction are relatively small mitigating most of the concern over this DDI.[72] With regard to MPH participating as a potential perpetrating agent (ie, inhibiting or inducing the metabolism of coadministered agents), package insert information on potential drug interactions for some products suggests that MPH may inhibit the metabolism of a number of coadministered medications including coumarin anticoagulants, some anticonvulsants. While this may be possible, the evidence base for most of these purported interactions is quite limited. In summary, pharmacokinetic DDIs with MPH serving as the victim drug are likely to be due to combined use with medications or other substances which are CES1 inhibitors. However, essentially none of the agents identified *in vitro* as CES1 inhibitors have been evaluated for their clinical effects in this regard.

Both psychostimulants are routinely used in combination with a variety of other medications from essentially every drug class on an acute or chronic basis. There are no known pharmacokinetic interactions that represent strict contraindications, or that rise to the level of prescriber warning. Available *in vitro* data and limited clinical data suggest that neither AMP nor MPH impair the activity of any major CYP450 oxidative enzyme or drug transporter, or that other drugs which inhibit or induce these catalytic enzymes or transporter expression alter the psychostimulant's disposition. The role of CYP2D6 in AMP metabolism is not firmly established and the potential for *in vitro* CES1 inhibitors to produce clinically significant effects on the disposition of MPH has not been evaluated.

SUMMARY

The psychostimulants AMP and MPH have been in clinical use for well more than 60 years. In general, it can be stated that both stimulants are rapidly absorbed, have relatively poor bioavailability and short half-lives. The development of an array of pharmaceutical dosage forms with once daily administration has largely addressed these issues. The pharmacokinetics of both stimulants are generally linear and dose proportional although substantial interindividual variability in pharmacokinetics is in evidence. AMP is highly metabolized by several oxidative enzymes including members of the CYP450 system forming multiple metabolites with approximately 5% to 30% excreted unchanged in the urine. Although CYP2D6 is believed to play a role in AMP metabolism, the extent of that role is not well-defined. There is some evidence of stereoselectivity in metabolism when racemic AMP is administered favoring the *d*-isomer. There are as of, yet no gene variants associated with decreased (or increased) AMP metabolism. MPH is primarily metabolized by CES1 catalyzed de-esterification to the major inactive metabolite ritalinic acid. When racemic MPH is administered profound stereoselective metabolism is observed favoring the inactive *l*-isomer. Less than 1% of MPH is excreted unchanged in the urine. A loss-of-function *CES1* variant G143E (rs71647871) associated with impaired metabolism of MPH has been identified. At present, pharmacogenomic testing as an aid to guide dosing and personalize treatment cannot be recommended for either agent on a routine basis. Few significant pharmacokinetically based DDIs have been documented for either stimulant but there has been relatively little systematic clinical study of this issue with either agent.

CLINICS CARE POINTS

- When considering dosage adjustments in patients, no matter the stimulant or formulation used, pharmacokinetics are generally linear and dose proportional.
- When treating patients with amphetamine (AMP) formulations avoid the coadministration of medications or substances which can significantly alter urinary pH. For example, known urine acidifiers (ie, ascorbic acid) and known urine alkalizers (ie, sodium bicarbonate) in sufficient quantity can significantly speed or reduce AMP clearance, respectively.
- With consideration to AMP treatment, pharmacogenomic testing centered on drug-metabolizing enzymes is not recommended at present as multiple enzymes are involved in its metabolism and the significance of CYP2D6 involvement requires further clarification.
- When treating patients with methylphenidate (MPH), be cognizant of the fact individuals that a loss of function *CES1* G143E (rs71647871) variant has been documented resulting in impaired clearance. However, pharmacogenomic testing is not routinely recommended at present.
- When treating patients with MPH, be aware that coadministration with known inhibitors of CES1 can potentially impede the drug's clearance.

DISCLOSURE

The authors have nothing to disclose.

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