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New methylphenidate formulations for the treatment of attention-deficit/hyperactivity disorder

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dl-Methylphenidate (MPH) remains the most widely used pharmacological agent in the treatment of attention-deficit/hyperactivity disorder (ADHD). The predominantly dopaminergic mechanism of the psychostimulant actions has become more clearly defined. Neuroimaging and genetic studies are revealing the underlying neuropathology in ADHD. Novel extended-release (ER) MPH formulations now offer drug delivery options to overcome both the short-term actions of immediate-release (IR) MPH and the acute tolerance associated with the first-generation ER-MPH products. These novel MPH products apply proprietary technologies such as OROS® (Alza), Diffucaps® (Eurand) and SODAS™ (Elan) to offer both the convenience of once-a-day administration and absorption profiles resembling, to varying degrees, the standard multiple dose schedules of IR-MPH. The pharmacodynamics of the separate MPH enantiomers is in the process of further neuropharmacological characterisation. It is well established that *dl*-MPH undergoes marked stereo-selective metabolism. Although *l*-MPH exhibits only minimal oral absorption, it may preferentially penetrate the brain, and interacts with ethanol to form the metabolite ethylphenidate. The newly approved resolved enantiomer product *d*-MPH is now available in an IR formulation, and when administered at one-half the dose to that of the racemate, is purported to produce a longer duration of clinical effect, despite essentially identical pharmacokinetics. A long-acting formulation of *d*-MPH, which employs the SODAS technology, is in the advanced stages of clinical development.

Keywords: dexmethylphenidate, dopamine, ethylphenidate, extended release, methylphenidate, pharmacodynamics, pharmacokinetics

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1. Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioural disorder, and is one of the most common chronic health problems afflicting school-age children in the US. ADHD has a prevalence rate generally estimated from 4 to 9% of school-aged youths [1-3], although estimates have been in the range of 1.7 – 17.8%, depending on the population and diagnostic criteria [4,5]. The incidence of ADHD is consistently greater in boys than in girls, with boy-to-girl ratios variously reported from 2:1 to 9:1[4,5]; however, the boy-to-girl ratio is greater in clinical studies compared with community studies, suggesting boys are more likely to be referred for treatment than girls [6,7]. Although once thought to be a disorder almost exclusively limited to childhood, and self-resolving at adolescence, recent reports now indicate that up to 50% or more of ADHD children will have symptoms persisting into

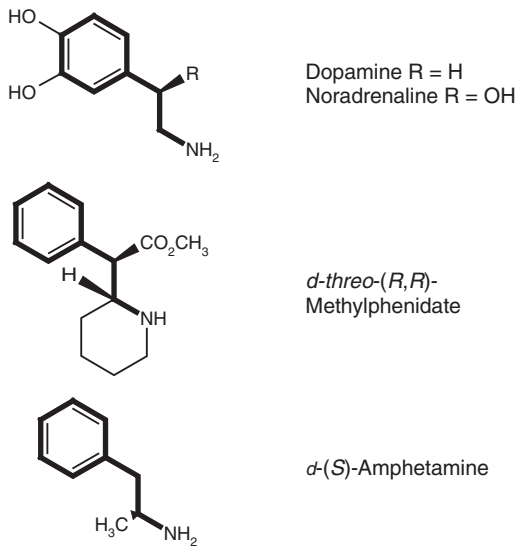

Figure 1. Phenethylamine pharmacophore common to stimulant drugs used to treat attention-deficit/hyperactivity disorder. Structures of d-methylphenidate and d-amphetamine isomers. The common phenethylamine pharmacophore (in bold) imparts dopamine transporter affinity.

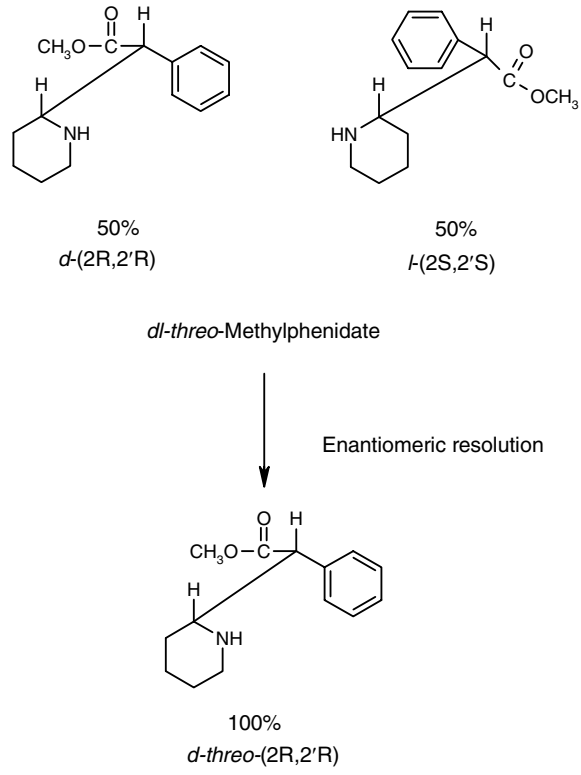

Figure 2. Racemic and enantiopure methylphenidate formulations.

adulthood and as a consequence additional medications have FDA approval for use in adult ADHD (i.e., amphetamine mixed salts and atomoxetine) [8].

The core behavioural symptoms of ADHD include inattention, hyperactivity and impulsivity, but all of such symptoms must be viewed in the context of age-appropriateness [9]. The disorder, if untreated, may result in academic underachievement, poor interpersonal relationships, and low self-esteem [1,10]. Furthermore, greater risks of physical injury, cigarette smoking, and substance abuse are present relative to non-ADHD afflicted peers [11-14]. Although an increased risk of substance abuse is recognised in patients with ADHD, appropriate pharmacological treatment during childhood and adolescence appears to reduce substance abuse rates significantly in adults with ADHD [14,15].

The underlying neuropathology of ADHD remains elusive. In some instances pre/perinatal complications [16] or cumulative lead exposure [17] appear pertinent. In addition, a substantial genetic predisposition for ADHD exists [18]. Candidate genes implicated in the pathogenesis of ADHD include those expressing the dopamine D4 [19] and D5 [20] postsynaptic receptors, the dopamine transporter [21-24], dopamine β-hydroxylase [25], and synaptosomal-associated protein 25 (SNAP-25; essential for presynaptic vesicule docking) [26]. The most widely prescribed medications to treat ADHD exhibit a prominent dopaminergic component of activity, as consistent with underlying dopaminergic dysfunction in ADHD [27-30]. Note, however, that medications with primarily noradrenergic [31,32] activity often exhibit efficacy in the treatment of ADHD; thus, a purely dopaminergic dysfunction hypothesis may be overly simplistic.

2. Pharmacotherapy of attention-deficit/hyperactivity disorder

Pharmacotherapy remains the mainstay treatment for ADHD [2,5,7,33], although multimodal treatment approaches that integrate medication with psychotherapeutics, environmental, educational, and school-based interventions are generally advocated, especially with certain demographics [34]. The psychostimulant medications methylphenidate (MPH) (**Figures 1** and 2), dextroamphetamine [35], and mixed isomers of amphetamine [36-41] containing a 75:25 stoichiometry of *d*- to *l*-amphetamine as multiple salts (Adderall®, Adderall XR®; Shire) are most commonly used to treat ADHD [33].

Clinical experience has demonstrated that 70 – 90% of children will respond favourably to at least one psychostimulant if the medication is properly titrated [42], with MPH typically used as comparator agent in clinical trials of other medications for ADHD [7]. In addition to the first-line ADHD treatments, other medication options include pemoline (Cylert®; Abbott Laboratories), whose use is limited by association with hepatoxicity [43]; the noradrenaline re-uptake inhibitor atomoxetine (Strattera®; Eli Lilly and Company) [44-46]; tricyclic antidepressants such as imipramine and desipramine, which

are not FDA approved for ADHD [32]; the histamine agonist modafinil (Provigil®; Cephalon); and the single isomer *d*-MPH (Focalin™; Novartis) (see Section 3.2).

2.1 Methylphenidate pharmacodynamics

The therapeutic effects of MPH in the treatment of ADHD appear to be elicited primarily through an inhibition of the presynaptic dopamine transporter [27,28,47,48], with a minor influence on the noradrenaline transporter. This action will amplify neurotransmission [49,50] by increasing synaptic cleft residence time of impulse-released dopamine [27,28]. Alternatively, others have proposed that dopamine re-uptake inhibition by MPH attenuates dopaminergic tone by increasing stimulation of presynaptic inhibitory autoreceptors [28,51,52]. The phenethylamine pharmacophore within the structure of MPH is common to both amphetamine and to the neuronal substrate dopamine (depicted in bold, **Figure 1**). This 'hot region' provides for transporter receptor affinity in competing with dopamine for binding [53]. MPH appears to bind with the dopamine transporter to block access of impulsed-released dopamine, but lacks the intrinsic activity required to induce the conformational change for its own translocation into the cytoplasm. Hence, MPH does not drive the transporter-facilitated release of cytoplasmic dopamine into the synaptic cleft as the transporter returns to its former conformation [54].

Conversely, amphetamine serves as an actual substrate for transport into the presynaptic terminal [27,28,47,53-57]. The dopamine transporter, despite being gated, does not possess the architecture of membrane pores or channels; that is, dopamine does not have direct access to both sides of the membrane simultaneously. Two sodium ions and one chloride ion serve as cosubstrates with dopamine, and supply the transport energy through their transmembrane concentration gradients. The amphetamine and sodium ions dock within the 12 neuronal membrane-spanning regions of the transporter. In the resting state, the pocket-like phenethylamine receptor faces the extraneuronal biophase, and then, upon binding by a chloride ion, a conformational change in the transporter translocates the binding regions to the cytoplasm. Subsequent unloading of amphetamine and the inorganic cosubstrates from the transporter presents a vacant binding site to which cytoplasmic dopamine docks. Return of the transporter to its former conformation state dispenses dopamine into the synaptic cleft [54].

2.2 Methylphenidate absorption and food effects

MPH formulations contain this basic drug (pK_a 8.9) [58] as the hydrochloride salt, providing a highly soluble form suitable for dissolution in the fluids of the gastrointestinal tract. An acidic environment suppresses nonenzymatic hydrolysis of MPH and, hence, little degradation is likely to occur in the stomach [59]. Once in solution, MPH is rapidly absorbed from the intestine to the colon [60,301]. Therefore, the main factor controlling MPH absorption from immediate-release (IR) dosage forms is most likely gastric emptying time, whereas for the various extended-release (ER) dosage forms, absorption is largely controlled by programmed drug release and dissolution pattern. Because of extensive first-pass metabolism, the systemic exposure of unchanged drug (i.e., the absolute bioavailability) after oral dosing is low and variable [61]. The low bioavailability and relatively large interpatient variability in the extent of systemic exposure of MPH has not been shown to be a factor limiting therapeutic effectiveness once the patient has been appropriately individualised. There is little evidence that intrasubject variability in MPH pharmacokinetics is of the magnitude seen between subjects [62,63].

Food may [64] or may not [65] significantly increase the extent of absorption and maximum plasma concentration (C_{max}) of either IR- or ER-MPH. Any potential food influence does not appear to be related to 'dose dumping' (premature release of drug), but rather to a slowing down of MPH absorption along with an increase in absorption. At least three theories have been advanced to account for this reported food effect: i) food increases liver blood flow to reduce hepatic first-pass metabolism; ii) dietary amino acids compete with MPH as metabolic substrates; and/or iii) food induces neurohormonal responses to increase area under the plasma concentration–time curve (AUC), for example, as seen with propranolol after food 'teasing', in which subjects only smell or see food. The latest ER-MPH formulations have also been evaluated for potential food effects and this is specifically discussed under the section on comparison of newer formulations. For the most part, the extent of absorption of MPH from all oral dosage forms is similar when dosed in the fasting state, but after consumption of a high-fat meal there is a potential for a delay in the time of peak concentrations (T_{max}), which is most likely due to a delay in gastric emptying. Actual peak concentration (C_{max}) may also be either increased or decreased after a high-fat meal, thus erratic responses in some patients may be traced to a temporal relationship with dietary fat intake. For those dosage forms that may be administered in soft food, such as applesauce, no changes in bioavailability have been observed, and they may be 'sprinkled' without the same concern one may have with a high-fat meal [66,67].

2.3 Methylphenidate distribution and elimination

On reaching the systemic circulation, MPH is rapidly distributed to highly perfused tissues. Plasma protein binding is 15% [68] and the drug accumulates in highly perfused tissues favouring kidney > lung > brain > heart > liver in a rat model [69]. Brain concentrations average eight times that of blood after oral or intravenous dosing, and attain this relationship within 1 min following intravenous MPH in rats [69]. Clearance of MPH is also rapid, with little or no accumulation of the drug from day to day, even with ER formulations. These have been reported to also exhibit linear pharmacokinetics [70-72]. Thus, steady-state conditions are never attained with MPH therapy. At higher oral doses there is some evidence of nonlinearity, which some have speculated may be related to saturation of the first-pass metabolism with oral dosing [73].

Table 1. Summary of nonenantiospecific parameters (mean) of methylphenidate .

Study	Dose, route	Number of subjects	Population	$T_{½}$ (h)	T_{max} (h)	C_{max} (ng/ml)
Hungund *et al.* 1979 [68]	10 – 20 mg	4	Child	2.56		
Chan *et al.* 1980 [61]	10 – 20 mg i.v.	6	Child	2.02		
Shaywitz *et al.* 1982 [75]	0.34 – 0.65 mg/kg	12 – 14	Child	2.53	1.9 – 2.5	11.2 – 20.2
Chan *et al.* 1983 [76]	0.25 – 0.68 mg/kg, fast	5	Child	2.10	1.6	
	0.25 – 0.68 mg/kg, fed	5	'	2.14	1.0	
Wargin *et al.* 1983 [77]	0.3 mg/kg	5	Child	2.43	1.5	10.8
	0.3 mg/kg	10	Adult	2.14	2.1	7.8
	0.15 mg/kg	5	'	2.05	2.2	3.5
Birmaher *et al.*1989 [78]	20 mg SR	9	Child	4.12	3.36	8.5
Patrick *et al.* 1989 [79]	10 mg IR b.i.d.	18	Adult		5.33	6.4
	20 mg SR, Ritalin	18	'		3.34	4.8
	20 mg SR, generic	18	'		3.25	4.6
Leis *et al.* 2000* [80]	20 mg	1	Adult	3	2.0	13
Markowitz *et al.* 2000‡ [81]	20 mg IR	6	Adult	2 – 5	1 – 4	8.4 – 27.3
Meyer *et al.* 2000§ [62]	20 mg, generic	20 x 2	Adult	2.56	1.55	7.6
	20 mg, Ritalin	20 x 2	'	2.47	1.97	6.9
Modi *et al.* 2000 [70]	18 mg q.d. OROS	35	Adult	3.5	6.7	3.8
	5 mg t.i.d. IR	34	'	3.0	6.5	4.2
	20 mg q.d. SR	33	'	3.9	3.7	4.8
	18 mg OROS	32	'	3.9	7.4	2.8
	18 mg OROS, multiple doses	32	'	3.9	6.6	3.0
Modi *et al.* 2000b [75]	18 mg OROS, fast	24	Adult	4.0	6.1	3.3
	18 mg OROS, fed	24	'	3.8	7.2	4.4
	36 mg OROS, fast	36	'	3.5	6.5	6.2
	36 mg, OROS, fed	36	'	3.3	7.4	6.9
Gonzales *et al.* 2002 [82]	18 mg CD	35	Adult	6.24	~ 5	3.9
	20 mg OROS	35	'	3.58	~ 6	3.4
	36 mg CD	21	'	6.82	~ 5	7.4
	2 x 20 mg OROS	21	'	3.84	~ 8	8.4
	54 mg CD	21	'	6.43	~ 5	12.4
	3 x 20 mg OROS	21	'	4.07	~ 7	12.6
Pentikis *et al.* 2002 [66]	20 mg CD	26	Adult	6.42	4.58	4.6
	20 mg CD sprinkled	26	'	6.27	4.39	4.8
Markowitz et al.2003 [83]	20 mg LA	24	Adult	3.4	5.5	9.9
	18 mg OROS	24	'	4.3	6.0	5.9
Wigal *et al.* 2003 [84]	10 mg IR	22	'	2.9	1.9	4.8
	10 mg IR b.i.d.	22	'	2.93	5.2	6.4
	20 mg SR	22	'	3.41	3.2	5.5
Lee *et al.* 2003 [67]	40 mg LA fed	18	'	NA	3.78	14.4
	40 mg LA sprinkled	17	'		3.6	14.5

*Approximately; ‡Given with ethanol 0.6 g/kg; §Mean values for two trials.
CD: Metadate®; C_{max}: Peak concentration; LA: Ritalin LA®; IR: Immediate-release; OROS®: Osmotic-controlled release system (Concerta®); SR: Sustained-release; T_{max}: Time of peak concentration; $T_{½}$: Half-life.

Table 1. Summary of nonenantiospecific parameters (mean) of methylphenidate (continued).

Study	Dose, route	Number of subjects	Population	$T_{½}$ (h)	T_{max} (h)	C_{max} (ng/ml)
	40 mg LA fasted	18	'		4.2	15.2
Rochdi *et al.* 2004 [72]	10 mg CD	24	Adult	5.6	4.7	2.4
	20 mg CD	24	'	6.1	4.5	4.8
	30 mg CD	24	'	5.6	5.0	7.4

*Approximately; ‡Given with ethanol 0.6 g/kg; §Mean values for two trials.
CD: Metadate®; C_{max}: Peak concentration; LA: Ritalin LA®; IR: Immediate-release; OROS®: Osmotic-controlled release system (Concerta®); SR: Sustained-release; T_{max}: Time of peak concentration; $T_{½}$: Half-life.

For intravenous and IR dosing, the elimination half-life is reported to be in the range of 2 – 6 h, with most studies reporting an average of 2 – 3 h. In an enantiospecific study of MPH administered intravenously, both isomers exhibited similar distribution characteristics, although the terminal elimination of the *l*-isomer was more rapid [74]. In recent studies utilising the newer ER dosage forms, longer half-lifes are reported; this is most likely related to prolonged absorption of MPH continuing into the elimination phase; thus masking the true elimination half-life.

The pharmacokinetics of MPH have not been found to differ significantly between children, adolescents or adults; although in a recent study evaluating two ER formulations in normal adults it was demonstrated that the relative bioavailability of MPH was greater in men than in women (see Section 2.6) [42]. Reported MPH pharmacokinetic parameters and associated references are summarised from nonenantiospecific studies in **Table 1** and from enantiospecific studies in **Table 2**. Although initial dose estimates are sometimes based on patient weight, final titration is more commonly driven by empirical dosing and therapeutic response than by body mass; thus negating the potential influence of interpatient variability on dosing parameters.

The presystemic metabolism and metabolic clearance of *dl*-MPH is an enantioselective process resulting in markedly higher plasma concentrations, and a longer half-life, for *d*-MPH compared with *l*-MPH. Until the recent approval of *d*-MPH (dexmethylphenidate, Focalin), all MPH formulations have consisted of a 1:1 (racemic) mixture of *d*-MPH and *l*-MPH. Yet, with few exceptions [97], therapeutic drug monitoring studies of MPH have been limited to nonenantiospecific analytical approaches; that is, reporting only pooled *d*- and *l*-MPH concentrations [53]. This lack of enantiospecific analyses may be of little clinical relevance in view of the much lower concentrations of *l*-MPH in plasma and in dopaminergic regions of the human brain [28]. In studies utilising different oral formulations, the AUC_{inf} value for the *l*-isomer has been reported to reach only 1 – 15% that of *d*-MPH [71,94,98] (**Table 2**).

Although *l*-MPH exhibits lower oral bioavailability, *l*-MPH has been reported to be more stable in human plasma than *d*-MPH, but less stable in human red blood cells [94,99]. Furthermore, radiolabelled *l*-MPH, or a metabolite with the same chromatographic retention time as *p*-hydroxy-MPH, has recently been reported to be taken up into the brain to a greater extent than *d*-MPH after oral administration of each isomer to either rats or baboons [101,102]. The enantioselective *p*-hydroxylation of *l*-MPH has previously been reported in rats, and the metabolite is known to possess CNS activity [103].

The wide range of relative concentrations of *d*- versus *l*-MPH reported in the literature may relate to the well-established interindividual variability in MPH pharmacokinetics [42]. Further, the apparent influence of specific MPH formulations may influence the relative bioavailability of *l*-MPH. The absorption of *l*-MPH from racemic IR-MPH may be greater than when compared with an ER formulation, an effect described in terms of input-based pharmacokinetics (see [104]), with a faster input rate resulting in higher *l*-MPH levels. The influence of input rate on enantioselective presystemic metabolism has precedent in the field of ER drug formulations [105], but such nonlinearity could only apply to the IR component of the newer ER-MPH products which contain both IR and ER properties (see Section 4). It should be noted that in a preclinical study, *l*-MPH appeared to increase the extent of *d*-MPH absorption [106].

2.4 Methylphenidate chiral analytical methods

Differences between interlaboratory enantiospecific methodologies can contribute to problematic quantitation of *d*- and *l*-MPH from biological matrices. Both chiral derivatisation gas chromatography methods and chiral liquid chromatography methods have been applied to these determinations, and each approach offers its own analytical performance attributes and limitations [107]. Appropriate chiral derivatisation requires that the derivatising reagent be enantiopure; that the derivatisation proceeds to completion for each MPH enantiomer; and that the resulting diastereomeric adducts not be subject to epimerisation, which may be of particular concern at the elevated temperatures of gas chromatography. Various detectors have been used in MPH gas chromatography analysis and specificity issues can be problematic, especially when detection is not by mass spectrometry.

Table 2. Summary of enantiospecific pharmacokinetic parameters (mean) of methylphenidate .

Study	Dose, formulation	Number of subjects	Population	$T_{½}$ (h) (d/l)	T_{max} (h) (d/l)	C_{max} (ng/ml) (d/l)
Lim *et al.* 1986 [85]	20 mg, IR	1	Adult	3.61(d)	2.17/3.05	5.5/0.4
	40 mg, IR	1	'	3.61(d)	2.08/2.08	2.24/1.7
Srinivas *et al.* 1987 [86]	10 mg	5	Child	3.1/5.59	2.15/2.01	7.1/1.0
Hubbard *et al.* 1989 [87]	20 mg, SR	6	'		2.8/3.1	18.8/1.6
Aoyama *et al.* 1990 [88]	20 mg, IR 20 mg, crystals	1	Adult	3.01/1.2		
	10 mg, (D)-MPH		'	2.9/1.4		
	10 mg, (L)-MPH		'	2.3 (d)		
Srinivas *et al.* 1990 [89]	40 mg, IR	1	Adult	4.06/3.76	2.0/2.0	11.7/2.0
Srinivas *et al.* 1992 [90]	10 mg, capsule	9	Child	1.87/1.43	2.3/2.4	6.4/1.3
	5 mg, (D)-MPH	9	'	1.84	2.44	5.6
	5 mg, (L)-MPH	9	'	0.98	2.1	0.78
Aoyama *et al.* 1993 [73]	10 mg, IR	3	Adult	2.5 (d)	0.9 (d)	5.0 (d)
	20 mg, IR	4	'	2.5 (d)	1.4 (d)	8.1 (d)
	30 mg, IR	4	'	2.5 (d)	1.2 (d)	17.1 (d)
	40 mg, IR	4	'	2.5 (d)	1.1 (d)	28.4 (d)
	60 mg, IR	2	'	3.1 (d)	3.0 (d)	24.7 (d)
Srinivas *et al.* 1993* [91]	10 mg, IV	11	Adult	5.96/3.6		
	40 mg, IR	11	'	5.69/3.93	2.36/2.14	18.1/3.1
	40 mg, SR	11	'	5.04/3.88	3.18/3.09	16.1/1.9
	40 mg, SR (chewed)	11	'	5.33/3.84	1.95/2.14	20.8/2.4
Aoyama *et al.* 1994 [92]	024-038 mg/kg, IR	8	Adult	1.7	2.8 (d)	7.67 (d)
Wong *et al.* 1998 [93]	40 mg	21	Adult	2.67/1.15	1.5/0.5	17.8/1.0
Ramos *et al.* 1999 [94]	17.5 mg	1	Child	3 (d)	1.5/1.5	10.8/0.25
Modi *et al.* 2000 [71]	18 mg OROS	35	Adult	3.8/n.d.	7.9/7.1	3.87/0.095
	36 mg OROS	35	'	3.9 (d)	7.5/7.0	7.28/0.17
	54 mg OROS	35	'	3.9 (d)	7.2/6.1	10.6/0.36
Midha *et al.* 2001 [64]	40 mg IR, fast	24	Adult	2.92 (d)	2.00 (D)	11.65 (d)
	40 mg IR, fed	24	'	2.67 (d)	2.54 (D)	14.3 (d)
	40 mg SR, fast	24	'	2.73 (d)	3.71 (D)	7.83 (d)
	40 mg SR, fed	24	'	2.70 (d)	3.62 (D)	9.19 (d)
Teo *et al.* 2004 [95]	2 x 10 mg Foc, fast	15	Adult	2.68 (d)	1.54	23.72 (d)
	2 x 10 mg Foc, fed	15	'	2.81 (d)	2.87	22.13
Duchin *et al.* 2001 [96]	26 mg dermal, 8 h	12	Child	3.3 (d)	7.5	22.3 (d)
	33 mg dermal, 12 h	12	'	n.d.	10.0	22.3 (d)
	36 mg dermal, 8 h	12	'	3.0	7.5	34.5 (d)
	44 mg dermal, 12 h	12	'	n.d.	10.8	31.4 (d)

*Approximtaely. Specific enantiomer indicated in parentheses. C_{max}: Peak concentration; ER: Extended-release (Metadate®); Foc: Focalin™; IR: Immediate-release; n.d.: Not detected; OROS®: Osmotic-controlled release system; SR: Sustained-release; $T_{½}$: Half-life; T_{max}: Time of peak concentration.

Chiral liquid chromatography may lead to spurious detection of MPH species formed from exchange of the routinely used acidic methanol mobile phase and the commercial internal standard: methyl-deuterated MPH (unpublished observation). This confounding chemical reactivity of the ester-labelled MPH internal standard has been overcome by the use of piperidine-labelled deuterated MPH [108]. A possible artefact in the detection of *l*-MPH has been proposed to reconcile earlier studies with more recent results [109].

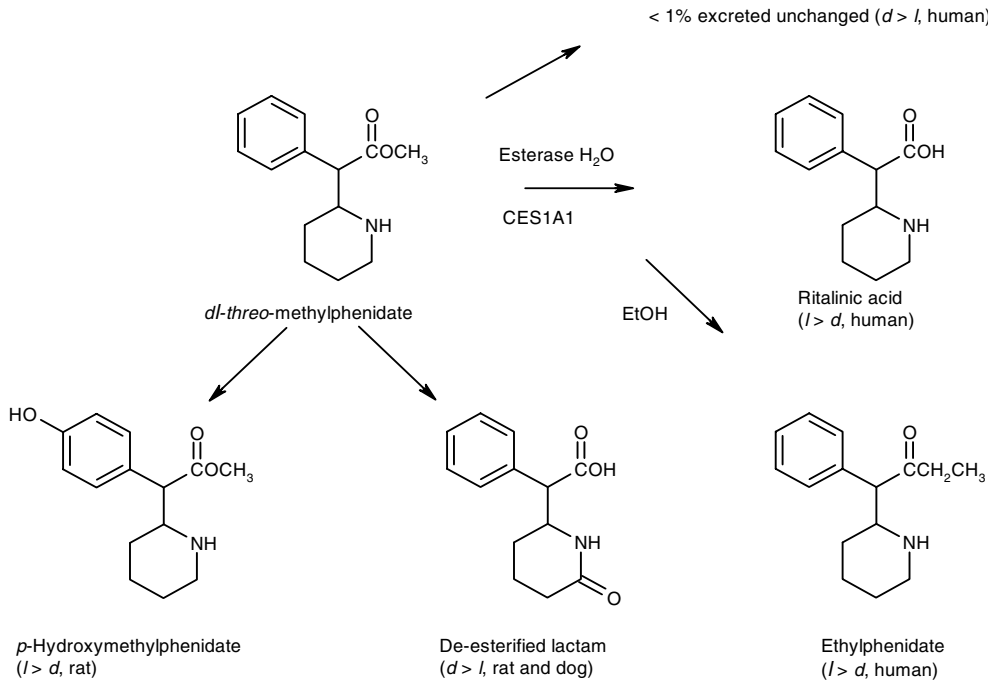

Figure 3. Metabolic pathways of methylphenidate.

2.5 Methylphenidate metabolism

The facile de-esterification of MPH to the inactive [110] metabolite ritalinic acid (**Figure 3**) limits the absolute bioavailability of MPH and contributes to variability. In one study the absolute bioavailability range was 11 – 53% [76]. Plasma concentrations of ritalinic acid far exceed those of the parent drug [65,70,71,111], and urinary elimination of ritalinic acid accounts for 60 – 80% of the dose [60,111,112]. This hydrolysis pathway appears primarily mediated by the carboxyesterase-1 isoform [113]. The enteric first-pass effect appears to account for the low fraction of a dose absorbed (%F). Evidence generated from portal vein versus oral versus intravenous dosing of MPH to rats indicates that, at least in this species, the intestines, rather than the liver, are the primary site of MPH presystemic metabolism [114,115].

2.5.1 Mass balance

In the interest of mass balance, other minor urinary elimination products of MPH include the pharmacologically inactive lactam (< 1%) [60], the de-esterified lactam (5 – 12% of dose) [111], and the unchanged parent drug (< 1%) [60,111,112]. In addition, the potential significance of the active metabolite [110,116] *p*-hydroxy-MPH [117] has recently come to the attention of Volkow and co-workers, who have explored the brain accumulation of radioactivity after administration of labelled *l*-MPH [102]. This metabolite has been reported to be enantioselectively formed; thus yielding primarily the *l*-isomer [103] (**Figure 2** and **3**).

2.5.2 Concomitant methylphenidate and ethanol

Since the 1980s, persistence of ADHD into adolescence and adulthood has been increasingly recognised. Appropriate drug therapy for this older ADHD population requires a special consideration of lifestyle and lifespan comorbidity. Treatment may be complicated by substance and/or alcohol abuse and dependence that is over-represented in adult ADHD [118,119], especially in women [118,120]. Note, however, that appropriate stimulant pharmacotherapy for ADHD may actually decrease substance abuse rates. Nonetheless, coadministration of ethanol with MPH results in the metabolic transesterification of MPH to yield the active metabolite ethylphenidate (**Figure 3**) [81,121-123]. This enzymatic combination of an ester-containing drug with ethanol finds precedent in the well-established formation of cocaethylene following coaministration of cocaine and ethanol [124-126]. The same carboxylesterase isoform may be responsible for both the hydrolysis [113] and ethanolysis pathways as based on structure–activity relationships of other drugs subject to transesterification [126].

Both the esteratic hydrolysis and transesterification of *dl*-MPH occurs enantioselectively, resulting in increased concentrations of *d*-MPH in human plasma [65,70,71,94] and urine [122], and increased *l*-isomer concentrations of ethylphenidate in plasma [123] and urine [122].

In effect, ethanol appears to increase the bioavailability of the *l*-isomer component of a racemic dose, but with a portion of the nonhydrolysed *l*-isomer component reaching the circulation as the ethyl ester, rather than the methyl ester.

This drug–drug interaction also appears to increase the plasma concentrations of *d*-MPH [122], presumably through esterase inhibition of MPH hydrolysis by ethanol.

Under conditions of chemical hydrolysis, ethylphenidate de-esterifies to ritalinic acid at a slower rate than MPH [59,127]. Likewise, ethylphenidate may exhibit a longer pharmacokinetic/pharmacodynamic half-life than MPH [123]. Racemic ethylphenidate has long been established as an active dopaminergic agonist [127,128], and, as with MPH, most of the *in vivo* and *in vitro* dopaminergic agonist activity has recently been shown to reside in the *d*-isomer of ethylphenidate [123]. Consistent with these findings, *d*-ethylphenidate has recently been patented as a potential treatment for ADHD with reduced abuse potential relative to MPH [201].

The potential pharmacodynamic significance of ethylphenidate formation in adult ADHD patients who drink socially, and/or in a high-dose abuse context, is the subject of ongoing investigations. If most transesterification occurs at the level of the gut, as appears to be the case for hydrolysis by the same esterase, then intravenous or intranasal abuse of MPH may still result in the drug being available as an enteric esterase substrate for transesterification. For instance, Levine *et al.* [129] reported MPH concentrations in gastric contents to be > 11-times that of blood in a fatality following intravenous MPH. This MPH accumulation in the stomach after intravenous administration represents a distribution phenomenon consistent with the ion-trapping effect of basic compounds [130,131] including meperidine [132] (which is also a metabolic transesterification substrate with ethanol [126]).

2.6 Methylphenidate gender differences

A population pharmacokinetic study in children with ADHD in which single samples were obtained from 212 boys and 61 girls concluded that few differences in the disposition of MPH existed between the sexes [63]. However, two bioavailability studies in male and female volunteers indicate that when the doses are normalised to the body weight of the subject, females have lower systemic exposure based on a mg/kg dose [133,134]. In addition, Modi *et al.* [70] have reported no differences in AUC between males and females receiving the same total dose, even though females generally weigh less than males. Modi also reported that the major metabolite, ritalinic acid, was significantly greater in female subjects.

Studies specifically designed to evaluate gender effects in MPH pharmacokinetics have only recently been conducted [83,123]. AUC versus normalised dose from a two-way crossover study in 10 males and 9 females, in which each subject received both a 20 mg and 18 mg MPH doses, revealed that the average mg/kg dose in the males was 30% less than the females, yet the average AUC was not significantly different between the sexes. Because the half-life between the two groups was also the same, it could be speculated that more extensive first-pass metabolism of MPH occurs in females. The potential implication of these observations is that females would require larger mg/kg doses to achieve the same MPH plasma concentration. Looking at individual data in this manner also allows one to see the extent of intersubject variability. The clinical significance of gender in MPH therapy has not been evaluated; these data reiterate the potential need for dose titration with frequent monitoring after initiation of therapy regardless of the patient's weight or sex. The apparent sex dimorphism in MPH bioavailability is further supported in ongoing studies by the present authors (unpublished results). The potential effects of the oestrous cycle on MPH pharmacokinetics has not been evaluated in humans.

Preclinical comparisons of *d*-MPH, *l*-MPH and *dl*-MPH reveal sex-dependent differences in both the pharmacodynamics and pharmacokinetics, depending on the isomer content of the dose. Observational evaluations have demonstrated that male rats responded significantly less than females after *dl*-MPH or *l*-MPH, and mean latency in the rota-rod test was shorter in females than in males only when dosed with *l*-MPH [135]. In toxicokinetic studies using rats, females showed approximately a twofold higher exposure to oral MPH than males [106].

3. Methylphenidate formulations

The nomenclature used to describe long-acting MPH dosage forms can sometimes lead to confusion relative to their mechanism for prolonging the drug release and their respective release profiles. A number of MPH product terms have been used to describe these products, such as sustained release (SR), ER/XR, long acting (LA), controlled delivery (CD) or CR. Undoubtedly this proliferation of names and abbreviations has even contributed to medication errors [136]. These abbreviations are commonly incorporated into proprietary names and the variety of terms is limited only by the imagination of the marketing departments, but they do not necessarily reflect an accurate description of the pharmaceutical mechanism used to control the delivery of MPH from a formulation. The difference in the names can be historical; for example, in that the term 'sustained-release formulations' fell out of favour and was replaced by 'controlled-release dosage forms', which later were replaced by 'modified-release drug delivery systems'. The US Pharmacopeia and FDA recognised the confusion generated by the multiplicity of terms used to describe similar products, and efforts were made to codify the terminology. The FDA Guidance for Industry uses the term 'extended-release' to describe dosage forms that allow a reduction in dosing frequency. Accordingly, for the purpose of this formulation review, MPH formulations (oral drug delivery systems) will be referred to as either IR, ER or as pulsed release (biphasic input), even if the initials used in proprietary names are not consistent with the terminology utilised in this review.

3.1 Immediate-release methylphenidate

The beneficial behavioural effects produced by IR formulations of MPH generally diminish sooner than those of amphetamine products [53]. Accordingly, the short actions of IR-MPH gener-

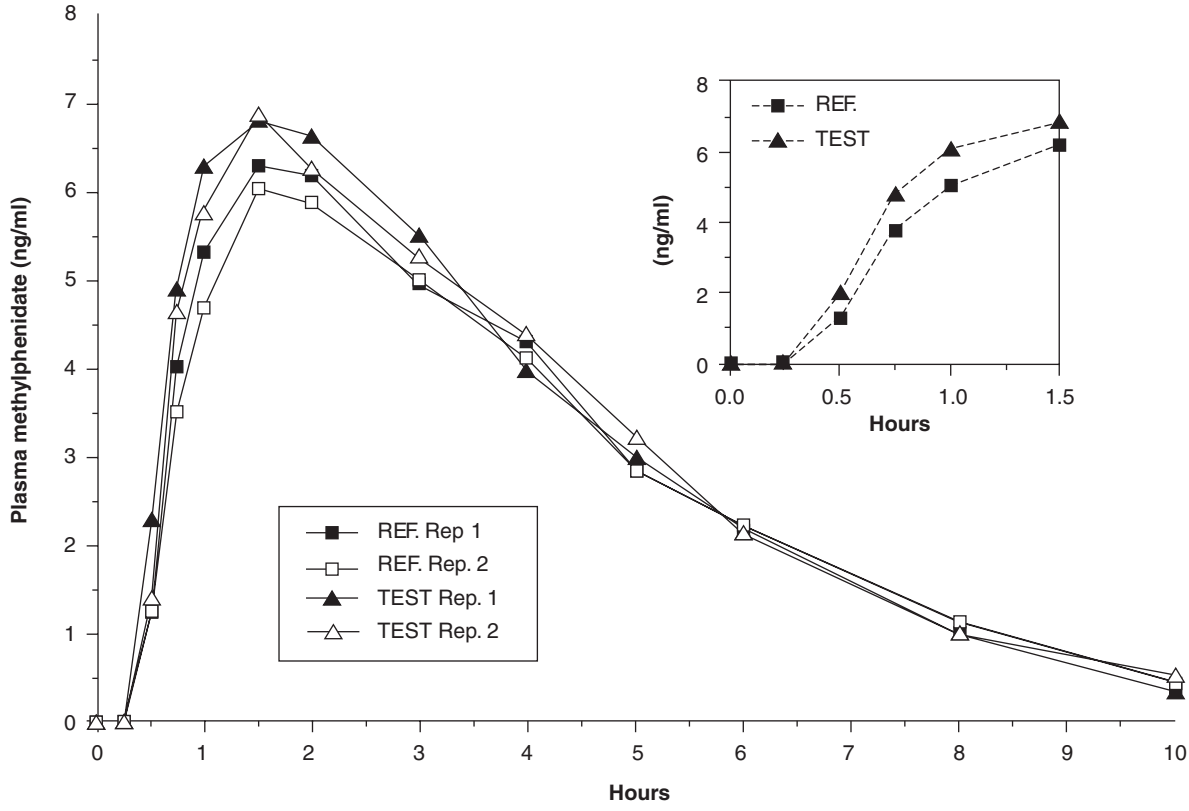

Figure 4. Pharmacokinetic profile of immediate-release methylphenidate. Mean individual replicate methylphenidate plasma concentrations for two 20 mg tablet formulations in 20 subjects. Each subject received the test and reference formulations twice (Rep. 1 and 2). Insert represents combined mean data for both replicates during the initial 1.5 h after dosing. Reproduced from MEYER MC, STRAUGHN AB, JARVI EJ *et al*.: Bioequivalence of methylphenidate immediate-release tablets using a replicated study design. *Pharmaceut. Res.* (2000) **17**(4):381-384, with permission from Spinger/the language of science.

ally dictate multiple daily dosing to medicate through the course of a typical school day. The resulting on-again-off-again absorption profile may result in the so-called 'roller-coaster' response for twice-daily or three-times-daily dosing regimens [39,302].

Anecdotal reports of nontherapeutic equivalence between the innovator IR-MPH (Ritalin®; Novartis) and generic IR-MPH [137,40] compelled the FDA to conduct a bioequivalence study in healthy adult volunteers using the rigor of a bioreplication study design. The two tablets were considered bioequivalent on the basis of the average bioequivalence criterion utilised by the FDA. However, the intrasubject variability of the generic product was greater than that of the innovator product [62] (**Figure 4**). A second branded IR-MPH product (Methylin®; Mallinckrodt, Inc.) has more recently been marketed in smaller tablets than those of the innovator without any known bioequivalence issues. The smaller size could offer an advantage in the ease of swallowing, especially in small children.

3.2 Dexmethylphenidate and methylphenidate enantiomers

Until the introduction of the enantiopure *d*-MPH product [*d-threo*-(*R,R*)-MPH, dexmethylphenidate, Focalin] in 2002 (the jargon 'racemic or chiral switch' product), all marketed MPH formulations contained a racemic (1:1) mixture of *d-threo-(R,R)*-MPH and *l-threo*-(*S,S)*-MPH isomers (**Figure 2**). The psychotherapeutic effects [90,92], as well as the undesired pressor [47] (see [138,139]) and anorexic action [140,141], reside primarily in the *d*-enantiomer.

Although the most widely prescribed medication for the treatment of ADHD is racemic *dl*-MPH, the clinical effectiveness appears to reside in the *d*-isomer [90,92,95,142,143]. Srinivas *et al.* [90] demonstrated similar improvement on sustained attention testing after treatment with *d*-equivalent doses of *d*-MPH and *dl*-MPH, but not after *l*-MPH. This study also demonstrated similar pharmacokinetics of *d*-MPH after the administration of equimolar doses of *d*-MPH as either a pure enantiomeric formulation or as a *dl*-racemic mixture. Consequently, the synthesis and clinical development of *d*-MPH was undertaken, which culminated in the approval of *d*-MPH in 2002 [141,143]. The clinical development and study doses utilised were half those of racemic MPH, and pharmacokinetic parameters are generally similar between *d*-MPH and *dl*-MPH with respect to C_{max}, T_{max} and half-life [133,134]. Likewise, metabolism and elimination are similar to racemic MPH, and *d*-MPH has not been found to inhibit CYP isoforms during *in vitro* studies [142].

Administration of *d*-MPH did not result in interconversion *in vivo* to the inactive *l*-isomer [143]. This lack of demonstrable interconversion is to be expected due to the presence of two chiral atoms, which would require the unprecedented inversion of configuration of *two* stereogenic centres. The possibility of epimerisation to the erythro stereoisomers, (*R,S*)-MPH and/or (*R,S*)-MPH (*R,S* and *S,R* designate absolute stereochemistry), as is known to occur at least under harsh chemical conditions [110], has not been addressed in the literature and would not be evident as a coeluting chromatographic peak except by coincidental retention time.

The administration of *d*-MPH with food has no significant effect on bioavailability, but as with racemic MPH, T_{max} was delayed by 1 h [95]. Treatment with *d*-equivalent doses of either *d*-MPH or *dl*-MPH significantly improved symptoms of ADHD compared with placebo. In addition, at least one study [109] suggested that *d*-MPH might have a longer duration of action than *dl*-MPH on tests measuring attention/concentration and work output, but this issue requires further controlled study. The use of *d*-MPH in ADHD allows the administration of lower doses than those currently prescribed with *dl*-MPH; *d*-MPH is available in 2.5, 5 and 10 mg IR tablets [142]. An ER formulation of D-MPH (Focalin-XR) is not marketed at present, but the efficacy of once-daily 20, 30 and 40 mg capsules utilising the SODAS™ (Elan) dosage form in adult ADHD has been recently reported [144], and is in the advanced stages of clinical study.

The *l*-MPH isomer of racemic MPH formulations has been regarded as innocuous, a 'passive component/isomeric ballast', and due to the added expense of commercially producing an enantiopure *d*-product, the continued development of racemic MPH formulations may be justifiable [145]. However, the *l*-MPH isomer of racemic formulations may not necessarily represent an inert component. For instance, there has been speculation that *l*-MPH contributes to the abuse potential of *dl*-MPH [146], and as indicated above, in the absense of *l*-MPH, the pharmacodynamic actions of *d*-MPH were reported to be extended [109]. *l*-MPH has recently been patented as an antidepressant and tested on healthy subjects [202,147], as well as patented as a potential therapy for anxiety, psychosis, mania, and as an 'antidote' for stimulant overdose [203].

Efforts have been directed at developing transdermal formulations of MPH (MethyPatch®, Noven Pharmaceuticals, Inc.) [148,149]. Such an approach could lay the groundwork for an *l*-MPH delivery system circumventing its profound extent of putative enteric first-pass metabolism. However, transdermal delivery may not overcome presystemic enantioselective metabolism. Ahmed *et al.* [150] reported that a racemic ester prodrug was subject to more extensive enantioselective de-esterification by mouse skin tissue than by liver or plasma. Accordingly, first-pass transdermal influences on MPH isomer disposition warrant investigation.

Recent preclinical studies assessing the comparative behavioural effects of *l*-MPH and *d*-MPH in rats has revealed that females were more sensitive than males to some effects of the *l*-isomer and more sensitive to both isomers in other elements of an observational battery [135]. In related studies, the degree of dilated pupils and vocalisation was greater for the racemate than the pure *d*-enantiomer given at half the dose [151]. No genotoxicity has been attributed to either MPH isomer in both *in vitro* and *in vivo* studies, although very high oral doses of even the *l*-isomer produced behavioural, and even lethal, effects in mice [152]. Behavioural activity may be attributable to *l*-MPH when comparing D-MPH with twice the dose of *dl*-MPH in pregnant animals. Inclusion of the *l*-isomer when comparing *dl*-MPH with *d*-MPH resulted in potentiation of repetitive pawing, dilated pupils and aggressive behaviour in rats, and head-bobbing and hyperpnea in rabbits [153].

A MPH enantiomer–enantiomer pharmacodynamic interaction has been associated with the neuropharmacology of racemic MPH. In human volunteers, *d*-MPH was reported to be less 'energising' than *dl*-MPH [202]. In preclinical studies, the *l*-MPH isomer inhibited the locomotor stimulation by *d*-MPH, cocaine or apomorphine in rats in a dose-dependent fashion [203]. These results contrast with those in mice, in which Ding *et al.* reported that *l*-MPH enhances the locomotor stimulatory activity following cocaine [101,102].

Davids and co-workers [154] assessed the activity of the separate MPH enantiomers in a rat model of ADHD which uses neonatal lesioning of cerebral dopaminergic systems with 6-hydroxydopamine to induce hyperlocomotion. Challenges with *d*-MPH, *l*-MPH, racemic MPH or saline in these rats demonstrated that *d*-MPH was more than three times more active in reducing motor activity than was racemic MPH. A twofold reduction would be predicted if *l*-MPH was inert. Furthermore, pretreatment of the lesioned rats with *l*-MPH attenuated the motor activity response *d*-MPH. Although not confirmed in a human clinical study, these findings suggest that clinical efficacy may be obtained with *d*-MPH administration in doses substantially lower than presumed equipotent doses (i.e., 50% of *dl*-MPH dose).

Toxicokinetic studies in rats also revealed a pharmacokinetic enantiomer–enantiomer interaction. Orally dosed racemic MPH increased the bioavailability of the *d*-isomer relative to dosing with only the *d*-isomer [106].

3.3 First-generation extended-release methylphenidate

The rapid metabolic de-esterification of MPH limits the drug's half-life to only 2 – 3 h (**Tables 1** and **2**); thus, usually requiring multiple daily dosing of IR-MPH to provide medication coverage throughout the day. Accordingly, after the availability of IR-MPH for 30 years, a 20 mg branded ER-MPH formulation became available in 1983 under the proprietary name Ritalin-SR®. At the time of its launch, the term 'sustained release' was popular and the abbreviation SR was more than reasonable, as the product was primarily developed for morning-only administration. Subsequently, a 20 mg generic equivalent to Ritalin-SR became available [79] (**Figure 5**), and is now also marketed as 10 and 20 mg Metadate®-ER (Celltech

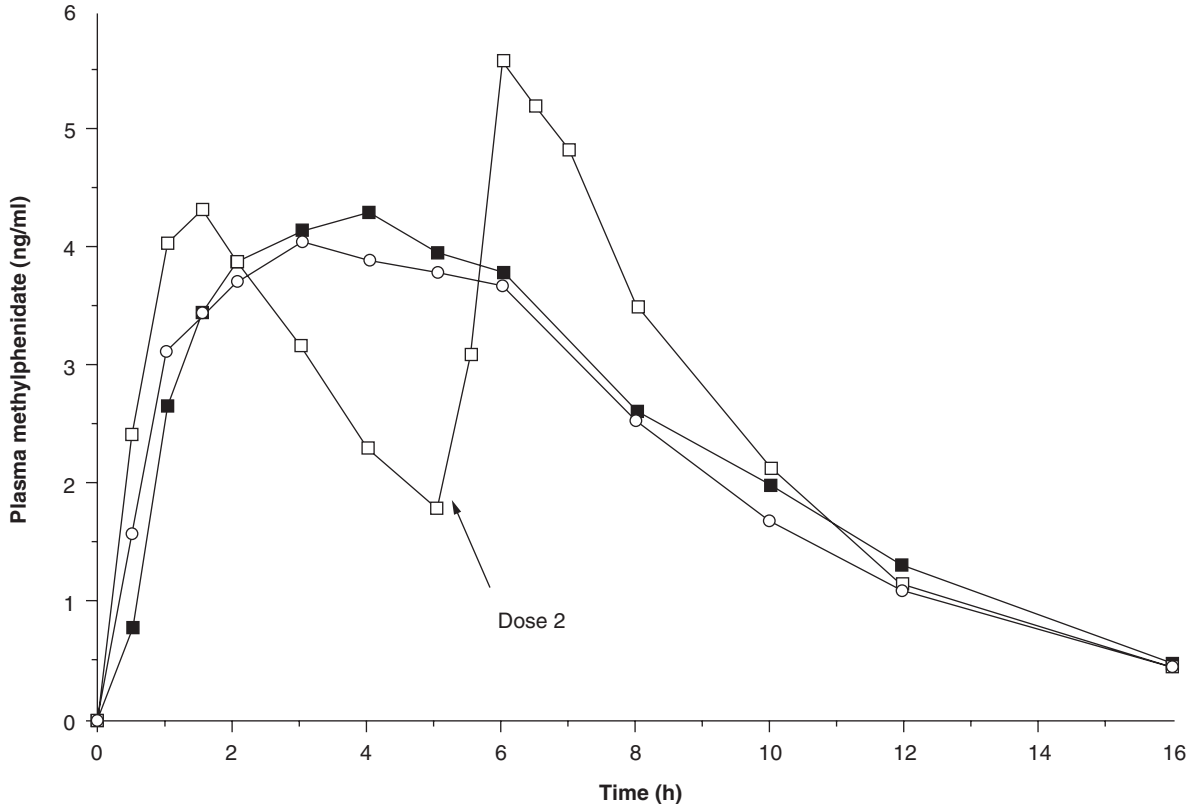

Figure 5. Pharmacokinetic profile of immediate-release methylphenidate (10 mg b.i.d.) compared with that of the Ritalin-SR® (20 mg) and the generic sustained-release product (20 mg). Mean concentration-time profiles (n = 18) comparing two 20 mg SR-MPH (closed squares, circles) formulations versus IR-MPH (open squares) dosed twice daily. From PATRICK KS, STRAUGHN AB, JARVI EJ, BREESE GR, MEYER MC: The absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. *Biopharm. Drug Dispos.* **10**:165-171, copyright (1989). Copyright John Wiley & Sons Ltd. Reproduced with permission.

Pharma, Ltd.) and Methylin-SR. All of these SR products share the property of being ER formulations intended to duplicate the efficacy of IR-MPH, and so decrease the dosing frequency. This allows greater dosing convenience and improved compliance, while minimising drug storage security issues at school, and avoiding stigmatising children who may be subject to peer ridicule due to dosing with IR-MPH during school hours [155,156].

The early ER formulations utilised a wax-matrix or similar vehicle to provide slow continual release of *dl*-MPH. These formulations ideally produce a more gradual rate of absorption than IR-MPH and reach a relative plateau at C_{max}, minimising plasma trough(s) during the day. The subsequent plasma MPH concentration decay for these early ER products occurred more gradually than that of IR.

A regimen of once-a-day ER-MPH has been suggested to also offer potential relief to individuals who experience stomach upset with IR-MPH [157]. The extended action of the ER formulation may be appropriate for those exhibiting significant behavioural rebound toward the end of the day on a twice-daily schedule [158]. The effects of the older ER-MPH such as Ritalin-SR may still be evident up to 8 h after dosing [159-161].

As an alternative to ER-MPH, three-times-daily IR-MPH may serve to ameliorate potential behavioural 'rebound' effects. The third dose (at 16.00 h) has been reported not to affect sleeping patterns [162], but may significantly diminish appetite [163]. Dosing optimisation for some individuals has been achieved by combined dosing of IR- and ER-MPH formulations [157].

A single morning dose of the first-generation 20 mg ER-MPH results in an 1 – 5 h delay in T_{max} relative to a morning 10 mg IR tablet [79]. This is consistent with clinical efficacy results that reported a delayed onset of action for SR versus IR MPH [159]. Whereas the ER formulation provides a C_{max} 20% lower than the C_{max} resulting after a 10 mg IR-MPH b.i.d. schedule (**Figure 5**; IR-MPH dosed twice), the AUC for the 10 mg b.i.d. schedule relative to a single 20 mg ER morning dose is nearly identical [79].

The relative efficacy of twice-daily IR versus morning ER-MPH is a subject of controversy. Both have been reported to produce comparable beneficial effects in the treatment of ADHD [159-161], although a few specific behavioural differences have been noted [159]. A greater tolerance liability [158] and a lower clinical efficacy for the original ER-MPH relative to IR have also been suggested [158,164]. Both regimens have been associated with less insomnia than with dextroamphetamine or pemoline [160].

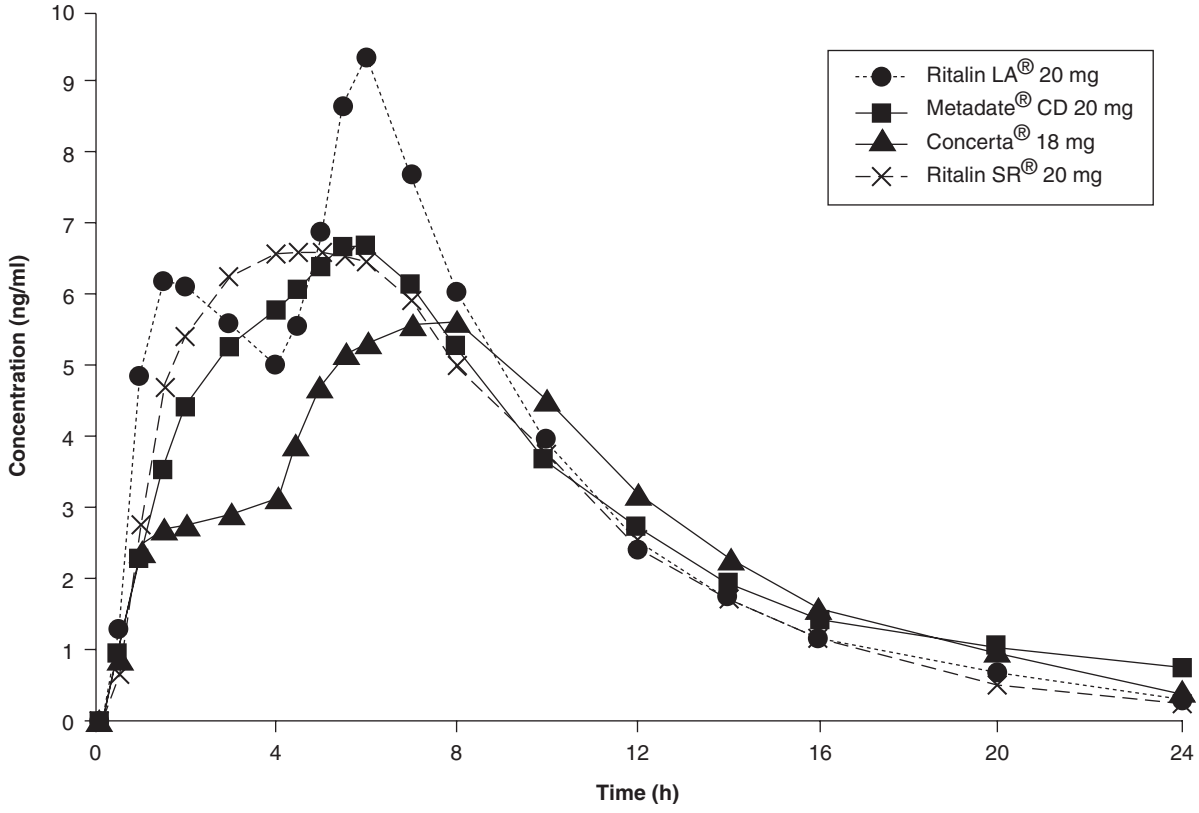

Figure 6. Pharmacokinetic profiles of newer extended-release methylphenidate formulations. Reproduced from MARKOWITZ JS, STRAUGHN AB, PATRICK KS: Advances in the pharmacotherapy of attention-deficit hyperactivity disorder: focus on methylphenidate formulations. *Pharmacotherapy* (2003) **23(**10): 1281-1299; with permission from *Pharmacotherapy.*

4. Newer extended-release methylphenidate formulations and 'acute tolerance': tachyphylaxis

Based on time–response analysis [165], the first 2 – 3 h after IR-MPH administration corresponds to the greatest improvement in cognitive performance. This period also corresponds to the absorption phase for IR-MPH, leading to the hypothesis that the therapeutic response to MPH is associated more with the rate of rise in the blood drug concentration than with the extent of drug absorption, or with the ultimate concentration attained. This absorption phase–response relationship for MPH has been termed the 'ramp' [157] or 'gradient' effect [53]. Taking this supposition further, the steeper absorption curve associated with IR-MPH relative to the SR form may constitute a basis for differential efficacies.

The potential benefit of an ascending blood concentration time course has been explored and supported by model systems in which ADHD children were administered up to 15 doses of an IR-MPH capsule at an increasing dose [166] over 8 h. These patients exhibited superior attention and deportment when compared with ADHD children who received similar multiple MPH administrations but given a constant dose such that plateau plasma levels were achieved. Nevertheless, the clinical significance of tachyphylaxis as pertains to MPH response remains theoretical in nature, and the need for 'ramp' plasma concentrations may not be as necessary as the achievement of optimised plasma concentrations in individual patients.

4.1 OROS® technology (Concerta®)

Seeking to avoid the aforementioned acute tolerance perhaps associated with first-generation ER-MPH formulations [79,167,168], the OROS® (osmotic, ER oral delivery system) MPH product was developed by Alza. This product combined IR and SR properties to provide for an initial rapid rise in circulating concentrations after the morning dose, followed by an ER phase which led to a second peak at a later time [65,70,71,169]. The formulation was designed to provide the same medication coverage as three-times-daily IR-MPH, providing a 12-h duration of action. The overall MPH blood concentration increase, or ascending plasma concentration period, over the first 6 – 8 h after dosing has been purported to offset tachyphylaxis by producing 'ramp' plasma levels. This product was approved in 2000 and is marketed by McNeal (Johnson & Johnson) under the name Concerta® with tablet strengths of 18, 27, 36 and 54 mg.

The tablet utilises osmotic pressure to deliver MPH at a controlled rate through a trilayer core. The drug overcoat contains 22% of the MPH dose and dissolves rapidly to provide an initial MPH absorption pulse. Subsequently, water permeates the osmotically active resin portion and releases MPH through a laser-drilled orifice [170]. The remainder of the tablet stays intact and is passed in the stool as a shell ('ghost') and insoluble core [301]. The OROS dosage form provides a plasma concentration–time profile characterised by an ascending absorption curve and lower peak plasma concentrations (**Figure 6**) with less fluctuation in plasma concentrations than IR-MPH [70]. It should be noted, however, that significant intersubject differences do exist in the Concerta release profiles [83]. In addition, tablets may not be opened, crushed or divided. The insoluble nature of this tablet shell may have implications in patients with swallowing difficulties or gastrointestinal narrowing/obstruction. The insoluble shell of the OROS product possesses some special risks in the event of lodging in the oesophagus [171].

Efficacy in controlling the core symptoms of ADHD was reported to be similar between once-daily OROS-MPH when compared against three-times-daily IR-MPH [172]. A 1-year follow-up study of 452 ADHD children receiving OROS-MPH found no tolerance to the pressor side effects of the drug [173].

As with IR-MPH [76], Concerta may be administered without special regard to meal time. A bioavailability study in normal volunteers comparing fasting versus fed states found that a high-fat breakfast did not significantly affect the extent of absorption of MPH from 18 or 36 mg tablets, but resulted in a 1 h delay in time to the initial peak concentration (T_{max}), and a 10 – 30% increase in maximum plasma concentration (C_{max}) and AUC [65]. No dose dumping was observed.

ADHD may be a risk factor in driving accidents. The delivery profile offered by Concerta MPH in ADHD prevented the worsening of evening driving scores 12 and 15 h after dosing. Doses were individualised for participants and the driving scores were better than when compared with IR-MPH (08.00, 12.00, 16.00 h) [174].

The OROS formulation contains *dl*-MPH hydrochloride combined with excipients and polymers to reduce the input rate of MPH. This reduces the possibility of using the tablet for intranasal abuse and preventing the usual 'high' experienced by a substance abuser who can pulverise an IR product prior to intranasal administration [175]. Intranasal abuse of both IR-MPH [176] and earlier ER-MPH [177] produces the characteristic stimulant effects, including euphoria, paranoia, tachycardia and even death [178]. Controlled clinical studies of intranasal MPH have recently established dose–response relationships for both subjective and physiological effects [179]. The rapid elevation of MPH blood levels associated with MPH after intranasal abuse significantly increases abuse liability [180]. It is important when prescribing MPH in ADHD patients with comorbid substance abuse disorder to consider the implications of the MPH formulation to be prescribed.

4.2 Diffucaps® technology (Metadate®-CD)

Another novel entrant to the ER-MPH market is Celltech Pharmaceutical's Metadate-CD which utilises Eurand International's Diffucaps® technology and is designed to mimic the usual schedule of IR-MPH. Metadate-CD is a multiparticulate product utilising a blend of pellets or beads in a hard gelatin capsule. The pellet blend is composed of 30% IR-MPH and 70% ER-MPH released gradually over 3 – 4 h (**Figure 6**) [181]. Initial formulation development studies indicated that the 30:70 IR:SR dose ratio provided more consistent therapeutic effects than either 20:80 or 40:60 ratios [84]. The resulting pharmacokinetic profile of this dosage form is biphasic in nature and distinctly different from OROS (**Figure 6**) [181,182]. Comparative pharmacokinetic studies in normal volunteers suggest that Metadate-CD provides more rapid absorption that may be indicative of an earlier pharmacodynamic response [82]. As with Concerta, the presence of food delays the T_{max} by 1 h and current packaging labelling suggests administering Metadate-CD prior to breakfast [181]. In a study in adults, a high-fat meal increased C_{max} by about 30% and the AUC by about 17% [181]. In addition, Metadate-CD capsules can be opened and sprinkled on soft food such as applesauce for ease of dosing without any significant changes in bioavailability relative to the administration of the intact dosage form. Metadate-CD is available as 10, 20 and 30 mg capsules [181].

González *et al.* [82] compared the pharmacokinetics of near mg equivalent dosages of Metadate-CD and Concerta in a crossover study conducted using healthy male and female volunteers. Although the MPH plasma profiles differed, with Metadate reaching higher levels at earlier times, the doses compared were equivalent in terms of total MPH exposure as measured by total AUC as well as maximal exposure (C_{max}). Differences between the products were quantified only when partial AUC values were calculated for the earlier time points, thus suggesting a lack of bioequivalence between Concerta and Metadate-CD. Efficacy differences due to time-related differences in plasma profiles were evaluated in a randomised, crossover, double-blind, placebo-controlled study in a laboratory classroom [182]. Paediatric patients were administered equivalent MPH doses of Concerta and Metadate-CD. Clinical superiority at any time point was achieved for the formulation with the highest expected plasma MPH concentration. This data supports optimising plasma concentrations of MPH by individualising dosage regimens. Thus, flexibility of doses is desirable for any ER-MPH formulation.

4.3 SODAS™ technology (Ritalin® LA)

The most recently available ER-MPH capsule is from Novartis Pharmaceuticals and utilises the Spheroidal Oral Drug Absorption System (SODAS) bead technology [183]. The capsule contains 50% IR-MPH beads and 50% ER beads. The latter are polymer coated to offer a 4 h delayed release of MPH (absorption lag-time) before gastrointestinal water erodes this coating to release the second pulse of MPH. The resultant MPH plasma profile is distinctly biphasic and

reminiscent of twice-daily IR-MPH (**Figure 6**) [83,183]. SODAS capsules can be opened and sprinkled on soft food such as applesauce if needed without altering the pharmacokinetic profile [184]. With regard to meals, Ritalin LA may be given without regard to food; although, as with the other modified-release MPH formulations, high-fat meals may delay the T_{max} by 1 h. The overall extent of absorption is not significantly affected by food [184]. Ritalin LA is available in 20, 30 and 40 mg capsule strengths.

5. Comparative bioavailability of newer extended-release methylphenidate dosage forms

From the perspective of most regulatory agencies, a drug's bioavailability is defined by the extent of absorption (total exposure) and by the rate of absorption. In most instances, measuring the extent of absorption is relatively straightforward through estimates of the AUC for the plasma concentration profile. The rate of absorption, however, is more elusive because a single parameter, such as absorption rate constant, is inadequate to characterise this complex process for most drugs. Therefore, most agencies accept a surrogate parameter (C_{max}) to define rate. This measure of maximum exposure is adequate for most conventional IR dosage forms, but this can be misleading for ER formulations.

To help evaluate early exposure, some agencies (e.g., US FDA) have adapted an additional absorption parameter known as a partial AUC, typically the AUC from 0 to the time of C_{max}. This parameter may also be of value when a rapid achievement of C_{max} is essential to the therapy (e.g., some analgesics). For the appropriate labelling of new drugs and formulations, bioavailability studies are essential to define these parameters, which are critical in aiding clinicians with the development of dosage regimens. In the instances where manufacturers make formulation changes, scale up the batch size from clinical trials formulation to production, or when a generic manufacturer seeks approval, bioequivalence (i.e., relative bioavailability) studies are usually needed to show therapeutic equivalence prior to regulatory approval. The acceptance criteria in these instances are based on the assumption that two formulations with the same bioavailability (i.e., bioequivalence) will exhibit the same pharmacodynamics (i.e., therapeutic equivalence).

In the US, an extensive listing of therapeutically equivalent drug products can be found in a continuously updated publication known as the Orange Book [201]. It should be noted that although there are several generic sources for IR and conventional ER-MPH products found in the Orange Book, there are no therapeutically equivalent ratings for the newer ER formulations (Concerta, Ritalin LA or Metadate-CD). Although all these ER formulations (OROS, Diffucaps and SODAS) have been shown to have essentially the same extent of MPH absorption relative to equivalent doses of the IR formulations, the bioavailabilities of these formulations are not the same because of the different absorption rates. The programmed drug release patterns in these products were intentional, and unless both the prescriber and dispenser are aware of the potential pharmacodynamic implications inherent in the different rates of absorption, interchanging these products based on the assumption that they are 'bioequivalent' can result in therapeutic failure. In fact, just based on the pharmaceutical classification of these products, the FDA would not consider them therapeutically equivalent – even if they there were bioequivalent – because of the differences in dosing strengths (18 versus 20 mg) and differences in dosage form (tablets versus capsules, respectively) [303]. Although these differences in dose and dosage form may seem inconsequential relative to substitution, the resulting plasma profiles from these products are distinctly different, and achieving appropriate therapeutic outcomes may be compromised by unwittingly switching patients from one to the other. On the other hand, these differences offer clinicians more options to use the same therapeutic moiety to achieve a positive outcome without having to change the drug (MPH) itself. For example, a casual evaluation of the plasma profiles achieved by these products (see **Figure 6**) shows why some patients may have a better response in the morning on one product, but better response in the afternoon on another. Ritalin LA produces approximately twice the exposure to MPH in the morning compared with Concerta, whereas the Concerta concentrations are generally higher in the afternoon/evening hours [83].

The clinician must be aware of these unique patterns of absorption in order to define the most appropriate product for their patients. This is especially true with more adolescent and adult patients now being treated for ADHD, and the relationship of the pattern of drug delivery to lifestyle may require even closer scrutiny for appropriate control. Finally, regardless of the formulation chosen, the clearance of MPH is such that residual drug concentrations will be minimal after 24 h, thus allowing evaluation of different formulations and doses in the same patient without an extensive washout period. This also presents options to individualise dosage regimens based on the patient's individual needs through the week.

6. Comparative pharmacodynamics among newer extended-release methylphenidate formulations

In general, pharmacodynamics can be defined as the relationship of drug exposure to response. The interpretation of this definition, however, depends on the context in which one uses 'response' and 'drug exposure'. Essentially, the literature on clinical pharmacodynamics can be divided into two categories: i) Phase III type trials evaluating efficacy (i.e., emphasis on response); and ii) Phase I and II type studies that attempt to elucidate the reasons for the specific drug actions (i.e., emphasis on the time course of both response and exposure). To most clinicians, the term pharmacodynamics is synonymous with pharmacological or therapeutic effect, with little

emphasis being given to the quantification of exposure outside of dose. Over the years the definition of pharmacodynamics has expanded to include the relationship of the dynamics of drug concentration at the receptor sites (exposure over time) to changes in response over time. Studies able to quantify this pharmacokinetic/pharmacodynamic link have greatly expanded our understanding of drug response. Therefore, a robust pharmacodynamic study will usually involve multiple response measurements paired with corresponding receptor site concentrations.

Obviously, because of technical and ethical considerations related to sampling of drug at specific receptors sites, human pharmacodynamic studies frequently utilise serial peripheral blood sample concentrations as a surrogate for drug at the effect site (i.e., CNS). Additional difficulties are also present when attempting to use serial blood sample collections to define the pharmacokinetics in children while at the same time monitoring multiple response variables. Nevertheless, valuable concentration and response data has been generated in children revealing nonlinear relationships of clinical importance. For example, with MPH the existence of hysteresis has been used to develop theories on acute tolerance. In addition, pharmacodynamic studies have alerted clinicians to the fact that the rate of MPH absorption can be an important factor in achieving therapeutic response. However, prior to accepting studies of this nature as proof that these new delivery systems result in improved pharmacodynamics of MPH, the logistical limitations of conducting these relatively complex clinical trials in children should be taken into account. For the most part these studies have made the link between kinetics and dynamics based on serial blood sampling of MPH concentrations in one group (sometimes adults and sometimes children) and the evaluation of response in another group.

The methodology of collecting pharmacodynamic data in children has been refined with natural classroom environment studies; however, aside from assessment of academic performance with math scores, the behaviour evaluations – although standardised – are subjective, and the time frame for the evaluations are usually only inclusive for the school day. Evaluation of these studies should also take into account whether or not blinding was utilised, especially when once-a-day therapy is compared with two- or three-times-daily IR-MPH. With this in mind, it should be realised that the limited published data comparing clinical differences among the newer ER formulations do not represent pharmacodynamic studies in the purest sense because of the lack of simultaneously collected pharmacokinetic data. In addition, each study needs careful evaluation to be assured that the 'measured' clinical responses are consistent with the 'implied' behavioural outcomes. Regardless of the shortcomings of most pharmacodynamic comparisons of ER-MPH formulations, well-controlled clinical trials do provide essential information related to the appropriate utilisation of this drug.

The performance of each of the new ER formulations has been well evaluated clinically, and all have shown to elicit positive behaviour modifications relative to placebo. Although some formulations have claimed aspects of superiority to the IR dosage regimen they were designed to replace, most studies have concluded essentially similar responses when comparing IR- with ER-MPH treatments.

Little published data are available with regard to clinical differences between the newer ER-MPH formulations. However, at least two trials have been published and some preliminary data are available. A head-to-head multisite, randomised, double-blind, placebo-controlled clinical trial (n = 184) between the Metadate-CD formulation and Concerta versus placebo was carried out in children (ages 6 – 12 years) diagnosed with ADHD [182]. Patients were stratified into one of three treatment groups based on pre-existing MPH dosage requirements. These groups were Metadate-CD versus Concerta in doses of 20 versus 18 mg, 40 versus 36 mg, and 60 versus 54 mg, respectively. It is noted that in each comparison, the Metadate-CD formulation contained 2 – 5% more MPH than the corresponding Concerta product. Within each assignment group, patients were randomised to receive one of six treatment sequences, receiving each of the three blinded treatments for 1 week. The study utilised the SKAMP deportment and attention subscales, and age-appropriate math test for permanent product score (PERMP) as primary measures of effectiveness. In addition, 26-item SNAP-IV rating scales were completed by parents or guardians. Metadate-CD was reported to be superior to the Concerta dosage form in ADHD symptom control as evidenced by a 47% reduction in SKAMP deportment scores between 1.5 and 7.5 h. At the 12 h time point, SKAMP scores were not significantly different from placebo for any dosage of either formulation, and there were no statistically significant differences between active treatment groups on the SKAMP attention subscale, PERMP or SNAP-IV. Of note, results were not reported for individual MPH dosing regimens. This study suggests a more rapid onset of effect with Metadate-CD compared with Concerta.

A second head-to-head comparison trial was also recently completed. This study utilised a single-blind, randomised, four-way crossover design and compared two doses of Concerta (18, 36 mg) versus Ritalin LA 20 mg or placebo in 36 children (ages 6 – 12 years) diagnosed with ADHD who were previously stabilised on MPH [185]. The study was designed to assess differences in treatment over an 8 h school day. All subjects were exposed to all treatments. Study subjects had been previously maintained on MPH doses equivalent to 10 mg IR-MPH b.i.d. Subjects were randomly assigned to four treatment periods over 4 weeks. The primary efficacy variable was the 0 – 4 h change from predose measurement in SKAMP-Attention ratings. For the secondary efficacy variables, the Math Test-Attempted, Math Test-Correct, SKAMP-Deportment and SKAMP-Combined ratings were used. In this study, Ritalin LA 20 mg proved superior over placebo and both doses of Concerta on all SKAMP measures over the first 4 h, and superior on SKAMP deportment scores over the entire 8 h. Subjects receiving Ritalin LA 20 mg were also found to have

attempted approximately twice as many math problems as those treated with Concerta 18 or 36 mg over an 8 h school day. In addition, subjects treated with Ritalin LA 20 mg achieved a greater percentage of problems correct over the first 4 h compared with Concerta 18 or 36 mg, and the difference reached statistical significance. The results of this small trial suggest that there are meaningful pharmacodynamic differences between these two MPH delivery systems, especially in terms of efficacy in the early part of the school day. A limitation of the study is that no measures were obtained beyond the 8 h time point where the Concerta dosage form is designed to allow extended coverage. Although preliminary, these two studies suggest that there may be some significant differences in efficacy among the newer once-daily formulations which may be attributable to MPH release profiles.

7. Expert opinion

IR-MPH has been in clinical use for 50 years. Its sustained record of clinical efficacy, tolerability and safety has established this agent as the 'gold standard' in the pharmacotherapy of ADHD. Conventional ER-MPH formulations initially became available in the early 1980s (e.g., Ritalin-SR) and were said to offer the convenience of once-a-day dosing while avoiding compliance, confidentiality and school storage security issues. In view of more recent pharmacodynamic/pharmacokinetic correlations, a focus on the absorption phase of MPH has resulted in a new generation of once-daily ER-MPH formulations. These employ novel modified-release technologies providing unique prolonged absorption profiles. Indeed, it is notable that in the last 5 years more novel MPH dosage forms have been introduced into the US marketplace than the previous four decades.

With the exception of the Focalin IR product (now in late clinical development of a long-acting SODAS formulation), these newer formulations employ novel modified-release technologies and provide prolonged absorption profiles. Concerta provides an 'ascending' absorption phase for an average of 8 h, with a lunchtime plateau, and is said to provide symptomatic coverage comparable to dosing of IR-MPH t.i.d. Metadate-CD also exhibits a biphasic profile (30:70 IR:ER ratio) with a faster absorption phase with an average duration of therapeutic plasma levels of 7 h, but may provide therapeutic efficacy for 8 – 10 h postdosing. Ritalin LA, another biphasic release dosage form (50:50 IR:ER ratio), better mimics the time course of a standard twice-daily schedule of IR-MPH than the former two formulations, although a between-peak trough is minimised relative to the IR product. It also provids 8 – 10 h of efficacy. Accordingly, each of these new modified-release products is characterised by a unique pharmacokinetic profile to allow greater prescribing flexibility for therapy optimisation in ADHD patients [42]. Comparative trials of ER dosage forms are beginning to emerge which may help to discern significant differences between products that may aid both clinical and formulary decision processes [185,186], as well as influence future formulation development.

d-MPH (Focalin) is the most recently introduced MPH formulation. Although presently available only as an IR formulation, this single isomer product offers potential advantages over the above racemic formulations in terms of potency (i.e., reduced overall drug exposure and, possibly, longer duration of action and 'cleaner' pharmacological effects). The availability of a long-acting *d*-MPH (Focalin-XR) is anticipated in the near future and could emerge as the long-acting MPH preparation of choice should comparative studies indicate superiority in effect sizes, tolerability and/or duration of action.

The availability of newer therapeutic alternatives to clinicians treating ADHD with pharmacotherapy is a welcome development in the management of this prevalent disorder. To be sure, drug development in this area of clinical psychopharmacology has been relatively stagnant over the last several decades prior to 2000. Numerous emotionally charged issues related to the treatment of ADHD play a role in the marketing strategy employed by pharmaceutical companies. No doubt, as more is understood about the underlying mechanisms of different therapies, the ability of the clinician to make decisions based on sound scientific judgments rather than 'marketing hype' will be enhanced. For the most part, these new formulations make therapy more convenient relative to IR regimens; and most patients, parents and teachers are more satisfied with the treatment. Although one ER-MPH formulation cannot be universally recommended over others at present, it is clear that the availability of additional choices among MPH pharmaceutical dosage forms brings clinicians closer to the desired goal of increasingly individualised pharmacotherapy for ADHD.

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