Advances in the Pharmacotherapy of Attention-Deficit-Hyperactivity Disorder: Focus on Methylphenidate Formulations

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Advances in the Pharmacotherapy of Attention-Deficit–Hyperactivity Disorder: Focus on Methylphenidate Formulations

John S. Markowitz, Pharm.D., Arthur B. Straughn, Pharm.D., and Kennerly S. Patrick, Ph.D.

The psychostimulant *dl*-methylphenidate (MPH) remains the most common drug therapy in child and adolescent psychiatry for the treatment of attention-deficit–hyperactivity disorder (ADHD). Evidence of a dopaminergic basis both for the actions of MPH and for the underlying neuropathology in ADHD continues to mount. Advances in the biopharmaceutics of MPH have been conspicuous. Novel approaches to formulation design have resulted in new MPH delivery options to overcome the short-term actions of both immediate- and sustained-release MPH. New modified-release MPH products offer the convenience of once-daily administration while providing extended absorption profiles that better mimic those of standard schedules of immediate-release MPH (i.e., the absorption phase of MPH better correlates with improved behavioral response than does the elimination phase). The oral bioavailability of MPH in females may be lower than in males. The *l*-MPH isomer exhibits only negligible oral bioavailability and, further, possesses little intrinsic activity at the dopamine transporter. This notwithstanding, a single-isomer *d*-MPH immediate-release product is now available for dosing recommended at one-half that of *dl*-MPH.
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From the Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston, South Carolina (Drs. Markowitz and Patrick); and the Department of Pharmaceutical Sciences, Drug Research Laboratory, University of Tennessee Health Science Center, Memphis, Tennessee (Dr. Straughn).

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Address reprint requests to John S. Markowitz, Pharm.D., The Institute of Psychiatry, Room 246N, Medical University of South Carolina, 67 President Street, P.O. Box 250861, Charleston, SC 29425-0742; e-mail: markowij@musc.edu.

Attention-deficit–hyperactivity disorder (ADHD) is a common neurobehavioral disorder and one of the most prevalent chronic health problems afflicting school-aged children in the United States. The disorder has a prevalence rate generally estimated at 4–9% of school-aged youths,[1–3] though estimates have ranged from 1.7–17.8% depending on the population assessed and the diagnostic criteria applied.[4, 5] Attention-deficit–hyperactivity disorder usually is diagnosed more often in boys than in girls, with boy:girl ratios ranging from 2:1–9:1[4, 5] However, a recent trend toward the more frequent diagnosis of ADHD in girls has been noted. For

instance, between 1991–1992 and 1997–1998, a 3-fold increase was noted in the diagnosis of ADHD among school-aged girls in the United States.[6] Recent data indicate that ADHD accounts for 30–50% of all mental health service referrals for children.[7] Although once thought to be a disorder largely limited to childhood, and self-resolving on reaching adolescence, now up to 50% or more of children with ADHD may have symptoms persisting into adulthood.[8] In those with adult ADHD, limited data suggest that the disorder is equally prevalent in men and women.[9] However, most of the statistics on adult ADHD are derived from a series of small studies.

The core behavioral symptoms of ADHD are inattention, hyperactivity, and impulsivity.[10] Characteristics of inattention include untidy work, careless mistakes, lack of follow-through, poor listening, distractibility, and forgetfulness. Hyperactivity can be manifested as fidgetiness or squirming, excessive running or talking, hand tapping or foot or leg shaking, and restlessness. Impulsivity is marked by impatience, interrupting or intrusive behavior, grabbing objects, or frequent accidents. Of importance, all of these symptoms must be viewed in the context of age-appropriateness.[10] The disorder, if untreated, may result in academic underachievement, poor interpersonal relationships, and low self-esteem.[1, 11] In addition, when compared with peers without the disorder, individuals with ADHD are at a greater risk for a variety of comorbid psychiatric disorders, including oppositional defiant disorder, conduct disorder, depression, and anxiety disorders.[12] Furthermore, greater risks of physical injury, use of tobacco, and substance abuse are present relative to these in non-ADHD peers.[13–15] Although an increased risk of substance abuse is recognized in patients with ADHD, appropriate pharmacologic treatment during childhood and adolescence appears to reduce substance abuse rates significantly in adults with ADHD.[15, 16] Emerging data indicate that health care utilization and costs are significantly higher in children and adolescents with ADHD than in those without the disorder.[17, 18] A recent population-based birth cohort study found that the median 9-year medical care costs in children with ADHD versus those without the disorder were more than doubled ($4306 vs $1944, respectively, $p<0.001$).[17] Also, the overall cost of care for children with ADHD may be comparable to that of other general medical conditions such as asthma.[18]

Etiology

The underlying neuropathology of ADHD remains unclear, but current research points to many factors. Genetic studies assessing families, twins, and adopted siblings support a substantial genetic predisposition for ADHD.[19, 20] Gene candidates implicated in the pathogenesis of ADHD include those expressing D_4 and D_5 dopamine receptors, the D_2 dopamine receptor, the dopamine transporter gene *DAT1,* and dopamine β-hydroxylase.[19–21] Further, the fact that the most widely prescribed drugs for ADHD have a prominent dopaminergic component of activity is consistent with underlying dopaminergic dysfunction in ADHD. However, the efficacy of drugs with prominent noradrenergic and/or serotonergic activity in the treatment of ADHD indicates that a purely dopaminergic dysfunction hypothesis may be overly simplistic.[22–24]

Results of neuroimaging studies with computed tomography, magnetic resonance imaging, and positron emission tomography indicate that some structural and functional differences may be found in the frontostriatal brain circuitry of patients with ADHD.[19, 25–28] Environmental factors also appear to contribute to the occurrence of ADHD, including complications of pregnancy and delivery, diet, and lead exposure. Psychosocial adversity may predispose a child to the development of ADHD. Furthermore, families who have children with ADHD, as with other behavioral disorders and chronic diseases, are more likely to experience marital discord, divorce, and family dysfunction.[4, 5, 11, 12]

Diagnosis

The diagnosis of ADHD is applied to children, adolescents, and adults who persistently demonstrate inattention and/or hyperactivity-impulsivity.[7] The diagnosis of ADHD in children or adolescents generally is preceded by documented behavioral and/or academic problems and an ensuing referral to a clinician for evaluation. The diagnosis remains largely dependent on direct interview and observation of the patient and the observations of parents and/or teachers supervising the child. A thorough psychiatric evaluation should occur to exclude other mental disorders (e.g., mood disorders) that may share some clinical features. In addition, both physical and neurologic examinations are of great importance to rule out other potential causes of observed symptomatology

(e.g., hyperthyroidism).[10, 25–27]

Although most individuals with ADHD have symptoms of both inattention and hyperactivity-impulsivity, one symptom may predominate as an ADHD subtype. Three primary subtypes are recognized: combined type, the most frequently observed; predominantly inattentive type, most often observed in adults; and predominantly hyperactive-impulsive type, which is usually more common in younger patients but overall the least frequently diagnosed subtype.[10]

In most patients with ADHD, hyperactivity and impulsivity decrease with age, while difficulties with inattention may persist. A number of validated rating scales are used in the assessment of ADHD and in monitoring response to treatment. Among these scales are the Inattention/Overactivity with Aggression Conners Teacher Rating scale, a 10-item scale used to separate inattention and overactivity ratings from oppositional defiance; the Swanson, Nolan, and Pelham (SNAP-IV) scale, a 26-item scale containing *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for ADHD and screens for other DSM diagnoses; and the Swanson, Kotkin, Afler, M-Flynn, and Pelham (SKAMP) scale, which measures impairment of functioning in attention or deportment (i.e., behavior) at home and at school.[29]

Treatment

Before starting any treatment, definitive target outcomes should be identified. With ADHD, the core symptoms of inattention, impulsivity, and hyperactivity can lead to dysfunction in multiple areas. Primary goals include improvement in relationships with parents, peers, and teachers; decreased disruptive behaviors; and improved academic performance, increased independence, and increased self-esteem.[2, 25, 27]

Nonpharmacologic Therapy

Although multimodal treatment approaches that integrate drug therapy with psychotherapeutic, environmental, educational, and school-based interventions are advocated, pharmacotherapy remains the mainstay treatment for ADHD.[2, 5, 6] The Multimodal Treatment Study of Children with ADHD (MTA study) assessed specific treatment modalities in 579 children with ADHD (combined type) who were aged 7–10 years.[7] In this 14-month randomized clinical trial, sponsored by the National Institutes of Mental Health and the Department of Education, patients were assigned to various treatment modalities including medical management (i.e., pharmacotherapy), behavioral treatment, a combination of medical and behavioral management, or community-based treatment.[7] The study demonstrated that children receiving medical management or combined treatment had significantly greater improvement in hyperactive-impulsive symptoms than those receiving either behavioral treatment alone or community-based treatment. Symptomatic improvement differences between those receiving only medical treatment and those receiving combined treatment were not statistically significant. Thus, the MTA study clearly demonstrated the benefits of pharmacotherapy in ADHD for a sustained period. Nevertheless, essentially all recently published practice guidelines or consensus statements support the use of psychosocial interventions either alone or in combination with pharmacotherapy.[2, 25, 27]

A variety of psychosocial treatment interventions for ADHD may be beneficial, including behavior modification, parent training, and social skills training. These interventions may be school- or home-focused but should provide consistency throughout in their approach. In general, techniques that use reward systems and consequences for failure to meet goals appear most effective. A variety of nonpharmacotherapeutic interventions are described extensively elsewhere.[2, 27]

Pharmacotherapy

Drug therapy often is indicated in the treatment of ADHD, with approximately 54% of children aged 6–11 years who have ADHD receiving prescription drugs.[30] When pharmacotherapy is used, it should be with the support and education of patients, family members, teachers, and others. Of the available drugs, the psychostimulant drugs methylphenidate (MPH), dextroamphetamine,[31] and mixed isomers of amphetamine[32–34] (containing 19% levamphetamine,[35, 36] Adderall; Shire Pharmaceuticals, Newport, KY) are commonly prescribed. More than 130 trials have assessed MPH, more than 20 have assessed dextroamphetamine, and at least five trials have studied amphetamine mixed isomers. Typically, such studies were of relatively short duration and had a fairly homogeneous population of prepubertal Caucasian boys, which does not represent the general population affected.[37–39] Clinical experience has demonstrated that 70–90% of children will respond favorably to at

least one psychostimulant if the dosage is titrated properly.[5] Although recently established practice guidelines, algorithms, and consensus statements on the pharmacotherapy of ADHD have not identified an agent of first choice,[2, 25, 27, 29, 40] MPH is widely viewed as the reference standard (e.g., its status as comparator agent in numerous clinical trials of other drugs for ADHD and its choice for the MTA study[7]). However, a patient who fails to respond to MPH, or exhibits intolerance, generally becomes a candidate for an alternative psychostimulant. There can be some differences in side effect burden among the psychostimulants, with adverse effects on sleep and appetite reported more commonly with dextroamphetamine and amphetamine isomers than with MPH.[29, 41]

The beneficial behavioral effects produced by immediate-release formulations of MPH generally offset sooner than do those of amphetamine products. Accordingly, the short-term actions of immediate-release MPH generally dictate multiple daily dosing to medicate through the course of a typical school day. The resultant on-again, off-again absorption profile may result in the so-called roller-coaster response for twice-daily or thrice-daily dosing regimens.[37, 42] In addition to the stimulant mainstays of MPH and amphetamine in ADHD treatment, other drug options include pemoline, the use of which is limited by association with hepatotoxicity[43]; tricyclic antidepressants such as imipramine and desipramine; and the newly available norepinephrine reuptake inhibitor atomoxetine.[24, 44, 45] In spite of atomoxetine being a structural congener of the prototypic serotonin selective reuptake inhibitor fluoxetine, it exhibits selectivity toward the noradrenergic transporter.[46] Bupropion,[47] clonidine,[23] and guanfacine[23, 48] also are efficacious in ADHD cases in which intolerance or incomplete response to classic psychostimulants occurs.[22, 40]

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,[49–51] with a minor influence on the norepinephrine transporter. This action appears to amplify neurotransmission[52, 53] by increasing synaptic cleft residence time of impulse-released dopamine.[54, 55] Alternatively, others have proposed that dopamine reuptake inhibition by MPH attenuates dopaminergic tone by increasing stimulation of presynaptic inhibitory autoreceptors.[54, 56, 57] The phenethylamine pharmacophore within the structure of MPH is common to dopamine and norepinephrine (Figure 1), providing for transporter receptor affinity as it competes with dopamine for binding.[58, 59] Theory holds that MPH binds with the dopamine transporter but does not possess the intrinsic activity required to induce the conformational change for trans-location of the ligand and binding site to the intraneuronal milieu. Thus, unlike amphetamine,[59, 60] MPH does not drive the transporter-facilitated release of cytoplasmic dopamine into the synaptic cleft as the transporter returns to its former conformation.[55]

Enantiomers

Approximately one in every four marketed drugs exists as a combination of isomers. Most of these mixtures exist as racemates owing to the presence of a chiral or asymmetric carbon atom (i.e., they contain a 50:50 mixture of enantiomeric structures related to one another as nonsuperimposable mirror images). However, owing to the presence of two chiral carbon atoms within the MPH molecule, a total of four isomers are

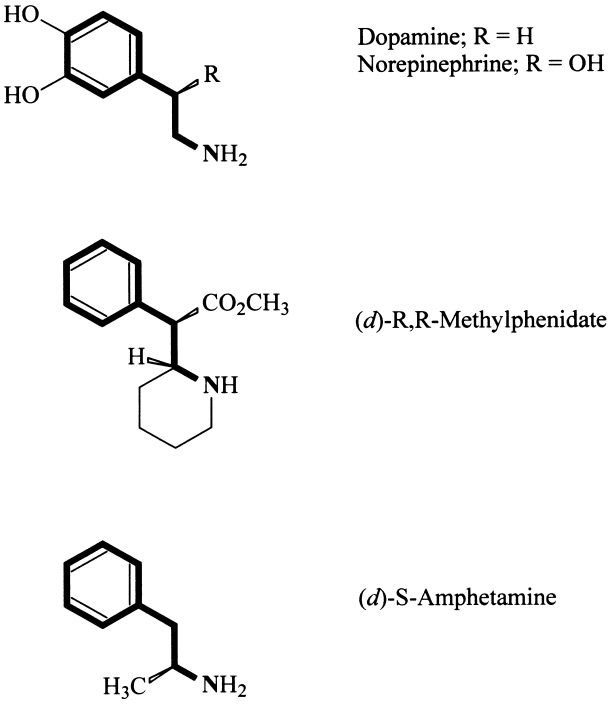


Figure 1. Structures of the most active methylphenidate and amphetamine isomers. The common phenethylamine pharmacophore (in bold) imparts dopamine transporter affinity.

possible. In fact, some early formulations of MPH such as Centedrin (Richter Works, Budapest, Hungary)[61] had contained a mixture of all four isomers, erythro-RS-*d*-MPH, erythro-SR-*l*-MPH, threo-RR-*d*-MPH, and threo-S,S-*l*-MPH, though in disproportionate amounts (Figure 2). The erythro isomers subsequently were removed from such formulations because of their association with some adverse effects.[62]

Until the introduction of enantiopure (*d*)-MPH product (threo-[+]-MPH, dexmethylphenidate) in 2002, all marketed MPH formulations have contained a racemic (50:50) mixture of threo-RR-*d*-MPH and threo-S,S-*l*-MPH isomers (Figure 2). The ADHD psychotherapeutic effects,[63–65] as well as the undesired pressor[59, 66, 67] and anorexic

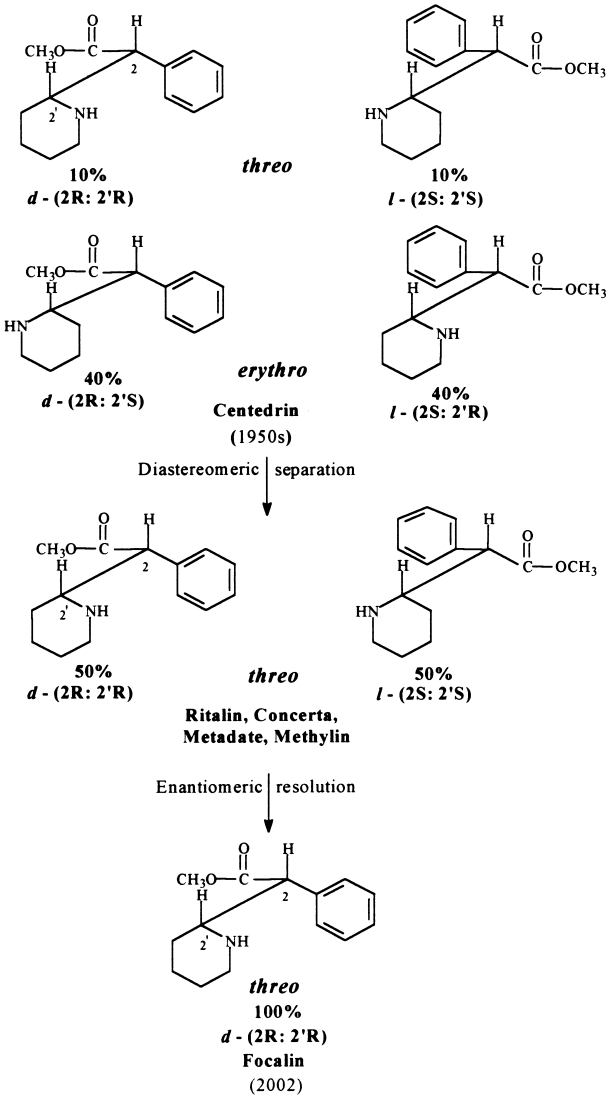


Figure 2. Evolution of methylphenidate formulations to improve therapeutic index and/or potency.

actions,[68, 69] reside primarily in the *d*-enantiomer. But, in view of recent efforts to develop *l*-MPH as an antidepressant,[70] the *l*-MPH isomer of racemic formulations may not necessarily represent a passive component. Neuropharmacologic activity has also been demonstrated for the *l*-isomer in preclinical studies. One group of researchers[71] assessed the activity of the separate MPH enantiomers in a rat model of ADHD that used 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 3 times more active in reducing motor activity than was racemic MPH. A 2-fold reduction would be predicted if *l*-MPH were inert. Further, pretreatment of the rats with lesions with *l*-MPH attenuated the motor activity response to *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). Comparative behavioral effects of *l*-MPH and *d*-MPH in rats without lesions revealed that female rats are more sensitive than male rats to some effects of the *l*-isomer and more sensitive to both isomers in other elements of an observational battery.[72] High-dose toxicity studies in rats found the racemate to be approximately half as toxic as *d*-MPH.[73]

Metabolism

Methylphenidate is metabolized primarily by deesterification to the inactive[74] metabolite ritalinic acid[75–77] (Figure 3). This facile process limits the absolute bioavailability to 11–53%.[78] The circulating concentrations of ritalinic acid greatly exceed that of the parent drug,[79–82] and urinary elimination of ritalinic acid accounts for 60–80% of the dose.[75–77] This hydrolysis pathway may be mediated primarily by the carboxyesterase-1 isoform (based on related substrate specificity)[83] and exhibits an enantioselectivity resulting in higher plasma concentrations and a longer half-life for *d*-MPH. With few exceptions,[84] therapeutic drug monitoring studies of MPH have been limited to nonenantiospecific analytic approaches (i.e., reporting only pooled *d*- and *l*-MPH concentrations).[58] However, the lack of enantiospecific analyses may be of little practical significance in view of the much lower relative concentration of *l*-MPH in plasma, as well as in

dopaminergic regions of the human brain.[51] The area under the plasma concentration–time curve (AUC) from time zero to infinity value for the *l*-isomer has been reported to reach only 1% that of *d*-MPH.[81] Surprisingly, radiolabeled *l*-MPH (or metabolite) was reported recently to be taken up into the brain to a greater extent than was *d*-MPH after oral administration of each isomer to either rats or baboons.[85] In the interest of metabolic mass balance, other minor urinary elimination products of MPH include pharmacologically inactive lactam (< 1%),[76] deesterified lactam (5–12% of dose),[75] active metabolite *p*-hydroxymethylphenidate[74, 86] (Figure 3), and unchanged drug (< 1%).[75–77]

Drug Interactions

Though most MPH is hydrolyzed by esterases, biotransformation to the lactam occurs through oxidative metabolism. The specific isoform(s) mediating this pathway has not been identified. A pilot clinical study using the prototypic cytochrome P450 (CYP) 2D6 inhibitor quinidine did not support a role for this isoform.[87] Although this quinidine study was not designed to assess the role of the drug efflux transporter P-glycoprotein, quinidine is also a recognized inhibitor of P-glycoprotein,[88] and the lack of effect on MPH pharmacokinetics[87] suggests MPH may not be a substrate of this transporter.

Literature reports of pharmacokinetic drug

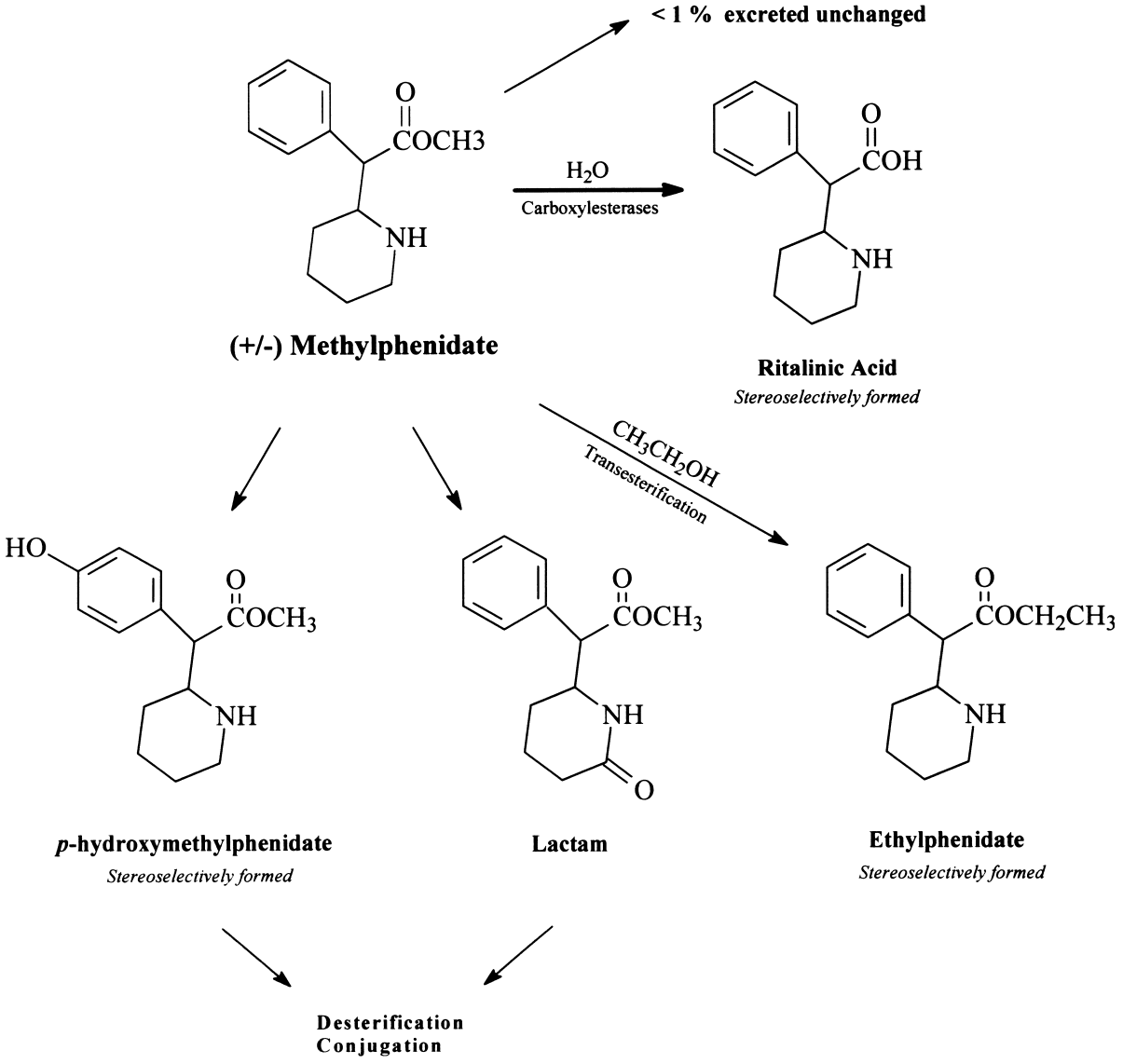


Figure 3. Metabolic pathways of methylphenidate in humans.

Table 1. Summary of Nonenantiospecific Parameters of Methylphenidate

No. of Subjects	Dosage, Formulation	Half-life (hrs)	T_{max} (hrs)	C_{max} (ng/ml)
Children				
4	10–20 mg[98]	2.56	NR	NR
6	10–20 mg i.v.[99]	2.02	NR	NR
12–14	0.34–0.65 mg/kg[100]	2.53	1.9–2.5	11.2–20.2
5	0.25-0.68 mg/kg (fasting)[78]	2.10	1.6	NR
5	0.25–0.68 mg/kg (fed)	2.14	1.0	NR
5	0.3 mg/kg[79]	2.43	1.5	10.8
9	20 mg, SR[101]	4.12	3.36	8.54
Adults				
18	10 mg b.i.d., IR[102]	NR	5.33	6.4
18	20 mg, SR (Ritalin)	NR	3.34	4.8
18	20 mg, SR (generic)	NR	3.25	4.6
1	20 mg[103]	~3	~2	~13
6	10 mg, IR (Ritalin)[87]	2.9	2.5	4.0
6	20 mg,[a] IR (Ritalin)[94]	2–5	1–4	8.4–27.3
20 x 2	20 mg (generic)[105, b]	2.56	1.55	7.59
20 x 2	20 mg (Ritalin)	2.47	1.97	6.85
10	0.3 mg/kg[79]	2.14	2.1	7.8
5	0.15 mg/kg	2.05	2.2	3.5
35	18 mg/day, OROS[80]	3.5	6.7	3.75
34	5 mg t.i.d., IR	3.0	6.5	4.17
33	20 mg/day, SR	3.9	3.7	4.84
32	18 mg, OROS	3.9	7.4	2.81
32	18 mg, OROS (multiple doses)	3.9	6.6	3.00
24	18 mg, OROS (fasting)[81]	4.0	6.1	3.3
24	18 mg, OROS (fed)	3.8	7.2	4.4
36	36 mg, OROS (fasting)	3.5	6.5	6.2
36	36 mg, OROS (fed)	3.3	7.4	6.87
35	18 mg, CD[105]	6.24	5[c]	3.89
35	20 mg, OROS	3.58	6[c]	3.43
21	36 mg, CD	6.82	5[c]	7.42
21	2 x 20 mg, OROS	3.84	8[c]	8.43
21	54 mg, CD	6.43	5[c]	12.41
21	3 x 20 mg, OROS	4.07	7[c]	12.60
26	20 mg, CD[106]	6.42	4.58	4.58
26	20 mg, CD (sprinkled)	6.27	4.39	4.78
24	20 mg, LA[107]	3.4	5.5	9.9
24	18 mg, OROS	4.3	6.0	5.9
22	10 mg, IR[108]	2.9	1.9	4.82
22	10 mg b.i.d., IR	2.93	5.2	6.38
22	20 mg, SR	3.41	3.2	5.53

T_{max} = time to peak concentration; C_{max} = peak concentration; NR = not reported; IR = immediate release; SR = sustained release; OROS = osmotic release oral system (Concerta); CD = controlled delivery (Metadate); LA = long acting (Ritalin LA).
[a]Given with ethanol 0.6 g/kg.
[b]Mean values for two trials.
[c]Estimated.

interactions of MPH generally have only suggested an influence of MPH on the disposition of other drugs, rather than an influence of other drugs on MPH pharmacokinetics. Relatively few clinically significant pharmacokinetic interactions with MPH have been confirmed through formal clinical study despite extensive precautions in MPH package labeling.[89, 90] The potential for racemic MPH and its major metabolite ritalinic acid to inhibit CYP enzymes was explored recently in an in vitro study with use of human microsomes; the results suggested the possible

Table 2. Summary of Enantiospecific Pharmacokinetic Parameters of Methylphenidate

No. of Subjects	Dose (mg), Formulation	Half-life, *d/l* (hrs)	T_{max}, *d/l* (hrs)	C_{max}, *d/l* (ng/ml)
Children				
5	10[110]	3.1/5.59	2.15/2.01	7.1/1.0
6	20, SR[111]	NR	2.8/3.1	18.8/1.6
9	10, capsule[63]	1.87/1.43	2.3/2.4	6.4/1.3
9	5, *d*-MPH	1.84 (*d*)	2.44 (*d*)	5.6 (*d*)
9	5, *l*-MPH	0.98 (*l*)	2.1 (*l*)	0.78 (*l*)
1	17.5[116]	3 (*d*)	1.5/1.5	10.8/0.25
Adults				
1	20, IR[109]	3.61 (*d*)	2.17/3.05	5.5/0.4
1	40, IR	3.61 (*d*)	2.08/2.08	22.4/1.7
1	20, IR[112]	NR	NR	NR
1	20, crystals	3.01/1.2	NR	NR
1	10, *d*-MPH	2.9/1.4	NR	NR
1	10, *l*-MPH	2.3 (*d*)	NR	NR
1	40, IR[113]	4.06/3.76	2.0/2.0	11.7/2.0
3	10, IR[114]	2.5 (*d*)	0.9 (*d*)	5.0 (*d*)
4	20, IR	2.5 (*d*)	1.4 (*d*)	8.1 (*d*)
4	30, IR	2.5 (*d*)	1.2 (*d*)	17.1 (*d*)
4	40, IR	2.5 (*d*)	1.1 (*d*)	28.4 (*d*)
2	60, IR	3.1 (*d*)	3.0 (*d*)	24.7 (*d*)
11	10, i.v.[115]	5.96/3.6		
11	40, IR	5.69/3.93	2.36/2.14	18.1/3.1
11	40, SR	5.04/3.88	3.18/3.09	16.1/1.9
11	40, SR (chewed)	5.33/3.84	1.95/2.14	20.8/2.4
8	0.24–0.38 mg/kg, IR[64]	1.7 (*d*)	2.8 (*d*)	7.67 (*d*)
21	40[111]	2.67/1.15	1.5/0.5	17.8/1.0
35	18, OROS[82]	3.8/ND	7.9/7.1	3.87/0.095
35	36, OROS	3.9 (*d*)	7.5/7.0	7.28/0.17
35	54, OROS	3.9 (*d*)	7.2/6.1	10.6/0.36
24	40, IR (fasting)[117]	2.92 (*d*)	2.00 (*d*)	11.65 (*d*)
24	40, IR (fed)	2.67 (*d*)	2.54 (*d*)	14.3 (*d*)
24	40, SR (fasting)	2.73 (*d*)	3.71 (*d*)	7.83 (*d*)
24	40, SR (fed)	2.70 (*d*)	3.62 (*d*)	9.19 (*d*)
15	2 x 10, Focalin (fasting)[118]	2.68 (*d*)	NR[a]	23.72 (*d*)
15	2 x 10, Focalin (fed)	2.81 (*d*)	T_{max} (fasting) + 1[a] (*d*)	22.13 (*d*)

MPH = methylphenidate; T_{max} = time to peak concentration; C_{max} = peak concentration; IR = immediate release; SR = sustained release; OROS = osmotic release oral system; ND = not detected; NR = not reported.
Specific enantiomer is indicated in parentheses.
[a]T_{max} for fed subjects was reported as 1 hour longer than T_{max} for fasting subjects (actual time not given).

inhibition of CYP2D6 and CYP2B6 by racemic MPH, but not by ritalinic acid.[91] A recent in vitro study found that *d*-, *l*-, and *dl*-MPH were not likely to inhibit CYP isoenzymes 1A2, 2C9, 2C19, 3A4, or 2D6 at relevant concentrations.[92]

A drug interaction between MPH and alcohol recently was reported and involved the formation of an active metabolite, ethylphenidate, identified initially in patients who overdosed,[93] then in human volunteers who received MPH and alcohol.[94] It is postulated that this metabolite is formed by an esterase-mediated transesterification pathway analogous to that forming cocaethylene after ethanol and cocaine coingestion. Any possible pharmacodynamic significance of ethylphenidate formation has not been established.[93] Further, the relative importance of polymorphism and expression of esterases,[95] as well as the potential for competitive inhibition of MPH deesterification by other ester-containing drugs or by ethanol,[96] has not been explored. As with the enzymatic deesterification of MPH to ritalinic acid, the transesterification of MPH to ethylphenidate appears to occur with enantioselectively, favoring the *l*-MPH isomer as a substrate.[97]

Pharmacokinetics

The pharmacokinetic parameters of MPH have been evaluated by numerous investigators in both children and adults, and there is little evidence that maturity has any clinically significant effect on either the drug's absorption or half-life, as summarized for nonenantiospecific studies in Table 1.[78–81, 87, 94, 98–108] and for enantiospecific studies in Table 2.[109–118] Although initial dose estimates sometimes are based on patient weight, because of the large interpatient variability final dose titration is driven more commonly by therapeutic response than by body mass.

Absorption and Food Effects

Methylphenidate, formulated as the hydrochloride salt, is highly soluble in the fluids of the gastrointestinal tract. Once in solution, MPH is rapidly and extensively absorbed from the intestine to the colon.[76, 119] Therefore, the main factor controlling MPH absorption from immediate-release dosage forms is most likely gastric emptying time, whereas for the various controlled-release dosage forms, it is the programmed drug release and dissolution pattern. Because of extensive first-pass metabolism, the systemic exposure of unchanged drug (i.e., absolute bioavailability) after oral dosing is low and variable.[99] As mentioned earlier, owing to preferential metabolism of the *l*-isomer, plasma concentrations of the *d*-isomer can be 10–40 times greater than those of the *l*-isomer. However, the low extent of systemic exposure of MPH and the relatively large interpatient variability in bioavailability are not factors that limit therapeutic effectiveness once the dosage has been titrated appropriately. There is little evidence that the variability in bioavailability within a single subject is of the magnitude of that seen between subjects.[104, 120]

All of the newer extended-release formulations of MPH have been evaluated for potential food effects, which are discussed specifically in the section on newer formulations. For the most part, the extent of absorption of MPH dosage forms is essentially unchanged, but after consumption of a high-fat meal there is a potential for a delay in the time of peak concentrations (most likely due to a delay in gastric emptying). Also, actual peak concentration may be either increased or decreased after a high-fat meal, so 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. Note that the extent of amphetamine absorption for the first 8 hours after dosing can be markedly reduced in the fed state.[121]

Disposition

On reaching the systemic circulation, MPH is rapidly distributed to the various tissues, with a steady-state volume of distribution of approximately 2 L/kg.[85] Clearance of MPH is also rapid, with little or no accumulation of the drug from day to day, even with the controlled-release formulations.[80] At higher doses, there is some evidence of nonlinearity, which may be related to saturation of the first-pass metabolism with oral dosing.[122] For intravenous and immediate-release dosing, the half-life is reported to be 2–6 hours, with most studies reporting an average of 2–3 hours (Tables 1 and 2). In a study of the individual isomers administered intravenously, both isomers exhibited similar distribution characteristics, though the terminal elimination of the *l*-isomer was more rapid.[85] Generally in studies of the extended-release dosage forms, longer half-lives are reported, but this is most likely related to prolonged absorption, which can mask the estimation of the true elimination half-life.

Sex Differences

To our knowledge, studies specifically designed to evaluate sex differences in MPH pharmacokinetics have not been conducted. In a population pharmacokinetic study in children with ADHD in which single samples were obtained from 212 boys and 61 girls, the authors concluded that little differences in the disposition of MPH existed between the sexes.[120] However, the results of two bioavailability studies with healthy subjects that included both male and female volunteers indicate that when the doses are normalized to the body weight of the subject, female subjects have lower systemic exposure based on a mg/kg dose.[123, 124] In addition, the authors of another study[80] reported no differences in AUC between male and female subjects receiving the same total dose, even though the female subjects generally weighed less than the male subjects. In that study, the

major metabolite ritalinic acid was significantly greater in female subjects. Figure 4 is a scatterplot depicting AUC versus normalized dose from a two-way crossover study in 10 male and 9 female subjects in which each subject received both a 20- and 18-mg extended-release MPH dose.[125] The average mg/kg dose in the male subjects was approximately 30% less than that in the female subjects, yet the average AUC was not significantly different between the sexes. Since 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 female subjects. The potential implication of these observations is that female patients would require larger mg/kg doses to achieve the same MPH plasma concentration, but further investigation is warranted to determine if both sexes require similar plasma concentrations to achieve the same therapeutic objective. Looking at individual data in this manner also allows one to see the extent of intersubject variability. Although the clinical consequence of such between, and within, sex differences has not been evaluated, these data reiterate the potential need for frequent dosage titration at the start of therapy regardless of the patient's weight or sex.

Newer Methylphenidate Formulations

The rapid metabolic deesterification of MPH limits the drug's half-life to only 2–3 hours (Tables 1 and 2), thus usually requiring multiple daily dosing of immediate-release MPH to provide drug coverage throughout the day. Accordingly, in addition to immediate-release MPH, several long-acting MPH formulations for single daily dosing have been developed in efforts to provide the proven efficacy of immediate-release MPH but to allow greater dosing convenience and compliance, minimize security issues at school, and avoid stigmatizing children who are subject to possible ridicule by peers during the school day when additional dosing is required.[29, 126–128]

The nomenclature used to describe long-acting pharmaceutical dosage forms sometimes can lead to confusion relative to their intended purpose: extended release, sustained release, long acting, controlled delivery, controlled release, and delayed release. The abbreviations for these terms (ER, SR, LA, CD, CR, and DR, respectively) commonly are incorporated into proprietary names and can serve an important function in conveying intended prescribing information to clinicians. For the purpose of this formulation review, we refer to MPH formulations as either immediate release or extended release, even though the mechanism of drug release and the resultant plasma profiles from the extended-release formulations might be described more appropriately with other nomenclature.

The first modified-release MPH product, an MPH extended-release formulation with a wax-matrix vehicle designed to provide slow continual release of drug, was introduced in 1983, with a generic MPH extended-release product appearing in 1988.[102] These formulations provided a more gradual rate of absorption than that of the MPH immediate-release formulations, then reached a relative plateau or flat concentration-time profile,

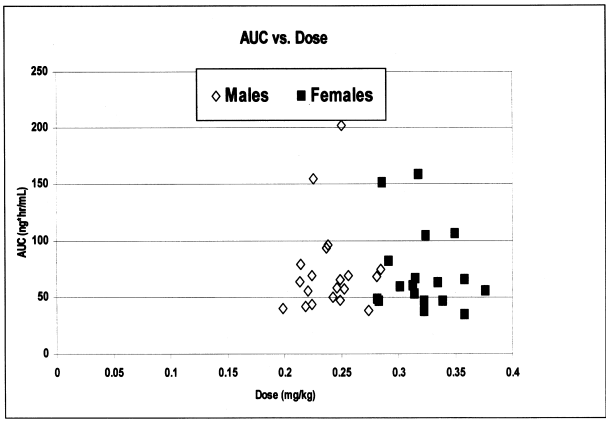


Figure 4. Apparent sex bimorphism in the extent of methylphenidate absorption. AUC = area under the plasma concentration–time curve.

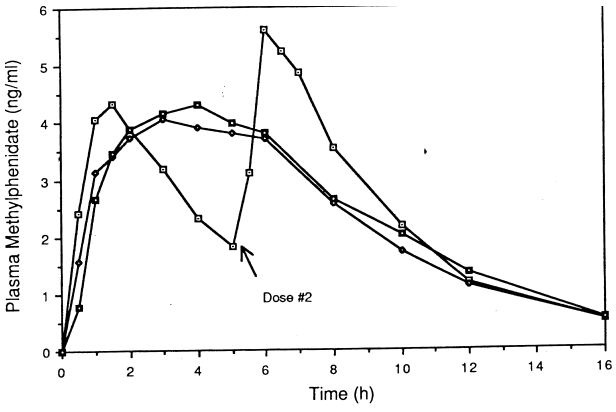


Figure 5. Pharmacokinetic profile of immediate-release methylphenidate (twice/day) compared with that of the branded and generic sustained-release products. (From reference 102 with permission.)

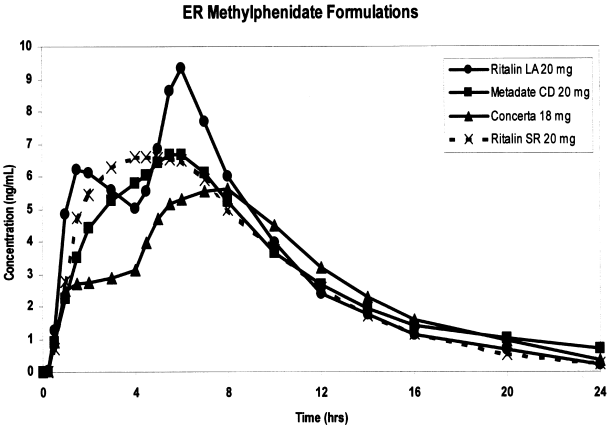
avoiding a plasma trough(s) during the day. Further, the subsequent plasma MPH concentration decay for extended-release forms occurred more gradually than that of the immediate-release forms (Figure 5).[102] However, some clinical experiences have since indicated a potential therapeutic advantage of immediate-release over conventional extended-release forms of MPH,[2, 129–131] even though both formulations provide comparable extents of absorption (Figure 5).[102]

In two reports by the same group of authors, the greatest behavioral improvements in children with ADHD who received immediate-release MPH corresponded to the absorption phase of the pharmacokinetic profile.[132, 133] This pharmacodynamic correlation with rising blood concentrations has been referred to as the "ramp"[131] or "gradient"[58] effect. A relatively constant blood concentration–time course of MPH, as produced by standard sustained-release forms,[101] may induce an acute psychotherapeutic tolerance (i.e., tachyphylaxis) and compromise efficacy.[132–134] The concept of acute tolerance remains a theoretical one and has not been replicated in a pharmacokinetic-pharmacodynamic study. Nonetheless, with these considerations in mind, as well as the need for a once-daily MPH dosage regimen, the osmotic controlled-release oral delivery system (osmotic release oral system [OROS]) MPH product (Concerta; McNeil Pharmaceuticals, Fort Washington, PA) was introduced in 2000; it combines immediate- and extended-release biopharmaceutics to provide for an initial rapid rise in circulating concentrations after the morning dose, followed by a short plateau, then a second steep rise.[80–82, 130, 136] The formulation was designed to provide the same drug coverage as thrice-daily immediate-release MPH, approximating a 12-hour duration of action. The overall concentration increase characterizing the first 6–8 hours after dosing has been purported to offset tachyphylaxis, although therapeutic superiority over immediate-release MPH or any long-acting MPH formulation has not been assessed or demonstrated.

Modified-Release Technologies

The OROS dosage form provides a plasma concentration–time profile characterized by an ascending absorption curve and lower peak plasma concentration and overall (Figure 6), less fluctuation in plasma concentrations compared with immediate-release MPH.[80] With this form, osmotic pressure delivers MPH at a controlled rate through a trilayer core. The tablet overcoat contains 22% of the MPH dose and dissolves rapidly to provide an initial MPH absorption pulse. Subsequently, water permeates the osmotically active polymer portion, releasing MPH through a laser-drilled orifice. The remainder of the dosage form remains intact and is passed in the stool as a tablet shell and insoluble core.[135] The nature of this nondeformable tablet may have implications in patients with swallowing difficulties[136, 137] or gastrointestinal narrowing[135] but has been suggested to limit intranasal abuse potential.[138] Thus, tablets may not be opened, crushed, or divided.[135] As with immediate-release MPH,[78] the OROS dosage form 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 an approximately 1-hour delay in time to initial peak concentration (T_{max}) and 10–30% increase in maximum plasma concentration (C_{max}) and AUC.[81] No "dose dumping" (i.e., premature release of drug from dosage form) was observed. Concerta tablets are available in 18-, 27-, 36-, and 54-mg doses; dosing and conversion recommendations are provided in Table 3.

The next entrant to the extended-release MPH



*Data presented are intended for illustrative purposes only and are not derived from a single cross-over study. These pharmacokinetic profiles represent the superimposition of data generated in three previously published bioavailability studies of MPH dosage formulations at similar strengths administered to healthy adult volunteers.[102,105,107]

Figure 6. Pharmacokinetic profiles of sustained-release methylphenidate and newer extended-release (ER) methylphenidate formulations. LA = long acting; CD = controlled delivery; SR = sustained release.

Table 3. Newer Methylphenidate Dosage Formulations

Formulation	Release Technology	Pharmacokinetic Release Profile	Doses Available (mg)	Can Formulation Be Opened and Sprinkled?
Concerta (*d,l*-MPH)	OROS, osmotically active trilayer CR system; 22% IR, 78% SR	Compares with t.i.d. dosing	18, 27, 36, 54	No
Metadate CD (*d,l*-MPH)	Diffucaps, beaded CR system; 30:70 ratio of IR:ER beads	Biphasic mimics b.i.d. dosing	10, 20, 30	Yes
Ritalin LA (*d,l*-MPH)	SODAS, beaded CR system; 50:50 ratio of IR:ER beads	Biphasic mimics b.i.d. dosing	20, 30, 40	Yes
Focalin (*d*-MPH)	IR tablet	Intended for b.i.d. dosing	2.5, 5, 10	No

MPH = methylphenidate; IR = immediate release; SR = sustained release; ER = extended release; OROS = osmotic release oral system; CR = controlled release; LA = long acting; SODAS = spheroidal oral drug absorption system.
[a]Based on clinical judgment.

market was Metadate CD (Celltech Pharmaceuticals, Rochester, NY) whose Diffucaps technology is designed to mimic a twice-daily schedule of immediate-release MPH. The disparate nature of the MPH-containing beads within the capsule allow for rapid dissolution of 30% of the MPH dose, while the remaining 70% is released in an extended fashion.[105] Initial formulation development studies indicated that an immediate-release:sustained-release dose ratio of 30:70 provided more consistent treatment effects than either a 20:80 or 40:60 ratio.[108] The resultant pharmacokinetic profile of this dosage form is biphasic in nature and distinctly different from that of Concerta.[105, 135] Results of a comparative pharmacokinetic study in healthy volunteers suggest that Metadate CD may provide a more rapid onset of action if higher early plasma concentrations are indicative of better response.[105] As with Concerta, the presence of food delays the T_{max} by approximately 1 hour, and current package labeling suggests administering Metadate CD before breakfast. In a study in adults, a high-fat meal increased C_{max} by about 30% and the AUC by about 17%.[106] In addition, unlike the Concerta dosage form, Metadate CD capsules may be opened and sprinkled on applesauce for consumption without any significant changes in bioavailability relative to the administration of the intact dosage form.[106] Metadate CD is available as 10-, 20-, and 30-mg capsules (Table 3).

The most recently available extended-release dosage form was Ritalin LA (Novartis Pharmaceuticals, East Hanover, NJ), which uses the spheroidal oral drug absorption system (SODAS) bead technology.[136] The capsule contains 50% immediate-release MPH beads and 50% extended-release beads. The latter are polymer-coated to offer an approximate 4-hour latency before gastrointestinal water erodes this coating to release the second pulse of MPH, with the resultant MPH blood profile being distinctly biphasic as with twice-daily immediate-release MPH.[10, 136] Ritalin LA capsules can be opened and sprinkled on applesauce if needed without altering the pharmacokinetic profile.[139] 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 approximately 1 hour. The overall extent of absorption is not significantly affected by food.[139] Ritalin LA is available in 20-, 30-, and 40-mg capsule strengths (Table 3).

Comparative Pharmacokinetics of Extended-Release Methylphenidate Dosage Forms

All of the newer extended-release formulations (Concerta, Metadate CD, and Ritalin LA) exhibit an adequate extent of MPH absorption compared with that of the immediate-release preparations. However, because of the way these formulations modulate the rate of drug delivery to the systemic circulation, they can by no means be considered bioequivalent to each other, to the immediate-release preparations, or to the older extended-release preparations such as Ritalin SR or Metadate ER and a number of generic

Table 3. (continued)

Conversion from IR or SR Dosage Forms of MPH to Newer Formulations	
From	To
5 mg b.i.d. or t.i.d., or 20 mg SR	18 mg/day
10 mg b.i.d. or t.i.d., or 40 mg SR	36 mg/day
15 mg b.i.d. or t.i.d., or 60 mg SR	54 mg/day
10 mg b.i.d. or 20 mg SR	20 mg/day
15 mg b.i.d.	20–40 mg/day[a]
20 mg b.i.d. or 40 mg SR	2 x 20 mg (40 mg)/day
10 mg b.i.d. or 20 mg SR	20 mg/day
15 mg b.i.d.	30 mg/day
20 mg b.i.d. or 40 mg SR	40 mg/day
5 mg b.i.d.	2.5 mg b.i.d.
10 mg b.i.d	5 mg b.i.d.
20 mg b.i.d	10 mg b.i.d.

formulations. Each formulation produces a distinctly different plasma profile with essentially the same overall exposure to MPH relative to the equivalent immediate-release dose (Table 3, Figure 6). In addition, from the standpoint of the United States Food and Drug Administration (FDA), the pharmaceutical characteristics of these formulations would preclude substitution based on generic equivalency criteria even if there were no patent protection issues with these products.[140] Although all have the same active moiety, *d,l*-MPH, to be considered substitutable (i.e., therapeutically equivalent) by the FDA, they must first be the same strength (Concerta 18 mg vs Metadate CD and Ritalin LA 20 mg) and be the same pharmaceutical dosage form (Concerta tablet vs Metadate CD and Ritalin LA capsule). It should be noted that under the above criteria, Ritalin LA and Metadate CD do qualify as pharmaceutical equivalents; however, they have not been compared in a head-to-head bioavailability study. For the clinician and the individual patient, however, these pharmaceutical differences are of minor concern relative to the impact the shape and magnitude of the plasma profile may have on therapeutic outcome. The way each of these formulations modulates the plasma profile may have a therapeutic advantage in some, but not all, patients, and unless the prescribing clinician is aware of the potential differences from these products, objective end-point evaluations in the patient may be obscured.

A therapeutic failure with any one of these newer formulations is not likely to result from the failure of the dosage form itself, but rather from a failure of the dosage form to deliver MPH concentrations in harmony with the patient's needs. For example, a comparison of the shape of the extended-release profiles (Figure 6) might give insight into why a given patient would respond optimally during morning classes on one formulation, but might not respond as well in after-school activities and vice versa. Compared with Concerta, the Ritalin LA formulation results in approximately twice the exposure to MPH in terms of both the C_{max} and AUC during the first 4 hours.[107] In addition, the results of one study[105] indicate that the Metadate CD formulation exhibits greater early exposure to MPH relative to Concerta; however, the latter formulation results in higher plasma concentrations of MPH at times later in the day. With more adolescent and adult patients now being treated for ADHD, the relationship of the pattern of drug delivery to lifestyle may require even closer scrutiny in order to achieve appropriate control. The performance of each of these formulations was well evaluated, both pharmaceutically and clinically, before marketing. All showed clinical improvements in patients relative to placebo. None have been shown in controlled clinical trials to be superior to the immediate-release MPH dosage regimens with which they were compared. Importantly, because there is little evidence of chronic tolerance to MPH, and patients essentially clear all of the drug before the next day's dose, every morning represents an opportunity for the clinician to evaluate a different formulation ideally tailored to the patient's specific needs.

Comparative Pharmacodynamic Studies of Extended-Release Methylphenidate Dosage Forms

Little published data are available with regard to clinical differences among the newer modified-release MPH formulations. However, at least two trials have been completed, and some preliminary data are available. A head-to-head multicenter, randomized, double-blind, placebo-controlled clinical trial (184 patients) between the Metadate CD formulation and Concerta versus placebo was carried out in children (aged 6–12 yrs) with ADHD.[141] This study was sponsored by Celltech Pharmaceuticals, manufacturer of Metadate CD. Most patients (91%) previously had been stabilized on a once-daily MPH formulation and were stratified into one of three treatment groups based on preexistent MPH dosage requirements. These groups were Medadate CD versus Concerta in doses of 20 versus 18 mg, 40 versus 36 mg, and 60 versus 54 mg, respectively. Within each assignment group, patients were randomly

assigned to receive one of six treatment sequences, receiving each of the three blinded treatments for 7 days. The study used the SKAMP-Deportment and -Attention subscales and age-appropriate math test for permanent product score as primary measures of effectiveness. In addition, 26-item SNAP-IV rating scales were completed by parents or guardians. One hundred seventy-one children completed all three treatments. Metadate CD was reported to be superior to the Concerta dosage form in ADHD symptom control as evidenced by a 43% reduction in SKAMP-Deportment scores between hours 1.5 and 7.5. At the 12-hour time point, however, the Concerta dosage form was statistically superior. There were no clinically significant differences in adverse effects experienced among the three treatment groups with regard to the frequency of treatment emergent adverse effects, ratings of adverse effects, or vital signs. Of note, results were not reported for individual MPH dosing regimens. Although this study suggests a more rapid onset of effect with Metadate CD compared with Concerta, it awaits full publication so that it may be reviewed in greater detail.

A second head-to-head comparison trial was completed recently. This study, sponsored by Novartis Pharmaceuticals Corporation, was a single-blind, randomized, four-way crossover design and compared two doses of Concerta (18 and 36 mg) with Ritalin LA 20 mg or placebo in 36 children (aged 6–12 yrs) with ADHD who were previously stabilized with MPH.[142] The study was designed to assess differences in treatment during an 8-hour school day. All subjects were exposed to all treatments. Study subjects previously had received maintenance MPH dosages equivalent to immediate-release MPH 10 mg twice/day and were randomly assigned to four treatment periods during 4 weeks. The primary efficacy variable was the 0–4-hour change in SKAMP-Attention ratings from predose measurements. For the secondary efficacy variables, the Math Test-Attempted, Math Test-Correct, SKAMP-Deportment, and SKAMP-Combined ratings were used. All subjects completed all phases of treatment, and no significant differences in side effects were evident. In this study, Ritalin LA 20 mg proved superior to placebo and both doses of Concerta on all SKAMP measures during the first 4 hours and superior to SKAMP-Deportment scores during the entire 8 hours. Subjects receiving Ritalin LA 20 mg attempted approximately twice as many math problems as those treated with Concerta 18 mg or 36 mg during an 8-hour school day. Also, subjects treated with Ritalin LA 20 mg achieved a greater percentage correct over the first 4 hours compared with those treated with Concerta 18 or 36 mg; the difference reached statistical significance.[142] The results of this trial provide preliminary evidence 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. The more rapid absorption and higher peak plasma concentration(s) associated with Ritalin LA 20 mg when compared with Concerta 18 mg (Figure 6) correlate with the greater efficacy at these doses. A limitation of the study is that no measures were obtained beyond the 8-hour time point at which the Concerta dosage form is designed to allow extended coverage.[135] This study, like the comparative study above, awaits full publication to fully examine the study design, results, and other potential limitations.

Although the available information is limited, the results of these two pharmacodynamic studies, the first to our knowledge to compare newer once-daily MPH formulations, suggest that some significant differences in efficacy may exist among the formulations that may be attributable to MPH release profiles. These clinical observations during the first 8 hours of the day indicate that the more robust MPH plasma concentrations achieved with the Metadate CD and Ritalin LA formulations could translate into a greater reduction in some ADHD symptoms compared with Concerta.

d-Methylphenidate

Although the most widely prescribed drug for the treatment of ADHD is racemic *d,l*-MPH, the clinical effectiveness appears to reside in the *d*-isomer[65, 66, 119, 143–145] as evidenced by the previous discussion on MPH enantiomers and a clinical study[65] that demonstrated similar improvement on sustained attention testing after treatment with equimolar doses of *d*-MPH and *d,l*-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 *d,l* racemic mixture.[124, 145] Consequently, the synthesis and clinical development of *d*-MPH were undertaken, culminating in the approval of Focalin (Novartis Pharmaceuticals) in 2002.[139, 140]

The clinical development and study doses used were one-half those of racemic MPH, and pharmacokinetic parameters were generally similar between *d*-MPH and *d,l*-MPH with respect to C_{max}, T_{max}, and half-life.[124, 145] Likewise, metabolism and elimination were similar to those of racemic MPH, and *d*-MPH did not inhibit CYP isoenzymes during in vitro studies.[145] Administration of *d*-MPH did not result in interconversion to the inactive *l*-isomer,[146] and administration of *d*-MPH with food had no significant effect on bioavailability, but as with racemic MPH, T_{max} was delayed by 1 hour.[119] Treatment with equimolar doses of either *d*-MPH or *d,l*-MPH significantly improved symptoms of ADHD compared with placebo. In addition, at least one study suggested that *d*-MPH might have a longer duration of action than that of *d,l*-MPH on tests measuring attention or concentration and work output, but this issue requires further formal study. Therefore, treatment with *d*-MPH in children with ADHD allowed for the administration of lower doses than those prescribed with *d,l*-MPH. Focalin is available in 2.5-, 5-, and 10-mg immediate-release tablets.[145] A long-acting formulation of *d*-MPH is not available but is the subject of clinical study.

Conclusions

Immediate-release MPH has been in clinical use for approximately 50 years and has long been established as the reference standard in the pharmacotherapy of ADHD. Conventional sustained-release MPH formulations became available in the 1980s to offer the convenience of once-daily dosing, while avoiding compliance, confidentiality, and storage security issues. However, sustained-release MPH was not viewed as an optimal dosage formulation nor was it widely embraced by clinicians. Hence, a new generation of once-daily MPH formulations has emerged since 2000. These use novel modified-release pharmaceutics to provide for prolonged absorption profiles. Concerta provides an "ascending" absorption phase for an average of 8 hours, with a lunchtime plateau. Metadate CD exhibits a more uniform absorption phase, for an average of 7 hours. Ritalin LA better mimics the time course of a standard twice-daily schedule of immediate-release MPH than do the former two formulations. Accordingly, each of these new modified-release products is characterized by a distinct pharmacokinetic profile to allow greater prescriptive flexibility in drug individualization for patients with ADHD. Head-to-head therapeutic comparisons of the potential differences and benefits between these formulations have recently been completed or are in progress.[141,142] *d*-Methylphenidate (Focalin) is the most recently introduced MPH formulation. Although currently available only as an immediate-release 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 pharmacologic effects.

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