Methylphenidate

An update on extended-release formulations

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ABSTRACT

Methylphenidate remains the mainstay of pharmacological management in attention deficit hyperactivity disorder (ADHD). Despite having been available for over half a century, methylphenidate's original formulation has been modified with the main purpose of extending its duration of action. This article will present a brief review of how these new formulations vary and how these should be selected, considering the evidence available on their effectiveness and on the individual needs of the patient.

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Attention deficit hyperactivity disorder (ADHD) is a psychiatric disorder characterized by inattention, hyperactivity, or impulsivity that is more frequent or severe than is appropriate for the patient's developmental level.[1] In the United States (US) it has been estimated that 3-7% of children have ADHD, making it one of the most common psychiatric disorders of childhood and adolescence. It is associated with significant comorbidity with other illnesses.[2] Approximately 25% of patients also have an anxiety disorder, up to one-third have depression, and 20-25% have a learning disorder. Additionally, 2% of patients have Tourette's disease; conversely, approximately half of all Tourette's patients have ADHD.[3] **Table 1** shows the diagnostic criteria for ADHD according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). It is important that once ADHD has been diagnosed, treatment should be strongly considered. Without treatment, up to two-thirds of patients will continue to exhibit symptoms in adolescence. Many of these adolescents also develop behaviors that often lead to suspension and expulsion from school, and even in some cases to criminal behavior. Adults who have had ADHD as children are much more likely to develop other psychiatric disorders, such as mood disorders, anxiety disorders, antisocial personality disorder, alcohol disorders, and even schizophrenia.[4] Stimulants are considered first-line agents for the treatment of children (greater than 6 years of age) with ADHD and are the only agents approved by the US Food and Drug Administration (FDA) for this purpose.[5] Stimulant medications (including methylphenidate [MPH] preparations, dextroamphetamine preparations, and pemoline) have CNS and respiratory stimulant properties and weak sympathomimetic activity. Though a clear mechanism by which stimulants improve ADHD symptoms is not fully elucidated, they appear to work by promoting the release of dopamine and norepinephrine from presynaptic neurons and by inhibiting the reuptake of these neurotransmitters in the CNS.[6]

Although ADHD has been widely studied, the use of MPH in ADHD still poses a number of unresolved questions, including its pharmacodynamic characteristics (drug concentration-effect relationship) and the effect of long-term treatment on the patient's psychopathology later in life. The objective of this review is to provide an analysis of the pharmacokinetic-pharmacodynamic properties of MPH and the rationale for the use of long-acting formulations, which may help to answer some of these questions.

Pharmacodynamic and pharmacokinetic properties of MPH. It has been reported that in the treatment of ADHD, MPH exerts its therapeutic effect primarily by inhibiting the presynaptic dopamine transporter, with a minor influence on the norepinephrine transporter.[6,7] Stimulants have been available in both immediate and sustained-release (SR) formulations. Methylphenidate is administered as a racemic mixture that undergoes stereoselective clearance. Methylphenidate is a short-acting stimulant with a duration of action of 1-4 hours and a pharmacokinetic half-life

of 2 to 3 hours. Maximum drug concentration after oral administration occurs at approximately 2 hours. Methylphenidate is absorbed well from the gastrointestinal tract and easily passes to the brain.[8] There is marked individual variability in the dose-response relationship for MPH, and therefore dosage must be titrated for optimal effect and avoidance of toxicity in each child. It is unclear whether this variability is predominantly pharmacokinetic or pharmacodynamic.[7,8] Until the development of the new longer-acting preparations, pharmacological options were limited to the use of SR MPH. Methylphenidate SR is limited by its duration of action (up to 8 hours), a slower onset of action, and is considered by some to be less effective than immediate-release dosage forms. **Table 2** summarizes the pharmacokinetic parameters of the MPH formulations available in Saudi Arabia.

The extended-release (ER)-MPH formulation is based on a specialized delivery system known as OROS (an osmotically active trilayer core surrounded by a semi-permeable membrane with an immediate-release drug overcoat).[9] The ER-MPH is delivered in a unique pattern that provides an initial maximum plasma concentration at approximately 1-2 hours followed by an ascending delivery profile of MPH that provides peak plasma concentrations at 6-8 hours. This delivery pattern is associated with a duration of effect of 12 hours, and it can be dosed once daily.[9] In single- and multiple-dose pharmacokinetic studies, no significant drug accumulation occurred with multiple dosing.[10]

Table 1 - Diagnostic Criteria for Attention Deficit Hyperactivity Disorder (ADHD) – Diagnostic and Statistical Manual for Mental Disorders.

I. Either A or B	
A. Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level	B. Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level
Inattention	**Hyperactivity**
1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities	1. Often fidgets with hands or feet or squirms in seat
2. Often has trouble keeping attention on tasks or play activities	2. Often gets up from seat when remaining in seat is expected
3. Often does not seem to listen when spoken to directly	3. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless)
4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)	4. Often has trouble playing or enjoying leisure activities quietly
5. Often has trouble organizing activities	5. Is often "on the go" or often acts as if "driven by a motor"
6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework)	**Impulsivity**
7. Often loses things needed for tasks and activities (for example toys, school assignments, pencils, books, or tools)	1. Often blurts out answers before questions have been finished
8. Is often easily distracted	2. Often has trouble waiting one's turn
9. Is often forgetful in daily activities	3. Often interrupts or intrudes on others (for example, butts into conversations or games)
II. Some symptoms that cause impairment were present before age 7 years	
III. Some impairment from the symptoms is present in 2 or more settings (for example, at school/work and at home)	
IV. There must be clear evidence of significant impairment in social, school, or work functioning	
V. The symptoms do not happen only during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder. The symptoms are not better accounted for by another mental disorder (for example, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder)	
Based on these criteria, 3 types of ADHD are identified:	
1. ADHD, Combined Type: if both criteria IA and IB are met for the past 6 months	
2. ADHD, Predominantly Inattentive Type: if criterion IA is met, but criterion IB is not met for the past 6 months	
3. ADHD, Predominantly Hyperactive-Impulsive Type: if criterion IB is met, but criterion IA is not met for the past 6 months	
Adapted from Reference 1.	

Table 2 - Pharmacokinetics of methylphenidate formulations available in Saudi Arabia.

Drug	Cmax (ng/mL)	Tmax (hours)	Half-life (hours)	Duration of action (hours)
Methylphenidate	4.2	0.3 - 4.4	1.5 - 2.5	3-4
Methylphenidate SR	4.56	1.3 - 8.2	4	6-8
Methylphenidate ER	3.7	6.8	3.5	Up to 14

Cmax = maximum concentration; Tmax = time to maximum concentration, SR - Sustained release, ER - Extended release
Adapted from product labeling[9]

Table 3 - Differences of psychostimulants available worldwide.

Drug	Dosage forms	Indication	Dose	Pharmaco-kinetics	Advantages/ disadvantages
Methylphenidate (MPH) formulations:					
MPH-IR	Tablet	ADHD Narcolepsy	Initial: 5mg before breakfast and lunch. Gradually increased by 5-10mg per week. May be dosed TID. Max = 60mg/day.	t1/2=2-3hrs DBE=3-5hrs	Requires multiple daily dosing.
MPH-SR	Tablet	ADHD Narcolepsy	Average daily dose is 30mg/day.	t1/2=3.4hrs DBE=8hrs	May require multiple daily dosing.
MPH-CD	Capsule	ADHD	Initial: 20mg QAM. Increase by 20mg/week to a max of 60mg/day.	t1/2=6.8hrs DBE=9hrs	Administered once daily. Quick onset.
Dex-MPH	Tablet	ADHD	Initial: 2.5mg BID Increase by 2.5-5mg weekly to max of 20mg/ day.	t1/2=2.2hrs DBE=3-5hrs	Requires multiple daily dosing.
Amphetamine mixtures	Tablet and capsules	ADHD Narcolepsy	IR initial: 2.5-5mg QD. Increase by 5mg weekly. Max=40mg/d.	IR: t1/2=4-6hrs DBE=4-6hrs	IR: May require multiple daily dosing.
			XR: Initial: 10mg QAM. Increase by 10mg weekly. Max=30mg/d.	XR: t1/2=9-11hrs DBE=12hrs	XR: Administered once daily.
Dextro-amphetamine	Tablet and Spansule	ADHD Narcolepsy Obesity	Initial: 5-10mg in divided doses. Increase weekly to max of 40-60 mg/day. Spansule (SR) dosed QD.	t1/2=4-6hrs DBE=4-6hrs Spansule t1/2=12hrs DBE=6-8hrs	May require multiple daily dosing. Spansule has a slow onset of action. Often higher doses must be used.
Pemoline	Chewable and regular tablets	ADHD	Initial: 37.5mg QD Mean effective dose range = 56.25-75mg per day.	t1/2=7-8hrs DBE=6-8hrs	May cause toxic hepatitis or hepatic failure. Monitor LFTs.

CD - controlled release, DBE - duration of behavioral effect, IR - immediate release, SR - sustained release, LFTs - liver function tests, XR - extended release formulation of amphetamine mixtures, TID - 3 times daily, QAM - daily in the morning, BID - twice daily, QD - daily, t1/2 - half life

Table 4 - Switching patients from methylphenidate (MPH) formulations to ER-MPH.

Current methylphenidate dose	Recommended ER-MPH dose
· 5mg methylphenidate BID or TID · 20mg methylphenidate SR	18mg QAM
· 10mg methylphenidate BID or TID · 40mg methylphenidate SR	36mg QAM
· 15mg methylphenidate BID or TID · 60mg methylphenidate SR	54mg QAM

BID - twice daily, TID - 3 times daily, SR - Sustained release, ER - Extended release, QAM - daily in the morning

When it was dosed at 18 mg/day, 36 mg/day, or 54 mg/day, the pharmacokinetics were linear and dose proportional. Food does not impede drug absorption and can be taken with, or without food.[10-12] A more detailed comparison of stimulant medications available worldwide is summarized in **Table 3**.

Clinical efficacy of ER-MPH. In 2 clinical trials, ER-MPH once daily was comparable to immediate-release (IR) MPH administered 3 times daily every 4 hours.[8,11] Measures of efficacy included behavior frequency, completion and accuracy of academic problems, independent observations, as well as teacher and counselor ratings. Details of these 2 important trials are summarized below:

1. A double-blind, cross-over study (n=68), 7-day courses of ER-MPH given once-daily demonstrated equivalent efficacy to IR-MPH given 3 times a day, and both forms of MPH were significantly superior to placebo for treatment of ADHD. Enrollees were children 6-12 years of age, who met diagnostic criteria for ADHD (DSM-IV) and who had received a stable dose of MPH for at least 4 weeks. Teachers rated each child's behavior on a daily report card, which was sent home to the child's parents (who provided rewards for a positive report card). Teachers completed weekly ratings on the Inattention/Overactivity (I/O) with Aggression (IOWA) Conners Rating Scale. Parents also completed IOWA and Abbreviated Conners Ratings Scales each week. Children attended 3 Saturday laboratory sessions, with ratings made on academic productivity and social interaction measures. On all domain ratings by all reviewers in all settings, ER-MPH and IR-MPH provided significantly improved results compared with placebo (p<0.001). The only differences between the 2 MPH formulations were in 2 parent ratings (I/O and Abbreviated Conners), with ratings for ER-MPH significantly better than IR-MPH ratings (p<0.05). In the laboratory sessions, rule violation frequency, negative behavior frequency, and observed disruptive behaviors were significantly different for MPH (both forms) compared with placebo.[12]

2. A multi-center, double-blind trial (n=277), a 4-week course of ER-MPH was demonstrated to be significantly more effective than placebo (p<0.001), and to have similar efficacy to IR-MPH in children 6-12 years of age with ADHD. Children who had not received MPH previously participated in an open-label titration study to determine their MPH dose; those who had previously used MPH were converted to one of the established dose levels. Subjects were randomized to ER-MPH, IR-MPH, or placebo. The average total daily dose was 29.5 mg/day for those taking the IR form (n=94) and 34.3 mg/day for ER-MPH (n=94). The primary efficacy measure was the IOWA Connors Ratings Scale, including the I/O and Oppositional/Defiance (O/D) subscales completed by both teachers and parents. Ratings on the IOWA Connors Ratings Scale showed equivalent efficacy for ER-MPH and IR-MPH. Fifty-nine subjects discontinued for lack of efficacy, 38 (48%) from the placebo group, 11 (16%) from the ER-MPH group, and 10 (14%) from the IR-MPH group.[11]

To date there has been no head-to-head trials of the long acting preparations of MPH. A recent trial has shown promising results with the use of ER-MPH in treating adolescents with ADHD.[13]

Dosing and administration. Patients new to MPH should start ER-MPH at a dose of 18 mg once daily. The dose may be adjusted based on the patient's response in increments of 18 mg per week to a maximum recommended dose of 54 mg/day. **Table 4** summarizes the recommended dose conversion for patients currently taking MPH. The tablet must not be chewed, crushed, or broken in order to maintain its long-acting system. The ER-MPH tablet sometimes does not fully dissolve after all the drug has been released and has appeared in the patient's stool. This is the shell of the tablet and should not be a cause for alarm.[14]

Tolerability. The side effect profile of ER-MPH does not significantly differ from the IR formulation. The most common side effects reported in controlled and open-label safety clinical studies were headache (14%), upper respiratory tract infection (8%), stomach ache (7%), vomiting (4%), loss of appetite (4%), sleeplessness (4%), increased cough (4%), sore throat (4%), sinusitis (3%), and dizziness.[9] The impact of ER-MPH on sleep quality, appetite and tics was evaluated prospectively in controlled studies and in a long-term open-label study.[11,12,15] No serious adverse events occurred, and no withdrawals due to adverse events. The most common adverse effects of MPH were headache and abdominal pain. Four children had reports of motor tics, all during IR-MPH therapy. Poor sleep was reported in 16%, 7%, and 10% of recipients during ER-MPH, IR-MPH, and placebo dosing. Usual appetite was reported for 77%, 66%, and 59% during the same 3 treatments.[12] In another study, no significant difference between ER-MPH, IR-MPH or placebo was observed in sleep quality; more children in the 2 active treatment groups were rated as eating less than usual compared with the control group. Five patients had tics reported as adverse effects (4 on placebo and one on IR-MPH).[11] The impact of ER-MPH on growth (height and weight) has also been evaluated in long-term studies.[15,16] Findings appear to indicate a lack of or minimal effect on various height/weight related issues, but clearly further analyses of growth in children in longitudinal studies with ER-MPH are still necessary before firm conclusions can be

made. Overall, the results of the studies showed minimal impact on sleep quality, appetite or tics.

Counseling and monitoring for stimulant medications. If insomnia is a problem, avoid late afternoon doses. Take the medication with meals to avoid stomach pain and possible weight loss. Discontinue medication several times a year to allow a growth spurt. Due to hepatic inhibition, MPH may increase blood concentrations of other medications. Discontinue if tics develop (contraindicated if tics are already present). Monitor heart rate and blood pressure initially.

In conclusion, selection of stimulant medication is not based on differences in efficacy. Factors to take into consideration include: dosing frequency, compliance, feasibility of medication administration during the school day, behavior that requires treatment in the late afternoon, and cost. New extended-release products are important therapeutic options for those patients requiring late afternoon drug coverage (children with after-school activities and homework) or who are unable to be compliant with multiple daily doses. Also, once-a-day medication for ADHD can help to eliminate the feelings of embarrassment that children may have when taking medication during the school day or after-school activities. The ER-MPH seems to be superior to IR-MPH and even the SR formulations, because the latter lose their effectiveness in approximately 6 hours. Nevertheless, ER-MPH has a few issues that need to be thoroughly explained to the patients, including: It cannot be cut or chewed because that will destroy the release mechanism. Dosing adjustments to account for meal times cannot be controlled; patients are not likely to feel hungry until the entire dose wears off. If the patient forgets to take the medication early morning, taking a 12-hour dose late in the day will possibly affect sleep. Remnants of this dosage form may appear in stool but should not be worrisome to the patient.

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