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A Review of Stimulant Medications

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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). It is estimated that 3 to 7 % of children have ADHD making it one of the most common psychiatric disorders of childhood and adolescence(2).

PHARMACOTHERAPY

Stimulants are considered first-line agents for the treatment of children (greater than six years of age) with ADHD and are the only agents approved by the Food and Drug Administration (FDA) for this purpose(3). Stimulant medications (including methylphenidate 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.

Stimulants have been available in both immediate and sustained release formulations. The duration of action for immediate release products is typically short (2 to 6 hours) necessitating multiple daily doses. Longer acting preparations eliminate the need for medication administration during the school day. Until the development of the new longer-acting preparations, pharmacological options were limited to the use of sustained-release methylphenidate (Ritalin SR, Methylin ER), Dexedrine Spansules, or pemoline (Cylert). 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. Dexedrine Spansules have a longer duration of action (up to 8-12 hours), but use is restricted by a slow onset of action. Potentially serious adverse hepatic effects further limit pemoline. Pemoline is not considered first or second line therapy for ADHD and its use should be limited (3). A more detailed comparison of available stimulant medications is summarized in Table 1.

NEWER STIMULANT MEDICATIONS

Focalin (dexmethylphenidate HCL) is a new formulation of Ritalin that contains only the active d-enantiomer instead of both the d- and l-enantiomers of methylphenidate. Currently there is no published data to support the use of this medication over generic methylphenidate. Side effects and dosing intervals are identical (4).

Patients new to methylphenidate products should start with 2.5mg of Focalin twice daily at least four hours apart. The dose may be increased at weekly intervals in 2.5 to 5mg increments. For patients switching from methylphenidate immediate release to Focalin, the total daily dose should be halved (e.g. 10mg BID methylphenidate IR = 5mg BID Focalin or dexmethylphenidate).

Concerta is an extended release methylphenidate preparation that can be dosed once daily. In clinical trials, Concerta once daily was comparable to immediate-release methylphenidate administered three times daily every

four hours (5,6). Measures of efficacy included behavior frequency, completion and accuracy of academic problems, independent observations, as well as teacher and counselor ratings. The extended release property of Concerta is based on its OROS[®] delivery system (an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat)(7).

Patients new to methylphenidate should start Concerta at a dose of 18mg once daily. The dose may be adjusted based on the patient's response in increments of 18mg per week to a maximum recommended dose of 54mg/day. The recommended dose conversion for patients currently taking methylphenidate is summarized as follows:

CURRENT METHYLPHENIDATE DOSE	RECOMMENDED CONCERTA DOSE
<ul style="list-style-type: none">5mg methylphenidate BID or TID20mg methylphenidate SR	18mg QAM
<ul style="list-style-type: none">10mg methylphenidate BID or TID40mg methylphenidate SR	36mg QAM
<ul style="list-style-type: none">15mg methylphenidate BID or TID60mg methylphenidate SR	54mg QAM

Metadate CD, another once daily extended release methylphenidate preparation, is dosed as a capsule containing both immediate release drug beads and extended release drug beads in a ratio of 30% to 70%, respectively. An initial serum level peak occurs at 1.5 hours followed by a second drug peak at 5 hours. In a four-week, double blind, placebo-controlled crossover study, Metadate CD 20mg once daily was comparable in efficacy to immediate release methylphenidate 10mg administered twice daily, 4 hours apart (8).

Metadate CD should be started at 20mg every morning. The dose may be increased in 20mg increments weekly to achieve the desired effect. The maximum daily dose is 60mg/day.

As mentioned above, none of the sustained release methylphenidate products have been shown to be superior to immediate release formulations in efficacy or tolerability. Patients who fail to respond to methylphenidate should not be expected to achieve better results with the newer products, unless compliance is the underlying factor.

Adderall XR is the once daily extended-release formulation of dextroamphetamine and amphetamine salts. Similar to Metadate CD, Adderall XR capsules contain two types of drug beads designed to give a double-pulsed delivery of amphetamines. Once daily Adderall XR is comparable to the same total daily dose of immediate release Adderall administered twice daily, four hours apart (9).

Patients new to Adderall should start with an Adderall XR dose of 10mg QAM. The dose may be increased by 10mg every week as needed. Amphetamines should be administered at the lowest effective dose. The maximum recommended daily dose is 30mg/day. For patients currently taking divided doses of immediate-release Adderall, the total daily dose can be converted directed to once daily Adderall XR. (e.g. Adderall 10mg BID = Adderall XR 20mg QD).

CONCLUSION

Stimulant medications are first-line therapy for the treatment of ADHD in children over six years of age. Many studies have been conducted comparing methylphenidate to other traditional stimulant medications. In randomized, double-blind studies comparing Adderall to methylphenidate, the two medications appear to be equally efficacious if given at equivalent doses (10,11,12). A review of 22 different studies showed no differences between methylphenidate and dextroamphetamine nor among the different forms of these stimulants (3). One study comparing Adderall to dextroamphetamine preparations determined that all of the studied medications are similar in efficacy, though Dexedrine Spansules proved to

have a slower onset to effect decreasing performance on morning efficacy scores(13).

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 including Concerta, Metadate CD and Adderall XR are important therapeutic options for those patients requiring late afternoon drug coverage or who are unable to be compliant with multiple daily doses.

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Table 1. Comparison of Stimulant Medications

Drug	Dosage Forms	Indication	Dose	Pharmacokinetics	Advantages/Disadvantages	Cost/Month (AWP)
Amphetamine Mixtures						
Adderall	Tablet 5, 7.5, 10, 12.5, 15, 20, 30mg	ADHD Narcolepsy	Initial: 2.5 to 5mg QD. Increase by 5mg weekly to optimal response. Max=40mg/d.	t1/2=4-6hrs DBE=4-6hrs	May require multiple daily dosing.	\$81.00 (10mg BID)
Adderall XR	Capsule 10, 20, 30mg	ADHD	Initial: 10mg QAM. Increase by 10mg at weekly intervals if needed. Max=30mg/d	t1/2=9-11hrs DBE=12hrs	Administered once daily.	\$70.20 (10mg QD)
Dextroamphetamine						
Dexedrine	Tablet 5, 10mg Spansule 5, 10, 15mg	ADHD Narcolepsy Obesity	Initial: 5 to 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	Cheaper therapeutic alternative. May require multiple daily dosing. Spansule has a slow onset to effect. Often higher doses must be used.	\$11.40 generic (5mg BID) \$38.40 (10mg Spansule QD)
Methylphenidate Preparations						
Concerta	Tablet 18, 27, 36, 54mg	ADHD	Initial: 18mg/day. Increase at weekly intervals. Max=54mg/d	t1/2=3-4hrs DBE=12hrs	Administered once daily. Quick onset. Longer duration of action.	\$73.20 (36mg QD)
Metadate CD	Capsule 20mg	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.	\$69.60 (40mg QD)
Focalin (dexmethylphenidate)	Tablet 2.5, 5, 10mg	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. More expensive alternative to generic methylphenidate.	\$37.18-\$55.78 (5mg BID-TID)
Ritalin IR	Tablet 5, 10, 20mg	ADHD Narcolepsy	Initial: 5mg before breakfast and lunch. Gradually inc. by 5 to 10mg per week. May be dosed TID. Max= 60mg/day.	t1/2=2-3hrs DBE=3-5hrs	Requires multiple daily dosing.	\$22.50 generic (5mg BID-TID)
Ritalin SR	Tablet 20mg	ADHD Narcolepsy	Average daily dose is 30mg/day.	t1/2=3.4hrs DBE=8hrs	May require multiple daily dosing. Typically used in combination with IR.	\$27.90 generic (20mg QD)
Other						
Cylert (Pemoline)	Tablet 18.75, 37.5, 75mg Chewable 37.5mg	ADHD	Initial: 37.5mg QD Increase by 18.75mg at 1-week intervals. Mean effective dose range = 56.25mg-75mg per day	t1/2=7-8hrs DBE=6-8hrs	May cause toxic hepatitis or hepatic failure. Monitor LFTs.	\$33.60 (37.5mg QD)

DBE = Duration of behavioral effect

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