Drugs for Attention Deficit Hyperactivity Disorder

This discussion is about medications for attention deficit hyperactivity disorder (ADHD). The focus is on new forms of and new information about the medications. The information in this column is not adequate to guide the treatment of ADHD, which should be initiated by a provider who has expertise in the field. Behavior therapy can be effective either by itself or used with medications.[1] The American Academy of Pediatrics develops clinical practice guidelines for ADHD. See the National Guideline Clearinghouse for the latest guideline (*www.guideline.gov*).

PRESCRIPTION PAD

Maren Mayhew

The Food and Drug Administration (FDA) has issued a number of alerts and warnings about some of the drugs used for ADHD in the past few years. Pemoline (Cyclert) (sold from 1975 to 1999) was removed from the market as a result of life-threatening hepatic failure. Pemoline is a central nervous system (CNS) stimulant with a different chemical structure from amphetamines and methylphenidate.

Atomoxetine (Strattera), introduced in 2002, received a warning for severe liver injury in 2004.[2] There were reports of two patients, a teenager and an adult, both of whom recovered. Atomoxetine received a black box warning in 2005 because of an increased risk of suicidal thinking in children and adolescents, but not in adults.[3]

Atomoxetine is the only nonstimulant indicated for treatment of ADHD. It is thought to act through selective inhibition of the presynaptic norepinephrine transporter, thus providing increased levels of norepinephrine in the synaptic cleft. Atomoxetine can increase blood pressure and heart rate, like the stimulants. Urinary hesitancy and retention are important risks. Somnolence and upset stomach are common.[4]

Adderall was briefly removed from the Canadian market in 2005 as a result of concerns about sudden deaths in children. Five of 12 cases were in patients with structural heart defects; others had concomitant conditions.[5] Currently, the FDA is considering a black box warning for all stimulants regarding the risk of cardiac death. The cardiac effects of stimulants are not well understood.

Daytrana, the transdermal methylphenidate patch, was released in June 2006.[6] It is probably as effective as oral long-acting forms of the drug. However, the delay (2-6 hours) in onset of action may cause difficulty. The advantage is that the patch can be removed in time to avoid insomnia. Absorption increases after chronic use. Plasma concentrations were similar to Concerta at first, but later the concentrations were almost double. Skin reactions may be a problem.[7]

The effect of stimulants on normal growth in children is unknown and is much debated. Incidents have been found of children with decreased growth rate on stimulants and on atomoxetine, but a causal effect has not been established.

Table 1. ADHD Drugs

Trade Name	Drug Name	Supplied As	Duration of Action	Cost, $*
Ritalin	Methylphenidate (MPH)	5, 10, 20 mg	IR	30
Ritalin LA	Methylphenidate	20 mg	50% IR; then 50% 4 h later	90
Ritalin SR	Methylphenidate	20 mg	Variable release over 5-8 h	110
Daytrana	Methylphenidate patch	12.5 = 10 mg/9 h 18.75 = 15 mg/9 h 25 = 20 mg/9 h 37.5 = 30 mg/9 h	Apply to hip for 9 h. Onset 1-6 h (average 3); half-life after patch removed 3-4 h	150
Concerta	Methylphenidate	18 mg	4 mg IR; then 14 mg over 8 h; total 12 h at 5 mg tid	100
Metadate CD	Methylphenidate	20 mg	30% IR then 70% XR = 10 mg in AM + 10 mg 4 h later	105
Focalin	Dexmethylphenidate (d-MPH)	2.5, 5, 10 mg	IR	70
Focalin XR	Dexmethylphenidate	5, 10, 20 mg	50% IR, second delayed release of 50%	100
Adderall	Amphetamine compounds	4, 7.5, 10, 12.5, 15, 20, 30 mg		75
Adderall XR	Amphetamine compounds	10, 15, 20, 25, 30 mg	Equivalent to two IR doses 4 h apart	75
Dexedrine	Dextroamphetamine sulfate	5 mg	Peak at 2 h; half-life 10-25 h	30
Dex Spansule	Dextroamphetamine sulfate	5, 10, 15 mg	Peak 8 to 10 h	65
Strattera	Atomoxetine	10, 18, 25, 40, 60, 80, 100 mg	Half-life 5 h	90

IR indicates immediate release; XR, extended release.
**Cost is approximate, from Medical and Drug Letter.*
Most information in chart comes from product information.

Stimulants have abuse potential. Also, many children and adolescents with ADHD also have comorbidity such as substance abuse disorder, oppositional defiant disorder, enuresis, depressive disorders, and anxiety disorders. Use can lead to tolerance and psychological dependence with abnormal behavior. Psychotic episodes can occur. Careful supervision is required during withdrawal.

There are three types of stimulants—methylphenidate, dextroamphetamine, and amphetamine compounds. Dexmethylphenidate is the right isomer of methylphenidate. Ten milligrams of methylphenidate is roughly equivalent to 5 mg of dexmethylphenidate, and each has immediate release and extended release forms (Table 1). The mechanism of action of stimulants is through two neurotransmitter systems, the monoamines dopamine and norepinephrine, making more dopamine available in the synaptic cleft.[8]

The most common effects are anorexia and insomnia, headaches, and stomachaches. Other adverse effects are nausea, rebound phenomena, anxiety, nightmares, dizziness, irritability, dysphoria, and weight loss.[9] JNP

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Maren Mayhew, MS, ANP, GNP, is the author and editor of Pharmacology for Primary Care Providers, *a textbook for NPs published by Mosby. She can be reached at* marenmayhew@comcast.net. *This is a monthly column on medication news and controversies. Suggestions for topics are welcome.*

1555-4155/07/$ see front matte

doi:10.1016/j.nurpra.2007.11.008