Stimulants and Related Agents Review

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FDA-Approved Indications

Drug	Manufacturer	ADHD			Narcolepsy (age ≥6 years)	Other Indications
		age 3-5 years	age ≥6 years	Adults		
Stimulants						
dexmethylphenidate IR (Focalin™)	generic		X			
dexmethylphenidate ER (Focalin XR™)	Novartis		X	X		
dextroamphetamine IR (DextroStat®, Dexedrine®)	generic	X	X		X	
dextroamphetamine ER (Dexedrine®)	generic		X		X	
dextroamphetamine solution (Procentra™)	Auriga Labs	X	X		X	
lisdexamfetamine dimesylate (Vyvanse™)	New River		X	X		
methamphetamine (Desoxyn®)	Ovation		X			Exogenous Obesity in adults
methylphenidate IR (Methylin®, Ritalin®)	generic		X		X	
methylphenidate SR (Methylin ER®, Ritalin SR®*, Metadate ER®)	generic		X		X	
methylphenidate ER (Concerta®)	McNeil		X	X		
methylphenidate ER (Metadate CD®)	UCB		X			
methylphenidate ER (Ritalin LA®)	Novartis		X		X	
methylphenidate transdermal (Daytrana™)	Shire		X			
mixed amphetamine salts IR (Adderall®)	generic	X	X		X	
mixed amphetamine salts ER (Adderall XR®)	Shire		X	X		
modafinil (Provigil®)	Cephalon					Excessive sleepiness associated with narcolepsy, OSA/HS and SWSD for age ≥16 years
armodafinil (Nuvigil)	Cephalon					Excessive sleepiness associated with narcolepsy, OSA/HS and SWSD for age ≥17 years

Drug	Manufacturer	ADHD			Narcolepsy (age ≥6 years)	Other Indications
		age 3-5 years	age ≥6 years	Adults		
Non-Stimulants						
atomoxetine (Strattera®)	Eli Lilly		X	X		

OSA/HS – obstructive sleep apnea/hypersomnia syndrome SWSD – shift work sleep disorder.

Overview

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

The most common use of stimulants is for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), for which they are considered first line therapy.[1,2,3,4,5,6] Attention-Deficit/Hyperactivity Disorder, which affects four to 12 percent of school age children and about four percent of adults, is a chronic condition with core symptoms of inattention, hyperactivity and impulsivity.[7,8,9] It may also be accompanied by internalized disorders such as sadness and anxiety, as well as aggressive and oppositional disorders.[10,11,12] The three main types of ADHD are primary hyperactive, primary inattentive and mixed.

Children with ADHD may experience academic underachievement, difficulties in personal relationships and low self-esteem.[13,14] Early recognition of the signs and symptoms of ADHD, assessment, and treatment can help redirect the educational and social development of most children with ADHD. The treatment of patients with ADHD should maximize function to improve relationships and performance at school, decrease disruptive behaviors, promote safety, increase independence and improve self-esteem.

Although symptoms of ADHD tend to improve with age, this may be due in part to improved coping skills. The continuation of synaptogenesis and myelinization into adolescence and young adulthood (especially in the frontal lobes) may also play a role in the improvement of symptoms with age. Sixty to eighty percent of children with ADHD will still require treatment through adolescence and into adulthood.[15,16,17,18]

Studies have shown that 70 to 75 percent of patients respond to the first stimulant medication on which they are started.[19] Response increases to 90 to 95 percent when a second stimulant is tried. Treatment failures with stimulants are often due to improper doses rather than ineffectiveness of the medication. It may take one to three months to adequately establish the best dose and form of medication for any given patient. The American Academy of Pediatrics (AAP) recommends that, if one or two stimulants are ineffective or poorly tolerated, a third stimulant might be tried prior to initiation of a second-line treatment.

The 2008 recommendations of the National Institute for Health and Clinical Excellence (NICE) recommends only starting drug treatment as first-line therapy in children and young adults with severe ADHD and impairment as diagnosed by a specialist.[20] The NICE guidelines further recommend starting drug treatment in adults with moderate to severe impairment as diagnosed by a specialist. First-line agents to consider are methylphenidate, atomoxetine, and dexamphetamine.

The 2006 treatment guidelines from The Medical Letter suggest that treatment of ADHD begin with an oral stimulant, noting that none of these agents has been shown to be more effective than another. This group indicates that short-acting stimulants may be useful in small children to demonstrate effectiveness or in instances where there is not an appropriately low dose of a long-acting agent. The methylphenidate patch (Daytrana) is recommended for use when oral administration is problematic. Atomoxetine (Strattera) is recommended if there are objections to using a controlled substance, if stimulant-induced weight loss is problematic or for patients with anxiety, mood, tic or substance abuse disorders.[21]

Clinical trials have identified several medications that may be used alone as second-line treatment or in combination with first-line agents depending upon the ADHD type or comorbidity profile. Tricyclic antidepressants have been shown to be effective as monotherapy for ADHD, but their use is limited by their adverse event profile. Alpha-2 agonists (e.g., clonidine) may be especially useful in patients with predominant hyperactivity or impulsivity. Bupropion is effective for patients (over eight years of age) with comorbid depression.

The stimulants most commonly used to enhance attention in ADHD are amphetamines and methylphenidate (MPH). Dexmethylphenidate HCl (Focalin, Focalin XR), is the d-threo-enantiomer of the racemic mixture of MPH, and is proposed to be the more active enantiomer.[22] Lisdexamfetamine (Vyvanse), a prodrug in which d-amphetamine is covalently bonded to L-lysine, is a newer formulation of amphetamine in the stimulant class.[23] Dextroamphetamine sulfate (Procentra) is a new liquid oral formulation of the dextro isomer of d,l-amphetamine sulfate.[24] Although effective, methamphetamine (Desoxyn) is not routinely used due to its potential for abuse. Atomoxetine (Strattera), a non-stimulant medication, is also approved for the treatment of ADHD.

HYPERSOMNOLENCE

Excessive sleepiness, or hypersomnolence, is the primary and often debilitating symptom experienced by patients with narcolepsy, obstructive sleep apnea/hypersomnia (OSA/HS) and shift work sleep disorder (SWSD). The defining characteristic of hypersomnolence is a consistent inability to stay awake and alert enough to safely and successfully accomplish tasks of daily living. Persons experiencing excessive sleepiness who seek medical attention typically complain of fatigue, tiredness, lapses of attention, lack of energy, low motivation, difficulty concentrating, disrupted sleep, snoring or difficulties at work.

While continuous positive airway pressure (CPAP) has been shown to improve daytime sleepiness in patients with obstructive sleep apnea (OSA), the level of sleepiness does not always normalize.[25,26,27,28,29,30] To address this residual daytime sleepiness, pharmacologic treatments may be beneficial in users of CPAP. While CNS stimulants, such as dextroamphetamine (Dexedrine, DextroStat, Procentra) and methylphenidate (Methylin, Ritalin, Methylin ER, Ritalin SR, Metadate ER, Ritalin LA), have been used for this purpose, the potential for adverse cardiovascular events may be of concern, especially in this overall high-risk patient population.[31] Due to its lack of sympathomimetic activity, modafinil (Provigil) is relatively free of adverse cardiovascular effects and may be preferable to the stimulants for the treatment of excessive daytime sleepiness resulting from OSA.[32] Armodafinil (Nuvigil) is another wakefulness-promoting agent that also lacks sympathomimetic activity.[33]

Pharmacology

Stimulants act by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space. Amphetamines appear to release newly synthesized dopamine while MPH causes the release of stored dopamine.[34] Unlike MPH, the amphetamine-induced elevation of synaptic dopamine does not appear to be highly dependent upon impulse-released dopamine. Stimulants tend to have selectivity for cortical, rather than striatal, dopamine presynaptic terminals. As a result, lower doses have more of an effect on attention than on motor activity.

Symptoms of inattention in ADHD may be due to dopamine and/or norepinephrine dysfunction in critical areas of the cerebral cortex controlling cognition. It seems as though patients with such symptoms need a boost in their dopamine/norepinephrine and, when they are given agents such as stimulants that boost these systems, their symptoms of inattentiveness can improve.

Symptoms of hyperactivity and impulsivity associated with ADHD are more likely mediated by the nigrostriatal dopamine pathway, which controls motor activity. Due to a presumed greater sensitivity of the mesocortical dopamine terminals in patients with ADHD, lower doses of stimulants prefer the cerebral cortex. Thus, the effects of stimulants on inattentiveness usually appear before their effects on motor behaviors.

Amphetamine and MPH are available as racemic or single isomer products. The d-enantiomer of amphetamine, dextroamphetamine (Dexedrine, DextroStat, Procentra), has much less of an effect on norepinephrine release than the l-enantiomer. Thus, the combination of the two isomers of amphetamine may provide additional benefit over dextroamphetamine in some patients. This combination is available as mixed amphetamine salts (MAS) (Adderall, Adderall XR), which contains d- and l-amphetamine in a 3:1 ratio. Mixed amphetamine salts (Adderall, Adderall XR) tends to have fewer adrenergic side effects than MPH. Methylphenidate is a racemic mixture of d- and l-enantiomers, the former of which is more pharmacologically active.[35,36] A product containing only the d-enantiomer, dexmethylphenidate (d-MPH, Focalin, Focalin XR), is available. Lisdexamfetamine dimesylate (Vyvanse) is a prodrug in which d-amphetamine is covalently bonded to L-lysine and converted to these components by enzymatic hydrolysis.[37] Lisdexamfetamine (Vyvanse) is rapidly absorbed from the gastrointestinal tract after oral administration and converted to dextroamphetamine, which is responsible for its activity. Conversion is believed to occur by first-pass intestinal and/or hepatic metabolism. Metabolism does not occur by cytochrome P450 enzymes.[38]

Compared to short-acting dosage forms, extended-release preparations and longer acting stimulants offer the advantages of less fluctuation in activity and removal of the need for dose administration in school. Their prolonged action, however, may be less intense, and their use forfeits the advantages of flexibility and control of titrating that shorter acting dosage forms allow by more frequent dosing.[39] It is also important that longer-acting dosage forms do not produce a flat plasma concentration of the stimulant, which could lead to acute tolerance.[40] There is increased experience with combining slow release and fast acting preparations to produce optimal symptom control throughout the day.

Atomoxetine (Strattera) is a selective inhibitor of the presynaptic norepinephrine transporter. It increases norepinephrine and dopamine levels, especially in the prefrontal cortex.[41] It has minimal affinity for other monoamine transporters. Mechanism of action suggests that atomoxetine is unlikely to have abuse potential or to cause motor tics.[42,43] Atomoxetine (Strattera) has a slower onset of action than do stimulants; therapeutic effects may not be seen

until a week after the start of treatment. Atomoxetine (Strattera) has a longer duration of action than the stimulants after once daily dosing with the possibility of symptom relief during the evening and early-morning hours.[44]

Modafinil (Provigil) appears to act by selective activation of the cortex without generalized stimulation of the CNS. It has wake-promoting actions like the sympathomimetic agents. It also causes psychoactive and euphoric effects, as well as the alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In vitro, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine. In vivo models, however, have not detected enhanced dopaminergic activity. Modafinil (Provigil), then, may also work through other neurotransmitter systems. The R-enantiomer of modafinil (Provigil) is included in the racemic mixturer known as armodafinil (Nuvigil). Both armodafinil and modafinil have shown similar pharmacological properties.

Pharmacokinetics

Drug	Time(s) to Peak Concentration(s) (hours)	Onset of Action (minutes)	Half-Life (mean, in hours)	Duration of Action (hours)	Extended-Release Delivery System (where applicable)
Stimulants					
armodafinil (Nuvigil)	2	--	15	--	--
dexmethylphenidate (Focalin)[45,46]	1-1.5	30	2.2	4-6	--
dexmethylphenidate (Focalin XR)[47]	1.5, then 6.5	--	children: 2-3 adults: 2-4.5	Children: 8-12 Adults: 8	50% each IR and enteric-coated, delayed-release beads
dextroamphetamine IR (Dexedrine, DextroStat)[48]	2-3	20-60	children: 6-8 adults: 10-12	4-6	--
dextroamphetamine ER (Dexedrine)[49]	8-10	60-90		6-10	initial dose delivered immediately with remaining medication released over 6-8 hours
dextroamphetamine solution (Procentra)[50]	--	--	11.75	--	--
methamphetamine (Desoxyn)[51]	--	--	4-5	--	--
lisdexamfetamine dimesylate (Vyvanse)[52,53,54]	3.5* (prodrug = 1)	--	10-13 (prodrug <1)	~ 10	Active drug slowly released by rate-limited hydrolysis
methylphenidate IR (Methylin, Ritalin)[55,56,57]	1.5-3	15-20	2-4	2-4	--
methylphenidate SR (Methylin ER, Metadate ER)[58,59,60,61]	1.5-4.7	30-180		3-8	various
methylphenidate ER (Concerta)[62,63]	1-2, then 6-8	30-60	3.5	8-12	22% IR overcoat; 78% controlled release core; osmotic-release oral system
methylphenidate ER (Metadate CD)[64]	1-1.5, then 4-4.5	30-90	6.8	7-12	30% IR, 70% ER beads
methylphenidate ER (Ritalin LA)[65]	1-3, then 4-8	30-110	2.5-3.5	7-12	50% dose IR beads, 50% dose enteric–coated, delayed release beads
methylphenidate transdermal (Daytrana)[66]	7.5-10.5	120	3-4	~ 3 hours after patch removal	concentrated drug cells in patch
mixed amphetamine salts IR (Adderall)[67]	3	30-60	children: 9-11 adults: 10-13	4-8	--
mixed amphetamine salts ER (Adderall XR)[68]	7**	30-60		8-10	50% each of immediate- and delayed-release beads
modafinil (Provigil)[69]	2-4	--	15	--	--

* Food prolongs the Tmax of converted prodrug (d-amphetamine) by 1 hour
** Food prolongs the Tmax of mixed amphetamine salts ER by 2.5 hours

Drug	Time(s) to Peak Concentration(s) (hours)	Onset of Action (minutes)	Half-Life (mean, in hours)	Duration of Action (hours)	Extended-Release Delivery System (where applicable)
Non-Stimulants					
atomoxetine (Strattera)[70,71]	1-2	3-4 weeks	5.2	~24	--

The half-life and blood concentration of amphetamine is directly related to urinary pH; increasing with alkaline pH and decreasing with acidic pH. For every unit increase in pH, the half-life of mixed amphetamine salts (Adderall, Adderall XR, Procentra) increases by an average of seven hours. As a result, urine acidifying agents (e.g., ammonium chloride, sodium acid phosphate) and urine alkalinizing agents (e.g., acetazolamide, some thiazides) should be avoided if possible to maintain consistent amounts of the active drug in the system.

Lisdexamfetamine dimesylate (Vyvanse), a prodrug of dextroamphetamine, is converted to dextroamphetamine and L-lysine presumably by first-pass intestinal and/or hepatic metabolism, however, not by cytochrome P450 enzymes. Except for MAS (Adderall, Adderall XR), stimulants are de-esterified in the liver to pharmacologically inactive metabolites. In contrast, MAS (Adderall, Adderall XR) are metabolized in the liver by hydroxylation, dealkylation and deamination. Urinary excretion accounts for nearly all of the elimination of the stimulants and atomoxetine (Strattera), as well as their metabolites.

Methylphenidate extended-release (ER) (Concerta) and dexmethylphenidate ER (Focalin XR) have similar pharmacodynamic profiles, with the main difference being that the latter contains only d-MPH. Similarly, the release profiles of Metadate CD and Ritalin LA, both extended-release formulations of methylphenidate, are very similar to each other.

When opened and sprinkled on cold applesauce, the bioavailability of Metadate CD and Ritalin LA, (extended-release formulations of methylphenidate), dexmethylphenidate ER (Focalin XR) and mixed amphetamine salts ER (Adderall XR) are the same as the intact capsules. Dextroamphetamine SR (Dexedrine Spansules) capsules can also be opened and sprinkled on food. Lisdexamfetamine (Vyvanse) capsules may be opened and the entire contents dissolved in water and consumed immediately. Atomoxetine (Strattera) capsules are not to be opened as they are an ocular irritant.

Atomoxetine (Strattera) is metabolized in most patients primarily by the CYP2D6 enzymatic pathway. Medications that inhibit CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase the bioavailability of atomoxetine. Atomoxetine does not appear to induce or inhibit the CYP2D6 enzyme system.[72] Approximately five to ten percent of patients are “slow metabolizers” in which the mean half-life of atomoxetine is 21.6 hours, over four times longer than in “rapid metabolizers.”[73]

Atomoxetine (Strattera) has a slower onset of action than the stimulants; onset of effect may take one week and full effect may not be seen for up to four weeks.[74,75] The effects of atomoxetine appear to last longer than would be expected from its pharmacokinetic profile.[76] The reasons for these pharmacokinetic – pharmacodynamic differences are not clear, but may be due to a variance between brain and plasma pharmacokinetics, or by continued effects on the norepinephrine transporter.

Contraindications/Warnings[77,78,79,80,81,82,83,84,85,86,87,88,89]

CONTRAINDICATIONS

The stimulants (amphetamines and MPH) and atomoxetine (Strattera) are contraindicated during or within 14 days following administration of a monoamine oxidase (MAO) inhibitor (MAOI). These drugs are also contraindicated in patients with glaucoma.

Stimulants are contraindicated in agitated patients.

Amphetamines are contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, or a history of drug abuse.

Methylphenidate (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) and dexmethylphenidate (Focalin, Focalin XR) are contraindicated in patients with anxiety, tension, tics or a diagnosis or family history of Tourette's syndrome.

Armodafinil (Nuvigil) is contraindicated in patients with known hypersensitivity to modafinil (Provigil) and armodafinil (Nuvigil) or its inactive ingredients.

WARNINGS

Stimulants have boxed warnings regarding the high potential for abuse. Prolonged use of these agents can lead to drug dependence. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events; use with approved doses of MPH's have an increased risk of sudden death due to cardiac events in adults and children that have pre-existing cardiac comorbidities. Patients should be carefully supervised during withdrawal from MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) and d-MPH (Focalin, Focalin XR) as it may result in depression and/or unmasking of symptoms.

Stimulants should be used with caution in patients with pre-existing psychosis, bipolar disorder or aggression as these conditions may be exacerbated. Modafinil (Provigil) has also been reported to induce mania, delusions, hallucinations, suicidal ideations, and aggression in patients with and without prior history of psychiatric illness. Treatment emergent psychotic or manic symptoms have been reported in 0.1 percent of patients receiving stimulants and 0.2 percent of patients receiving atomoxetine (Strattera).

Stimulants may cause long-term suppression of growth.

Stimulants may lower the seizure threshold and may cause visual disturbances.

Rare cases of GI obstruction have been reported with nondeformable controlled-release formulations similar to MPH OROS (Concerta).

Limited reports of multi-organ hypersensitivity reactions have been reported after initiation of treatment between four to 33 days in patients taking Modafinil (Provigil). Some of the presenting signs and symptoms for the disorder were fever, rash, pruritus, asthenia, myocarditis, hepatitis, liver function test abnormalities, and dermatological abnormalities.

Rare cases of serious rash, such as Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, and drug rash with eosinophilla and systemic symptoms has occurred in patients taking modafinil. The cases reported have occurred within one to five weeks after initiating drug treatment, and predictors to occurrence of rash are not known.

Rare cases of serious rash including Stevens-Johnson Syndrome and drug rash have occurred in pediatric patients taking armodafinil. No serious skin rashes have been reported in adults in clinical trials. However, because armodafinil is the R-isomer of racemic modafinil, a similar risk of serious rash with armodafinil cannot be ruled out. Since it is impossible to determine the risk of rash severity, armodafinil should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of the treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

Atomoxetine (Strattera) has a box warning that it can increase the risk of suicidal ideation in children and adolescents. In a combined analysis of 12 short-term placebo-controlled trials of over 2,200 patients, suicidal ideation occurred in approximately 0.4 percent of patients compared with no patients receiving placebo. All occurrences were reported during the first month of treatment in children ≤12 years of age. Monitoring including face to face contact with patients or caregivers should occur weekly during the first four weeks of treatment, then every other week for four weeks, then at 12 weeks.

Atomoxetine (Strattera) has a warning regarding severe liver injury; rare, but marked, elevations of hepatic enzymes and bilirubin have been reported. In two case reports, liver injury resolved after discontinuation of atomoxetine (with concomitant immunosuppressive therapy in one case).[90] The manufacturer warns to discontinue atomoxetine permanently in patients with any sign of jaundice or hepatic lab abnormality; other treatment options should be considered.

Drug Interactions

Gastrointestinal (e.g., antacids) and urinary (e.g., acetazolamide, some thiazides) alkalinizing agents increase blood levels and activity of amphetamines. Gastrointestinal (e.g., ascorbic acid) and urinary (e.g., ammonium chloride) acidifying agents decrease absorption and activity of the amphetamines.

Effects can be additive when stimulants are used concurrently with other psychostimulants or with sympathomimetics.[91,92,93] Due to the potential for excessive CNS or cardiovascular stimulation, combination use should be avoided unless necessary, and if unavoidable then used with caution.[94] In general, the concurrent use of MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) with amphetamines is not recommended.[95] Since there are no clinical data regarding the concurrent use of MPH and atomoxetine (Strattera), concurrent use should be avoided.[96]

Amphetamine may stimulate the release of serotonin in the CNS and thus may interact with other serotonergic agents, such as the serotonin-receptor agonists. These interactions could lead to serotonin excess, which could increase the risk of 'serotonin syndrome' occurring.[97] Melatonin may exacerbate the monoaminergic effects of amphetamine-related medications. Coadministration of melatonin with methamphetamine (Desoxyn) in animal studies resulted in increased dopaminergic and serotonergic stimulation.[98]

Like the MAOIs, stimulants and atomoxetine (Strattera) potentiate the effects of catecholamine neurotransmitters.[99] Monoamine oxidase inhibitors or drugs that possess MAO-inhibiting activity, such as procarbazine, can prolong and intensify the cardiac stimulation and vasopressor effects of the stimulants. Stimulants and atomoxetine should not be administered during or within 14 days following the use of MAOIs or drugs with MAO-inhibiting activity.[100,101,102] Selegiline, an inhibitor of MAO type B, may also predispose patients to this reaction, and should be avoided in patients receiving stimulants or atomoxetine.[103]

Use of modafinil (Provigil) with other psychostimulants has not been extensively studied, and concurrent use is not recommended. Coadministration of amphetamine and modafinil may increase stimulant-associated side effects.[104,105] Single-dose studies of MPH combined with modafinil showed that the rate of absorption of modafinil was delayed up to one hour in the presence of MPH. No changes occurred in the metabolism and extent of absorption of either medication.

Modafinil (Provigil) has not been evaluated for drug interactions with MAOIs, including drugs with MAO-inhibiting activity (such as procarbazine).[106] Until more is known regarding the pharmacology of modafinil (Provigil), it may be prudent to caution against the use of modafinil (Provigil) in the presence of a MAOI.

Armodafinil (Nuvigil) has several potential drug interactions that may necessitate dosage adjustment. The package insert should be consulted for specific interactions.[107]

Lithium may antagonize the central stimulating effects of amphetamines and should be avoided.[108,109] Likewise, MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) should not be used concurrently with lithium since this may alter the effects of these agents on the underlying mood disorder. Stimulant medications occasionally worsen mania.[110,111] Haloperidol and chlorpromazine also inhibit the central stimulant effects of the amphetamines.

Serious adverse events have been reported during concomitant use of MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) and clonidine; no causality has been established.

Adverse Effects

For the most part, adverse effects of stimulants are dose-dependent, mild to moderate in severity, and diminish with alteration of medication dose or timing.[112] They commonly subside spontaneously during the first one to two weeks of treatment.[113] Nonetheless, the majority of children treated with stimulants do experience some adverse effects, and these adverse effects are often the reason stimulant treatment is discontinued.[114,115]

In a double-blind study, investigators found that based on parent assessment, only two adverse effects were more prevalent after initiation of stimulants than prior to initiation. These were insomnia (dextroamphetamine) and poor appetite (dextroamphetamine and MPH).[116] Investigators also found that the severity of several adverse effects (insomnia, irritability, crying, anxiousness, sadness/unhappiness, and nightmares) was higher in dextroamphetamine than in MPH; there were no adverse effects with higher severity in MPH than in dextroamphetamine.

In 2001, the American Academy of Pediatrics has released a policy statement indicating that adverse effects of stimulant medications are usually “mild and short lived”, and there is “no significant impairment of height attained” in adult life. The guidelines state that stimulants used for ADHD do not require routine “serologic, hematologic or electrocardiogram monitoring.”[117]

Most side effects associated with stimulants, such as decreased appetite, headaches, stomachaches, insomnia, nervousness and social withdrawal, can usually be managed by adjusting the dosage and/or timing of administration. For instance, administering stimulants with or after meals can reduce appetite suppression. Moving the last daily dose to an earlier time can reduce insomnia. In children on too high of a dosage or overly sensitive to the stimulants, the agents may cause them to be over focused or appear dull or overly restricted. Lowering the dosage of medication or changing to a different medication can usually reduce the effects.

Long term use of stimulant therapy has not demonstrated any obvious ill effects through observational data; there are no formal long-term studies.

In general, a review of the evidence shows no statistically significant differences in the incidence of adverse effects between immediate-release and modified-release formulations. There is no evidence to support statistically significant differences with respect to adverse effects of dextroamphetamine (Dexedrine, DextroStat, Procentra) and MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana).

Adverse Effects in children

Drug	Headache	Abdominal pain	Anorexia	Insomnia
Stimulants				
dexmethylphenidate (Focalin)[118]	nr	15 (6)	6 (1)	nr
dexmethylphenidate (Focalin XR)[119]	25 (11)	nr	30 (9)	reported
dextroamphetamine (Dexedrine, DextroStat, Procentra)[120,121]	reported	nr	reported	reported
lisdexamfetamine (Vyvanse)[122]	12 (10)	12 (6)	nr	19 (3)
methamphetamine (Desoxyn)[123]	reported	nr	nr	reported
methylphenidate ER (Concerta)[124]	14 (10)	7 (1)	4 (0)	4 (1)
methylphenidate ER (Metadate CD)[125]	12 (8)	7 (4)	9 (2)	5 (2)
methylphenidate ER (Ritalin LA)[126]	>5 (nr)	>5 (nr)	>5 (nr)	>5 (nr)
methylphenidate IR (Methylin, Ritalin)[127]	reported	reported	reported	reported
methlyphenidate ER (Methlin ER, Metadate ER)[128]	reported	reported	reported	reported
methylphenidate transdermal (Daytrana)[129]	nr	nr	5 (1)	13 (4)
mixed salt amphetamines IR (Adderall)[130]	reported	nr	reported	reported
mixed salt amphetamines (Adderall XR)[131]	reported	14 (10)	22 (2)	17 (2)
modafinil (Provigil)[132]	34 (23)	1 (≥1)	4 (1)	5 (1)
Non-Stimulants				
atomoxetine (Strattera)[133]	27 (25)	20 (16)	14 (6)	2 (≥2)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported

Other side effects common to the stimulants include irritability, flattened affect, social withdrawal, weepiness, mood lability, tremor, weight loss, reduced growth velocity.

The majority of patients in the pivotal phase III clinical trial of MPH transdermal (Daytrana) had minimal to definite erythema. Erythema generally caused little discomfort and did not usually result in discontinuation from treatment.

Stimulants can cause unpredictable motor tics, which transiently occur in 15 to 30 percent of children. Tics may appear in some patients when they are on stimulant medication and disappear with discontinuation of the medication. Fifty percent of patients with Tourette's disorder also have ADHD which may present two or three years before the tics appear. It is believed that stimulants do not cause Tourettes disorder, but simply unmask the disorder. Motor and verbal tics have not been associated with atomoxetine.[134]

Cardiovascular side effects of atomoxetine (Strattera) occurring in clinical trials at a rate greater than placebo include increased systolic blood pressure (2 mm Hg increase versus 0.7 mm Hg decrease), increased heart rate (6.8 bpm increase versus 1.2 bpm decrease) and weight loss (0.9 kg loss versus 0.8 kg gain).[135] In a meta-analysis of 13 studies that included 272 children, ages six to seven years, 24 months of treatment with atomoxetine (Strattera) resulted in statistically significant increases in pulse and blood pressure, as well as decreases in cardiac PR interval; these changes were deemed by the investigators not to be clinically significant.[136]

Effects on Growth

The 2001 American Academy of Pediatrics Clinical Practice Guideline for the School Aged Child with ADHD acknowledges that appetite suppression and weight loss are common adverse effects of stimulants, but studies of stimulant use have found little or no decrease in expected height, any decrease in growth early in treatment is later compensated.[137] A temporary slowing in growth rate (2 cm less growth in height and 2.7 kg less growth in weight over three years) has been noted in children starting treatment with MPH at ages seven through 10 years.

With stimulants, delayed growth may be a concern through mid-adolescence but normalizes by late adolescence. This appears to be an effect of the ADHD and not its treatment; however, there have been reports of decreased growth with continuous stimulant treatment. Drug holidays can be used, but the benefits of this strategy in mitigating growth delays have not been demonstrated in a controlled setting.

Over 18 months, patients on atomoxetine (Strattera) were reported to gain weight (average 6.5 kg) and height (average 9.3 cm), although there was a net loss in mean weight and height percentile points. Mean weight decreased from the 68th to 60th percentile, and mean height decreased from the 54th to 50th percentile. Attenuation of the effects on growth occurs by 24 months.[138]

Special Populations

Pediatrics

Most of the agents in this class are indicated for children six years of age and older. Some of the immediate-release stimulants are indicated for children as young as three years. The prescribing information for the drugs in this class used for the treatment of ADHD include a warning about using the drugs in children younger than the indicated age, but there are some data on the use of these drugs in younger children.

Children under three years of age – Numerous studies indicate that stimulants are effective in the treatment of ADHD in preschool children.[139,140] Although, some have expressed concern that the use of neuropsychiatric drugs in children in this age group could have long term effects on neurotransmitters in the brain.[141] The 2004 American Academy of Child and Adolescent Psychiatry (AACAP) guidelines recommend initial parent training and a structured preschool setting that may progress to low dose medication with frequent monitoring. Behavior modification therapy may be useful if implemented consistently. The AACAP suggests medication use only in the most severe cases, or where parent training/school placement are unavailable or unsuccessful. If medications are used, the AACAP suggests daily treatment without weekend holidays.

Children under six years of age - Although not indicated for children under six years of age, six small controlled studies have reported on the use of MPH in 187 children (ages 1.8 to 5.9 years) with ADHD.[142,143,144,145,146] In the trials, MPH doses ranged from 0.15 mg/kg twice daily up to 0.6 mg/kg three times daily. Other studies have not used weight-based dosing of MPH, with total doses ranging from 2.5 to 30 mg/day.[147] In general, only MPH IR (Methylin, Ritalin) should be used in children less than six years of age with children under 25 kg receiving no more than 45 mg/day. The National Institute of Mental Health's ongoing Preschool ADHD Treatment Study (PATS) is expected to provide clinical guidance for children with ADHD three to five years of age. In the study, the initial dose of MPH IR (Methylin, Ritalin) is 1.25 mg three times daily.

Bipolar disorder – ADHD coexists with bipolar disorder in 29 to 98 percent of pediatric patients. For children and adolescents with ADHD and bipolar disorder, mixed amphetamine salts (Adderall, Adderall XR) have shown effectiveness after mood stabilization with divalproex.[148] Stimulants and atomoxetine (Strattera) should be used with caution in patients with bipolar disorder as they may induce mixed/manic episodes.

Oppositional Defiant Disorder (ODD) - In a preliminary report of a phase III, randomized, double-blind, placebo-controlled study, mixed amphetamine salts ER (Adderall XR) has also been shown to be efficacious and safe for the short-term treatment of children and adolescents with ODD.[149]

Autism - Recent studies have shown that at least some stimulants may be effective for treating autistic children with symptoms of hyperactivity.[150] In a pilot crossover study of 16 children, ages five to 15 years, with autism spectrum disorders, atomoxetine (Strattera) was superior to placebo in terms of the primary endpoint, effect on the Hyperactivity subscale of the Aberrant Behavior Checklist ($p=0.043$).[151] Nine patients responded to atomoxetine while four responded to placebo.

Mental Retardation – Patients may respond well to stimulant treatment; however, patients may become irritable. Clonidine may be more helpful for some patients with mental retardation as the main problems are often hyperactivity and impulsivity.

Cerebral Palsy (CP) – Data from a retrospective review indicate that modafinil may improve tone and ambulation in spastic diplegic CP.[152] In this study, 29 of 59 pediatric patients given modafinil (Provigil) for CP, were noted to have an improving gait on modafinil (Provigil). By contrast, only three of 61 patients who did not receive modafinil showed such improvement.

Closed Head Injury – Patients may respond to stimulant treatment only or may require other medications, such as antipsychotics (risperidone) or mood stabilizers (carbamazepine, valproic acid).

Fetal Alcohol Syndrome (FAS) and Alcohol-Related Neurobehavioral Disorder (ARND) – Patients may respond to stimulant treatment but may require higher doses than typical ADHD patients or may require other medications such as antipsychotic medication or mood stabilizers.

Substance abuse – Medication treatment for ADHD has been demonstrated to reduce the risk of subsequent substance use disorders. Medication treatment of co-morbid ADHD and substance use disorders is possible, but patients require careful monitoring. Amphetamines are contraindicated in patients with a history of substance abuse. Non-controlled substances, such as bupropion or atomoxetine, may be useful.

Pregnancy [153,154,155,156,157,158,159,160,161,162,163,164,165]

All agents in this class are Pregnancy Category C.

Dosages

ADHD

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants				
dexmethylphenidate (Focalin)	≥6 years	2.5 mg twice daily	10 mg twice daily	Tablets: 2.5, 5, 10 mg
dexmethylphenidate ER (Focalin XR)	6-17 years	5 mg once daily	20 mg per day	Capsules: 5, 10, 15, 20 mg
	≥18 years (adults)	10 mg once daily	20 mg per day	
dextroamphetamine IR (Dexedrine, DextroStat)	3-5 years	2.5 mg once daily	0.5 mg/kg/day in 2-3 divided doses	Tablets: 5, 10 mg
	≥6 years	5 mg two or three times daily	40 mg/day in 2-3 divided doses	
dextroamphetamine ER (Dexedrine)	5-11 years	Total daily IR dosage given once daily	45 mg once daily	Capsules: 5, 10, 15 mg
	≥6 years	Total daily IR dosage given once daily	60 mg once daily	
dextroamphetamine solution (Procentra™)	3-5 years	2.5mg once daily	40 mg per day	Oral solution: 5 mg/5 ml
	≥6 years	5mg once or twice daily	40 mg per day	
lisdexamfetamine (Vyvanse)	6-12 years and adults	30 mg daily in the morning	70 mg daily in the morning	Capsules: 20, 30, 40, 50, 60, 70 mg
methamphetamine (Desoxyn)	≥6 years	5 mg once or twice daily	20-25 mg/day in two divided doses	Tablets: 5 mg
methylphenidate IR (Methylin, Ritalin)	≥6 years	5 mg twice daily	60 mg/day in 2-3 divided doses	Tablets: 5, 10, 20 mg Chewable tablets: 2.5, 5, 10 mg Oral solution: 5 mg/5 ml, 10 mg/5 ml
methylphenidate ER (Methylin ER, Metadate ER)	≥6 years	20-60 mg/day in 1-2 divided doses	60 mg/day in 1-2 divided doses	Tablets: 10, 20 mg
methylphenidate ER (Concerta)	6-12 years	18 mg once daily	54 mg once daily	Tablets: 18, 27, 36, 54 mg
	13-17 years	18 mg once daily	72 mg once daily (≤2 mg/kg/day)	
	18-65 years (adults)	18 or 36 mg once daily	72 mg once daily	
methylphenidate ER (Metadate CD)	≥6 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40, 50, 60 mg
methylphenidate ER (Ritalin LA)	≥6 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40 mg
methylphenidate transdermal (Daytrana)	≥6 years	10 mg patch worn 9 hours daily	30 mg patch worn 9 hours daily	Patches: 10, 15, 20, 30 mg per 9 hours
mixed amphetamine salts IR (Adderall)	3-5 years	2.5 mg once daily	40 mg/day in 2-3 divided doses	Tablets: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	≥6 years	5 mg two or three times daily		
mixed amphetamine salts ER (Adderall XR)	6-17 years	5-10 mg once daily	30 mg once daily	Capsules: 5, 10, 15, 20, 25, 30 mg
	≥18 years (adults)	20 mg once daily	20 mg once daily	

Dosages (continued)

ADHD

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Non-Stimulants				
atomoxetine (Strattera)[166]	≥6 years and ≤70 kg	0.5 mg/kg/day in 1-2 divided doses	1.4 mg/kg/day in 1-2 divided doses	Capsules: 10, 18, 25, 40, 60, 80, 100 mg
	≥6 years and ≥70 kg (adults)	40 mg/day in 1-2 divided doses	100 mg/day given in 1-2 divided doses	

MPH IR (Methylin, Ritalin) should be administered 30 to 45 minutes before meals. Dexmethylphenidate (Focalin, Focalin XR) and MPH ER can be administered without regard to meals. The timing of the midday dose of MPH IR (Methylin, Ritalin) and dexmethylphenidate IR (Focalin) should be individualized based on patient response. The last daily dose of MPH ER should be given several hours before bedtime.

Methylphenidate transdermal patches (Daytrana) should be applied two hours prior to the desired onset of activity and should be worn for nine hours. Wear time can be individualized based on patient response.

For patients with moderate (Child-Pugh Class B) hepatic impairment, the initial and target doses of atomoxetine (Strattera) should be reduced by 50 percent. For patients with severe (Child-Pugh Class C) hepatic impairment, the initial and target doses should be reduced by 75 percent. For patients taking strong CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine), the daily dose of atomoxetine (Strattera) should not exceed 80 mg.[167]

For patients with moderate (Child-Pugh stage B) hepatic impairment, the dosage of modafinil (Provigil) should be reduced by 50 percent. For patients with severe (Child-Pugh stage C) hepatic impairment, the manufacturer recommends a dosage of 100 mg every morning. The bioavailability of the inactive metabolite, modafinil acid, is increased nine-fold in patients with severe renal impairment (CrCl ≤20 mL/min); safety and efficacy of modafinil (Provigil) in this patient group have not been determined.

HYPERSOMNOLENCE

Armodafinil (Nuvigil) – for adults (≥17 years) with narcolepsy or obstructive sleep apnea/hypopnea syndrome, 150 or 250 mg is given once daily in the morning. For patients with shift-work sleep disorder, 150 mg should be administered one hour prior to the start of the work shift.[168]

Dextroamphetamine (Dexedrine, DextroStat, Procentra) – for adults and adolescents, 5 mg twice daily titrated to a maximum of 60 mg/day in 2-3 divided doses; for children six to 12 years, 5 mg once daily titrated to maximum of 60 mg/day in 2-3 divided doses. Once the dosage has been stabilized, patients can be converted to an equivalent dosage of dextroamphetamine ER (Dexedrine Spansule) given once daily.

Methylphenidate (Ritalin, Methylin, Methylin ER, Metadate ER, Ritalin SR) – dosages for the treatment of narcolepsy are the same as those for ADHD.

Modafinil (Provigil) - for adults (≥16 years) with narcolepsy or obstructive sleep apnea/hypopnea syndrome, 200 mg is given once daily in the morning. For patients with shift-work sleep disorder, the dose should be administered one hour prior to work.

OBESITY

For adjunctive treatment of obesity, methamphetamine (Desoxyn) 5 mg is administered before each meal. Treatment should last only a few weeks.

Clinical Trials

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of ADHD of less than four weeks' duration were excluded as it is generally accepted that it takes at least this long to adequately titrate to the optimal dosage of a given agent. Studies conducted more than 25 years ago were excluded, primarily due to a lack of well-controlled clinical trials from that time period. Many of these older studies verified the effectiveness of the stimulants available at that time in treating the symptoms of ADHD.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Rating Scales

Specific

- Conners' Parent Rating Scale (CPRS) – The scale provides the parents' or caregivers' perspective on a child's behavior. The scale is 92 percent sensitive and 94 percent specific.
- Swanson, Nolan and Pelham scale (SNAP) – The scale has been shown to have greater than 94 percent sensitivity and specificity in distinguishing hyperactive, inattentive and impulsive children with ADHD from those without ADHD based on DSM-III-R criteria.
- ADHD Rating Scale-IV (ADHD RS) – The scale, which can be completed by a parent, teacher or clinician, is less effective than the SNAP in differentiating children with ADHD from those without ADHD. It has been shown to have good internal consistency and test-retest reliability. The parent form is 84 percent sensitive and 49 percent specific; the teacher form is 72 percent sensitive and 86 percent specific.

Global

Broad-band scales are not useful as tools to detect clinical-level problems in children presenting; they have low sensitivities and specificities of 70 to 80 percent.

- CGI-I – Clinical Global Impression improvement subscale
- CGI-S - Clinical Global Impression severity subscale
- C-GAS – Children's Global Assessment Scale

CLINICAL TRIALS

atomoxetine (Strattera) versus MPH IR

Two identical 12-week double-blind trials were conducted in 291 children (ages seven to 13 years) with ADHD.[169] Patients were randomized to atomoxetine (up to 2 mg/kg/day or 90 mg), MPH (up to 1.5 mg/kg/day or 60 mg) or placebo. Patients with prior stimulant exposure were randomized only to atomoxetine or placebo. Atomoxetine significantly reduced ADHD RS total scores, the primary endpoint, compared with placebo in each study ($p<0.001$). Changes in the CGI-S and CPRS also showed atomoxetine to be significantly superior to placebo in reducing ADHD symptoms. There was no significant difference between atomoxetine and MPH. A subsequent subanalysis of 51 female subjects showed that atomoxetine was similarly superior to placebo in this patient subset.[170]

atomoxetine (Strattera) versus MPH OROS (Concerta)

A randomized, double-blind, placebo controlled study compared the response as measured by the ADHD Rating Scale to atomoxetine, MPH OROS, and placebo.[171] A total of 516 children ages six to 16 years with ADHD were randomized to receive 0.8-1.8 mg/kg per day of atomoxetine (n=222), 18-54 mg/day of MPH OROS (n=220), or placebo (n=74) for six weeks. Patients who had previously had an inadequate response to stimulant treatment were excluded from the study. After six weeks, using double-blind conditions, the patients receiving atomoxetine were switched to MPH OROS. Response was determined by a 40 percent reduction from baseline as measured by the ADHD Rating Scale. Response results indicated that atomoxetine and MPH OROS were better than placebo, with atomoxetine resulting in a 45 percent response, MPH OROS resulting in a 56 percent response, and placebo resulting in a 24 percent response. The response rate for MPH OROS was significantly higher than atomoxetine ($p=0.016$). Seventy patients who received MPH OROS did not respond, but 30 of these patients (43 percent) responded after being switched to atomoxetine. Also, note that 69 patients did not respond to atomoxetine treatment, but 29 (42 percent) of these patients previously responded to MPH OROS treatment. Completion and discontinuations rates due to adverse events were low and similar for all treatment groups. Results indicated that response to MPH OROS was greater than atomoxetine, but patients not responding to MPH OROS initially may respond to atomoxetine treatment instead. Both agents had a superior response rate over placebo.

atomoxetine (Strattera) versus methylphenidate

A randomized, double-blind, crossover trial compared the efficacy of atomoxetine and methylphenidate for treating ADHD as well as their effects on the sleep of children with ADHD.[172] Eighty-five children with ADHD, either in a private practice setting or a hospital setting, were given twice daily atomoxetine (mean dose 42.29 mg/day) and three times daily methylphenidate (mean dose 58.27 mg/day), each for approximately seven weeks. Relative to baseline, actigraphy data indicated that methylphenidate increased sleep latency significantly more than did atomoxetine; these results were consistent with polysomnography data.

Compared with methylphenidate, child diaries indicated that taking atomoxetine had less sleep disturbance adverse effects. For example, it was easier to wake up in the morning, took less time to fall asleep, and the patients recorded better sleep with atomoxetine treatment. Parents reported similar findings such as the children were less irritable, had fewer difficulties with waking in the morning, and were less resistant at night to prepare for bed when administered atomoxetine as opposed to methylphenidate. Using the main measures of efficacy, the medications had similar efficacy for treatment of ADHD; atomoxetine was superior on some secondary-efficacy measures based on parent reports. Greater incidence of decreased appetite and insomnia with methylphenidate were the only significant differences in treatment-emergent adverse events. Both medications decreased nighttime awakenings, but the decrease was greater for methylphenidate.

mixed amphetamine salts XR (Adderall XR) versus MPH OROS (Concerta)

A randomized, double-blind placebo controlled study compared mixed amphetamine salts ER, MPH OROS and placebo on ADHD neuropsychological functioning.[173] Adolescents (n=35, 19 males) with a diagnosis of ADHD completed three separate assessments (5 PM, 8 PM, 11 PM) on three different days and medications (Adderall XR, Concerta, placebo). Delayed Matching-to-Sample and Go/No-go (GNG) neuropsychological tests which measure visual memory, attention span and response inhibition were used to evaluate outcomes. Neuropsychological functioning, as measured by commission errors, reaction time and recall accuracy, showed significant improvement when patients were taking MPH OROS as opposed to placebo. Results suggest that MPH OROS impacts both symptomatic behavior as well as cognitive functioning which have implications for both academic performance and daily functioning.

d-MPH (Focalin), MPH IR and placebo

In a randomized, double-blind study, 132 subjects received d-MPH, MPH or placebo twice daily for four weeks, with titration of the dose based on weekly clinic visits.[174] The primary efficacy variable was change from baseline of Teacher SNAP to last study visit. Secondary efficacy measures included the change on Parent SNAP, CGI-I and Math Test performance. Treatment with either d-MPH ($p=0.0004$) or MPH IR ($p=0.0042$) significantly improved Teacher SNAP ratings compared with placebo. The d-MPH group showed significant improvements compared with placebo on the afternoon Parent SNAP ($p=0.0003$) and on the Math Test scores obtained at 6:00 PM. ($p=0.0236$). Improvement based on CGI-I occurred in 67 percent of patients on d-MPH and 49 percent of patients on MPH IR. Both active treatments were well tolerated.

MPH IR, MPH OROS (Concerta) and placebo

A double-blind, placebo-controlled, randomized, five-period crossover study in 49 healthy subjects with a history of light (occasional) recreational stimulant use, to evaluate the abuse-related subjective effects of MPH OROS with comparable doses of MPH IR.[175] Patients were included in the study if they demonstrated a positive response to a 20-mg dose of d-amphetamine and a negative placebo response. Patients were then randomized to receive single doses of placebo, 54 and 108 mg MPH OROS, and 50 and 90 mg MPH IR. For each treatment, patients were observed for 24 hours to assess pharmacokinetics, pharmacodynamics, and safety. Both doses of MPH IR produced statistically significant higher positive stimulant effects with respect to placebo for all measures ($p<0.001$). MPH OROS 108 mg dose also produced statistically significant differences from placebo ($p<0.01$), but the more commonly prescribed dose, MPH OROS 54 mg, did not produce significant differences from placebo. Overall, for comparable dose levels, MPH OROS produced lower positive and stimulant subjective effects than MPH IR, and the lowest MPH IR doses produced more of an

effect than the highest of MPH OROS doses, showing that formulation can help reduce abuse potential.

In a multicenter, double-blind trial, 282 children (ages six to 12 years) with ADHD were randomized to receive MPH IR 5, 10 or 15 mg three times daily, MPH OROS 18, 36 or 54 mg once daily or placebo for 28 days.[176] Response, defined as >30 percent reduction from baseline IOWA Conners Oppositional/Defiance (O/D) score, occurred in 52, 59 and 26 percent of patients in the MPH IR, MPH OROS and placebo groups, respectively, as rated by parents ($p<0.0001$ for comparison of both active treatments to placebo). Teacher-rated response rates were 63, 68 and 43 percent, respectively ($p<0.0107$ for comparison of active treatments to placebo). The response rate for the two higher doses of MPH OROS (77 percent) was significantly higher than for MPH IR based on parent ratings ($p<0.05$). Forty-eight percent of the placebo group discontinued study drug early compared with 14 percent and 16 percent in the MPH and OROS MPH groups, respectively.

MPH OROS (Concerta), MPH transdermal (Daytrana) and placebo

In a double-blind study, 270 children (ages six to 12 years) with ADHD were randomized to one of three treatment arms: MPH OROS + placebo patch, MPH transdermal + placebo capsule or placebo capsule + placebo patch.[177] The study consisted of a five-week dose-optimization phase followed by a two-week maintenance phase. At the conclusion of the study, the mean daily doses were 43.4 and 22.9 mg for the oral and transdermal dosage forms, respectively. The primary endpoint was the change in ADHD RS from baseline. A reduction in ADHD RS of at least 30 percent was observed in 66, 78 and 29 percent of patients receiving MPH OROS, MPH transdermal and placebo, respectively (p=NS for comparison of active treatments; $p<0.05$ for comparison of each active treatment to placebo). Reductions from baseline in both the hyperactivity/impulsivity and the inattentiveness subscales were similar in both active treatment groups and were significantly greater than in the placebo group. The manufacturers of MPH transdermal funded the study.

lisdexamfetamine dimesylate (Vyvanse) versus placebo

A phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study was conducted at 40 centers across the United States.[178] The purpose of the study was to assess the efficacy and tolerability of lisdexamfetamine in school-aged children with ADHD treated in the community, and to characterize the duration of action of lisdexamfetamine (Vyvanse) compared with placebo. The study included 290 randomized patients; 230 patients completed the study. Sixty patients didn't complete the study mostly due to either lack of efficacy or adverse effects. Significant improvements in ADHD-RS-IV scores were seen with all doses (30, 50 or 70 mg) of lisdexamfetamine compared with placebo, and in CPRS scores with all lisdexamfetamine (Vyvanse) doses versus placebo throughout the day. Efficacy was observed by the first week of treatment, and improvements were observed throughout the day up to about 6 PM. The most frequently reported adverse effects among patients receiving lisdexamfetamine were typical of amphetamine products. Most adverse effects were mild to moderate and occurred in the first week. The study demonstrated the effectiveness and tolerability of lisdexamfetamine dimesylate over placebo.

HYPERSOMNOLENCE

Scales commonly used in the evaluation of hypersomnolence and its treatment include:

- Epworth Sleepiness Scale (ESS) – This is a self-administered questionnaire that has been shown to provide a measurement of the subject's general level of daytime sleepiness.[179] This scale has a high level of internal consistency.[180]

- Maintenance of Wakefulness Test (MWT) – In the test, the subject sits in bed, resting against pillows, in a quiet dimly lit room, attempting to stay awake for 20 (or 40) minutes while under scrutiny and with electrodes and wires attached.[181]

- Multiple Sleep Latency Test (MSLT) – The test measures how quickly the subject falls asleep, when asked to do so, when lying down in a quiet, darkened bedroom while under scrutiny and with electrodes and wires attached.[182] The test is considered by many to be the gold standard for measuring daytime sleepiness, although analysis has recently shown it to be the least accurate of the three tests.[183,184]

modafinil (Provigil) versus placebo - narcolepsy

A total of 285 subjects between the ages of 18 and 68 years with a diagnosis of narcolepsy were enrolled in a randomized trial to receive modafinil 200 mg, modafinil 400 mg or placebo once daily for nine weeks.[185] The mean ESS score was significantly lower for each modafinil treatment group compared to placebo at weeks three, six and nine. Subjective sleepiness ratings at each evaluation were reduced from baseline in all three groups. At baseline, three percent of the modafinil 400 mg group, four percent of the modafinil 200 mg group and three percent of the placebo group were able to remain awake for at least three MWTs. At week nine, the percentage of subjects able to stay awake for at least three tests significantly increased to 20 percent for the modafinil 400 mg group and 14 percent for the modafinil 200 mg group; no change occurred in the placebo group. Headache was reported to occur statistically significantly more often in the modafinil groups versus the placebo group. This study had an open-label treatment arm with demonstrated efficacy and safety for up to 40 weeks.

modafinil (Provigil) versus placebo – OSA related daytime sleepiness

In a double-blind, parallel group, randomized study, investigators studied the efficacy and safety of modafinil (Provigil) verses placebo in 157 patients with OSA-related daytime sleepiness despite CPAP for a total of four weeks. [186] Patients were randomized to receive modafinil (n=77) at an initial dose of 200 mg per day during week one, then increasing over three weeks up to 400 mg per day, or placebo (n=80) once daily. Modafinil significantly improved daytime sleepiness, with significantly greater mean changes from baseline in ESS scores at weeks one and four ($p<0.001$), but not significantly different from placebo in MSLT at week four ($p<0.05$). The percentage of patients with normalized daytime sleepiness (ESS <10) was significantly higher with modafinil (51 percent) than with placebo (27 percent; $p<0.01$). There was no difference between groups in the percentage of patients with normalized MSLT (25 to 29 percent).

Meta-analyses

Several meta-analyses and reviews support the short-term efficacy of stimulant medications in reducing the core symptoms of ADHD - inattention, hyperactivity and impulsivity.[187,188,189,190,191] Research to date has not shown clear advantages of one stimulant medication over another or between dosage forms of a given agent. In the policy statement, AAP states that stimulants are equally effective for ADHD. Many children who fail to respond to one medication will have a positive response to an alternative stimulant.[192]

A meta-analysis of 29 randomized, double-blind, placebo-controlled studies involving over 4,465 children (mean age 10 years) with ADHD showed that the stimulants, MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) and MAS (Adderall, Adderall XR), are significantly more effective than non-stimulant ADHD medications (atomoxetine, bupropion, desipramine and modafinil) in the treatment of ADHD.[193] Among stimulants, the meta-analysis found no difference in efficacy among MAS (Adderall, Adderall XR) and MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, Daytrana) or among immediate-acting or long-acting agents. The manufacturer of MAS ER (Adderall XR) and MPH transdermal patch (Daytrana) funded this meta-analysis.

Summary

Several medications have been shown to be effective in treating ADHD. Except for atomoxetine (Strattera), all of the drugs approved for treatment of ADHD by the FDA are stimulants and are classified as controlled substances by the United States Drug Enforcement Agency (DEA). The individual agents used for the treatment of ADHD are associated with different contraindications and precautions for use; this may influence the selection of appropriate therapy in patients with commorbidities (i.e., coexistent tic disorders or Tourette's syndrome).

The American Academy of Pediatrics Clinical Practice Guideline for the School Aged Child with ADHD recommends stimulant medication and/or behavioral therapy for the treatment of ADHD in children. They state that in many cases the stimulants improve the child's ability to follow rules and decrease "emotional overactivity, thereby leading to improved relationships with peers and parents."

Due to potential difficulties created by multiple daily dosing (e.g., compliance, social stigma, availability and willingness of schools and school staff to store and administer medication, potential for drug diversion), once-daily dosage forms may, in some situations, be preferred.

The most commonly prescribed stimulant for the treatment of ADHD is MPH (Methylin, Methylin ER, Metadate ER, Metadate CD, Ritalin, Ritalin LA, Ritalin-SR, Concerta, and Daytrana). For school-age children, the once daily dosage forms of MPH enhance compliance and decrease the risk of diversion. Mixed amphetamine salts (Adderall, Adderall XR) provide an alternative for patients who can not tolerate MPH. Clinical trials of dextroamphetamine (Dexedrine, DextroStat) are generally of poor quality and are somewhat dated. Additionally, it has a greater potential for diversion and misuse than the other drugs used for ADHD. The new liquid formulation of dextroamphetamine (Procentra) was approved based on previous dextroamphetamine clinical trials and has the same efficacy, warnings, and adverse reactions as the solid dosage forms of dextroamphetamine. As a result, the dextroamphetamine formulations would not be the best initial choice over MPH to be used as first-line therapy for the majority of children and adolescents with ADHD.

Lisdexamfetamine dimesylate (Vyvanse), a prodrug of dextroamphetamine, is now available and was designed to have an extended duration of effect to allow for once daily dosing and to

have less potential for abuse, diversion or overdose toxicity. However, there is no evidence that it offers an advantage over any other formulation of amphetamine for treatment of children with ADHD. Older drugs with more established dosages and safety records are preferred.

Atomoxetine (Strattera) is a non-stimulant that should not be addictive and is not a scheduled drug. It may be a useful agent in patients with a co-morbid diagnosis such as anxiety and tic disorders. Atomoxetine (Strattera) has some of the same adverse effects as the stimulants, including increased heart rate, blood pressure, and potential growth retardation. Children treated with atomoxetine (Strattera) have also exhibited modest decreases in weight from baseline. Atomoxetine (Strattera) has a boxed warning regarding an increased risk of suicidal ideation in children treated with the drug.

Modafinil (Provigil) is currently indicated for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. It may provide a slightly different profile of adverse effects than the stimulant medications traditionally used for the treatment of narcolepsy.

The newest agent is armodafinil (Nuvigil) which is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, narcolepsy and shift work sleep disorder. This agent is the R-enantiomer of modafinil (Provigil) and shares a similar pharmacological profile.

References

[1] Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002;41:26S—49S.

[2] American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:1033-44.

[3] Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005;115:e749-57.

[4] Goldman LS, Genel M, Bezman RJ, et al. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. JAMA. 1998;279:1100-7.

[5] Elia J, Ambrosini J, Rapoport JL. Treatment of attention -deficit hyperactivity disorder. N Engl J Med. 1999;340:780-8.

[6] National Institute of Health: National Institutes of Health consensus development conference statement: Diagnosis and treatment of attention-deficit/hyperactivity disorder (ADHD). J Am Acad Child Adolesc Psychiatry. 2000;39:192-3.

[7] Barkley RA. Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 2nd ed. New York, NY: Guilford Press; 1996.

[8] American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:1033-44.

[9] Kessler RC, Adler L, Barkley R, et al. The prevalence and correlated of adult ADHD in the United States; results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163:716-23.

[10] Zentall SS. Research on the educational implications of Attention Deficit Hyperactivity Disorder. Exceptional Child. 1993;60:143-53.

[11] Almond BW, Tranner JL, Goffman HG: The Family is the Patient: Using Family Interviews in Children 's Medical Care, 2nd ed. Baltimore, MD: Williams & Wilkins, 1999, pp 307–13.

[12] Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 1993;150:1792–8.

[13] Zentall SS. Research on the educational implications of attention deficit hyperactivity disorder. Exceptional Child. 1993;60:143-53.

[14] Schachar R, Taylor E, Weiselberg MB, et al. Changes in family functioning and relationships in children who respond to methylphenidate. J Am Acad Child Adolesc Psychiatry. 1987;26:728-32.

[15] American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:1033-44.

[16] Rappley MD. Clinical practice. Attention deficit-hyperactivity disorder. N Engl J Med. 2005;352:165-73.

[17] Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 1993;150:1792–8.

[18] Biederman J, Faraone S, Milberger S, et al. Predictors of persistence and remissions of ADHD into adolescence: Results from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry. 1996;35:343–51.

[19] Barbaresi WJ, Katusic SK, Colligan RC, et al. Long-term stimulant medication treatment of attention-deficit/hyperactivity disorder: results from a population-based study. J Dev Behav Pediatr. 2006;27:1-10.

[20] Attention Deficit Hyperactivity Disorder. Diagnosis and management of ADHD in children, young people, and Adults. National Institute for Health and Clinical Excellence. 2008. http://www.nice.org.uk/nicemedia/pdf/CG72QRG.pdf. Accessed May 19, 2009.
[21] Drugs for Treatment of ADHD. Treatment Guidelines from The Medical Letter. 2006:4:77-82.
[22] Focalin [package insert]. East Hanover, NJ; Novartis; April 2007.
[23] Vyvanse [package insert]. Blacksburg, VA; New River Pharmaceuticals Inc. November 2008.
[24] Procentra [package insert]. Suwannee, GA; Tiber Pharmaceuticals; January 2009.
[25] Kingshott RN, Vennelle M, Hoy CJ, et al. Predictors of improvements in daytime function outcomes with CPAP therapy. Am J Respir Crit Care Med. 2000;161:866–71.
[26] Engleman HM, Martin SE, Deary IJ, et al. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. Lancet. 1994;343:572–5.
[27] Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis. 1993;147:1162–8.
[28] Bedard M-A, Montplaisir J, Malo J, et al. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol. 1993;15:330–41.
[29] Sforza E, Krieger J. Daytime sleepiness after long-term continuous positive airway pressure (CPAP) treatment in obstructive sleep apnea syndrome. J Neurol Sci. 1992;110:21–6.
[30] Stradling JR, Davies RJO. Is more NCPAP better? Sleep. 2000;23:Suppl 4:S150–S153.
[31] Gilman AG, Goodman LS, Rall TW, et al. The pharmacologic basis of therapeutics. New York: Macmillan; 1985.
[32] U.S. Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology. 2000;54:1166–75.
[33] Nuvigil [package insert]. Frazer, PA; Cephalon; July 2008.
[34] Shenker A. The mechanism of action of drugs used to treat attention-deficit hyperactivity disorder: focus on catecholamine receptor pharmacology. Adv Pediatr. 1992;39:337-82.
[35] Srinivas NR, Hubbard JW, Quinn D, et al. Enantioselective pharmacokinetics and pharmacodynamics of dl-threo-methylphenidate in children with attention deficit hyperactivity disorder. Clin Pharmacol Ther. 1992;52:561-8.
[36] Patrick KS, Caldwell RW, Ferris RM, et al. Pharmacology of the enantiomers of threo-methylphenidate. J Pharmacol Exp Ther. 1987;241:152-8.
[37] The Medical Letter. 2007;49(1265):58-9.
[38] Vyvanse [package insert]. Blacksburg, VA; New River Pharmaceuticals Inc; November 2008.
[39] Pelham WE Jr, Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics. 1990;86:226-37.
[40] Swanson J, Gupta S, Guinta D, et al. Acute tolerance to methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder in children. Clin Pharmacol Ther. 1999;66:295–305.
[41] Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005;115:e749-57.
[42] Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of noradrenaline and dopamine in the prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2002;27:699–711.
[43] Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomised, placebo-controlled, dose-response study. Pediatrics. 2001;108:1-9.
[44] Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005;115:e749-57.
[45] Focalin [package insert]. East Hanover, NJ; Novartis; April 2007.
[46] Mandelkorn T. ADHD Medications: Adderall, Concerta, Daytrana, Dexedrine, Focalin, Metadate, Ritalin, Strattera and More. Attention Deficit Disorder Resources; 2007. http://www.addresources.org/article_adhd_medications_mandelkorn.php. Accessed May 19, 2009.
[47] Focalin XR [package insert]. East Hanover, NJ; Novartis; October 2008.
[48] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[49] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[50] Procentra [package insert]. Suwannee, GA; Tiber Pharmaceuticals; January 2009.
[51] Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; May 2007.
[52] The Medical Letter. 2007;49(1265):58-9.
[53] Vyvanse [package insert]. Blacksburg, VA; New River Pharmaceuticals Inc; November 2008.
[54] Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther. 2007;29(3):450-63.
[55] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[56] Swanson JM, Kinsbourne M, Roberts W, et al. Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. Pediatrics. 1978;61:21–9.
[57] Mandelkorn T. ADHD Medications: Adderall, Concerta, Daytrana, Dexedrine, Focalin, Metadate, Ritalin, Strattera and More. Attention Deficit Disorder Resources; 2007. http://www.addresources.org/article_adhd_medications_mandelkorn.php. Accessed May 19, 2009.
[58] Methylin ER [package insert]. St. Louis, MO; Mallinckrodt; March 2007.
[59] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[60] Patrick KS, Straughn AB, Jarvi EJ, et al. The absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. Biopharm Drug Dispos. 1989;10:165–71.
[61] Birmaher B, Greenhill LL, Cooper TB, et al. Sustained release methylphenidate: Pharmacokinetic studies in ADHD males. J Am Acad Child Adolesc Psychiatry. 1989;28:768–72.
[62] Concerta [package insert]. Mountain View, CA; ALZA Corporation; June 2008.

[63] Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). Pediatrics. 2004;113:e206-16.
[64] Metadate CD [package insert]. Smyrna, GA; UCB, Inc.; February 2007.
[65] Ritalin LA [package insert]. East Hanover, NJ; Novartis; April 2007.
[66] Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; July 2008.
[67] Adderall [package insert]. Florence, KY; Shire US; May 2006.
[68] Adderall XR [package insert]. Wayne, PA; Shire US; March 2009.
[69] Provigil [package insert]. West Chester, PA; Cephalon; May 2008.
[70] Strattera [package insert]. Indianapolis, IN; Eli Lilly; August 2007.
[71] Mandelkorn T. ADHD Medications: Adderall, Concerta, Daytrana, Dexedrine, Focalin, Metadate, Ritalin, Strattera and More. Attention Deficit Disorder Resources; 2007. http://www.addresources.org/article_adhd_medications_mandelkorn.php. Accessed May 19, 2009.
[72] Belle DJ, Ernest CS, Sauer JM, et al. Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. J Clin Pharmacol. 2002;42:1219–27.
[73] Sauer JM, Ponsler GD, Mattiuz EL, et al. Disposition and metabolic fate of atomoxetine hydrochloride: the role of CYP2D6 in human disposition and metabolism. Drug Metab Dispos. 2003;31:98–107.
[74] Corman SL, Fedutes BA, Culley CM. Atomoxetine: the first nonstimulant for the management of attention-deficit/hyperactivity disorder. Am J Health Syst Pharm. 2004;61:2391-9.
[75] Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005;115:e749-57.
[76] Michelson D, Allen A, Busner J, et al. Once daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomised, placebo controlled study. Am J Psychiatry. 2002;159:1896–901.
[77] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[78] Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; May 2007.
[79] Vyvanse [package insert]. Blacksburg, VA; New River Pharmaceuticals Inc; November 2008.
[80] Adderall [package insert]. Florence, KY; Shire US; May 2006.
[81] Adderall XR [package insert]. Wayne, PA; Shire US; March 2009.
[82] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[83] Concerta [package insert]. Mountain View, CA; ALZA Corporation; June 2008.
[84] Ritalin LA [package insert]. East Hanover, NJ; Novartis; April 2007.
[85] Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; July 2008.
[86] Focalin [package insert]. East Hanover, NJ; Novartis; April 2007.
[87] Focalin XR [package insert]. East Hanover, NJ; Novartis; October 2008.
[88] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[89] Provigil [package insert]. West Chester, PA; Cephalon; May 2008.
[90] Lim JR, Faught PR, Chalasani NP, et al. Severe liver injury after initiating therapy with atomoxetine in two children. J Pediatr. 2006;148:831-4.
[91] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[92] Focalin [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corp.; April 2007.
[93] Keating GM, Figgitt DP. Dexmethylphenidate. Drugs. 2002;62:1899-904.
[94] Thiel A, Dressler D. Dyskinesias possibly induced by norpseudoephedrine. J Neurol. 1994;24:167-9.
[95] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[96] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[97] Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. Gilman AG, Rall TW, Nies AS, Taylor P, (eds.) In: Goodman and Gilman's Pharmacological Basis of Therapeutics. 8th ed., New York, Pergamon Press. 1990:211-12.
[98] Gibb JW, Bush L, Hanson GR. Exacerbation of methamphetamine-induced neurochemical deficits by melatonin. J Pharmacol Exp Ther. 1997;283:630-5.
[99] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[100] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[101] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[102] Focalin [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corp.; April 2007.
[103] Eldepryl [package insert]. Tampa, FL: Somerset Pharmaceuticals, Inc.; July 1998.
[104] Wong YN, Wang L, Hartman L, et al. Comparison of the single-dose pharmacokinetics and tolerability of modafinil and dextroamphetamine administered alone or in combination in healthy male volunteers. J Clin Pharmacol. 1998;38:971-8.
[105] Provigil [package insert]. West Chester, PA; Cephalon; May 2008.
[106] Provigil [package insert]. West Chester, PA; Cephalon; May 2008.
[107] Nuvigil [package insert]. Frazer, PA; Cephalon; July 2008.
[108] Angrist B, Gershon S. Variable attenuation of amphetamine effects by lithium. Am J Psychiatry. 1979;136:806-10.
[109] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; November 2007.
[110] Eskalith [package insert]. Research Triangle Park, NC: GlaxoSmithKline; September 2003.
[111] Koehler-Troy C, Strober M, Malenbaum R. Methylphenidate-induced mania in a prepubertal child. J Clin Psychiatry. 1986;47:566-7.
[112] Weiss G, Hechtman LT. Medication treatment of ADHD. In: Weiss G, Hechtman LT, eds. Hyperactive Children Grown Up. 2nd ed. New York, NY:Guilford Press;1993:348–65.
[113] Barkley RA, DuPaul GJ, Costello A. In: Werry JS, Aman MG, eds. Practitioner's Guide to Psychoactive Drugs for Children and Adolescents. New York, NY: Plenum Publishing Corporation; 1993:205–37.
[114] Elia J, Borcherding BG, Rapoport JL, et al. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res. 1991;36:141–55.
[115] Rapoport JL, Buchsbaum MS, Zahn TP, et al. Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. Science. 1978;199:560–3.

[116] Efron D, Jarman F, Barker M. Side Effects of Methylphenidate and Dexamphetamine in Children With Attention-Deficit Hyperactivity Disorder: A Double-blind, Crossover Trial. Pediatrics. 1997;100:662-6.
[117] American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:1033-44.
[118] Focalin [package insert]. East Hanover, NJ; Novartis; April 2007.
[119] Focalin XR [package insert]. East Hanover, NJ; Novartis; October 2008.
[120] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[121] Procentra [package insert]. Suwannee, GA; Tiber Pharmaceuticals; January 2009.
[122]Vyvanse [package insert]. Blacksburg, VA; New River Pharmaceuticals Inc; November 2008.
[123] Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; May 2007.
[124] Concerta [package insert]. Mountain View, CA; ALZA Corporation; June 2008.
[125] Metadate CD [package insert]. Smyrna, GA; UCB, Inc.; February 2007.
[126] Ritalin LA [package insert]. East Hanover, NJ; Novartis; April 2007.
[127] Methylin ER [package insert]. St. Louis, MO; Mallinckrodt; March 2007.
[128] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[129] Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; July 2008.
[130] Adderall [package insert]. Florence, KY; Shire US; May 2006.
[131] Adderall XR [package insert]. Wayne, PA; Shire US; March 2009.
[132] Provigil [package insert]. West Chester, PA; Cephalon; May 2008.
[133] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[134] Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. Pediatrics. 2005;115:e749-57.
[135] Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. Drug Saf. 2003;26:729-40.
[136] Kratchovil CJ, Wilens TE, Greenhill LL, et al. Effects of long-term atomoxetine treatment for young children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45:919-27.
[137] Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. American Academy of Pediatrics Clinical Practice Guideline: Treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:1033-44.
[138] Kratchovil CJ, Wilens TE, Greenhill LL, et al. Effects of long-term atomoxetine treatment for young children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45:919-27.
[139] Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002;41:26S-49S.
[140] Zito J. Trends in the prescribing of psychotrophic medications to preschoolers. JAMA. 2000;283:1025-30.
[141] Ruff ME. Attention Deficit Disorder and Stimulant Use: An Epidemic of Modernity. Clin Pediatr. 2005;44:557-63.
[142] Barkley RA. The effects of methylphenidate on the interactions of preschool ADHD children with their mothers. J Am Acad Child Adolesc Psychiatry. 1988;27:336-41.
[143] Musten LM, Firestone P, Pisterman S, et al. Effects of methylphenidate on preschool children with ADHD: cognitive and behavioral functions. J Am Acad Child Adolesc Psychiatry. 1997;36:1407-15.
[144] Conners CK. Controlled trial of methylphenidate in preschool children with minimal brain dysfunction. J Ment Health. 1975;4:61-74.
[145] Mayes SD, Crites DL, Bixler EO, et al. Methylphenidate and ADHD: influence of age, IQ and neurodevelopmental status. Dev Med Child Neurol. 1994;36:1099-107.
[146] Handen BL, Feldman HM, Lurier A, et al. Efficacy of methylphenidate among preschool children with developmental disabilities and ADHD. J Am Acad Child Adolesc Psychiatry. 1999;38:805-12.
[147] Schleifer M, Weiss G, Cohen N, et al. Hyperactivity in preschoolers and the effect of methylphenidate. Am J Orthopsychiatry. 1975;45:38-50.
[148] Scheffer RE, Kowatch RA, Carmody T, et al. Randomized, Placebo-Controlled Trial of Mixed Amphetamine Salts for Symptoms of Comorbid ADHD in Pediatric Bipolar Disorder After Mood Stabilization With Divalproex Sodium. Am J Psychiatry. 2005;162:58-64.
[149] Spencer TJ, Hodgkins P, Biederman J, et al. Safety and efficacy of Adderall XR in children with ODD. Poster presented at the 17th Annual US Psychiatric and Mental Health Congress, San Diego, CA; November 19, 2004.
[150] Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Randomized, Controlled, Crossover Trial of Methylphenidate in Pervasive Developmental Disorders With Hyperactivity. Arch Gen Psychiatry. 2005;62:1266-74.
[151] Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. Am Acad Child Adolesc Psychiatry. 2006;45:1196-205.
[152] Hurst DL, Lajara-Nanson WA, Lance-Fish ME. Walking with modafinil and its use in diplegic cerebral palsy: retrospective review. J Child Neurol. 2006;21:294-7.
[153] Dexedrine [package insert]. Research Triangle Park, NC; GlaxoSmithKline; July 2008.
[154] Desoxyn [package insert]. Deerfield, IL; Ovation Pharmaceuticals; May 2007.
[155] Vyvanse [package insert]. Blacksburg, VA; New River Pharmaceuticals Inc; November 2008.
[156] Adderall [package insert]. Florence, KY; Shire US; May 2006.
[157] Adderall XR [package insert]. Wayne, PA; Shire US; March 2009.
[158] Ritalin/Ritalin-SR [package insert]. East Hanover, NJ; Novartis; April 2007.
[159] Concerta [package insert]. Mountain View, CA; ALZA Corporation; June 2008.
[160] Ritalin LA [package insert]. East Hanover, NJ; Novartis; April 2007.
[161] Daytrana [package insert]. Wayne, PA; Shire Pharmaceuticals; July 2008.
[162] Focalin [package insert]. East Hanover, NJ; Novartis; April 2007.
[163] Focalin XR [package insert]. East Hanover, NJ; Novartis; October 2008.

[164] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[165] Provigil [package insert]. West Chester, PA; Cephalon; May 2008.
[166] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[167] Strattera [package insert]. Indianapolis, IN; Eli Lilly; September 2008.
[168] Nuvigil [package insert]. Frazer, PA; Cephalon; July 2008.
[169] Spencer T, Heiligenstein JH, Biederman J, et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63:1140-7.
[170] Biederman J, Heiligenstein JH, Faries DE, et al. Efficacy of Atomoxetine Versus Placebo in School-Age Girls With Attention-Deficit/Hyperactivity Disorder. Pediatrics. 2002; 110:75-82.
[171] Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008;165(6):721-730.
[172] Sangal RB, Owens J, Allen AJ, et al. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep. 2006;29(12):1573-85.
[173] Wilson HK, Cox DJ, Merkel RL, et al. Effect of extended release stimulant-based medications on neuropsychological functioning among adolescents with Attention-Deficit/Hyperactivity Disorder. Arch Clin Neuropsychol. 2006;21(8):797-807.
[174] Wigal S, Swanson JM, Feifel D, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2004;43:1406-14.
[175] Parasrampuria DA, Schoedel KA, Schuller R, et al. Assessment of pharmacokinetics and pharmacodynamic effects related to abuse potential of a unique oral osmotic-controlled extended-release methylphenidate formulation in humans. J Clin Pharmacol. 2007;47(12):1476-88.
[176] Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:883-92.
[177] Buckstein OG, et al. Parent and Teacher Rated Effects of MTS and OROS Methylphenidate in ADHD. Poster presented at the 159th Annual Meeting of the American Psychiatric Association Annual Meeting, Toronto, Canada; May 24, 2006.
[178] Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther. 2007;29(3):450-63.
[179] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540-5.
[180] Johns MW. Reliability and factor analysis of the Epworth sleepiness scale. Sleep. 1992;15:376-81.
[181] Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment of patients with excessive somnolence. Electroencephalogr. Clin. Neurophysiol. 1982;153:658-61.
[182] Richardson GS, Carskadon MA, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr. Clin. Neurophysiol. 1978;45:621-7.
[183] Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. Sleep. 1986;9:519–24.
[184] Johns M. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: Failure of the MSLT as a gold standard. Journal of Sleep Research. 2000;9:5-11.
[185] US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998;43:88-97.
[186] Pack AI, Black JE, Schwartz JRL, et al. Modafinil as Adjunct Therapy for Daytime Sleepiness in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2001;164:1675-81.
[187] Kavale K. The efficacy of stimulant drug treatment for hyperactivity: a meta-analysis. J Learn Disabil. 1982;15:280-9.
[188] Ottenbacher KJ. Drug treatment of hyperactivity in children. Dev Med Child Neurol. 1983; 25:358-66.
[189] Thurber S. Medication and hyperactivity. A meta-analysis. J Gen Psychol. 1983;108:79-86.
[190] Swanson JM, McBurnett K, Wigal T, et al. Effect of stimulant medication on children with attention-deficit disorder: a review of reviews. Except Child. 1993;60:154-62.
[191] Faraone SV. Comparing the Efficacy of Medications for ADHD Using Meta-Analysis. Poster presented at the 159th Annual Meeting of the American Psychiatric Association, Toronto, Canada; May 24, 2006.
[192] Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. American Academy of Pediatrics Clinical Practice Guideline: Treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:1033-44.
[193] Faraone SV. Comparing the Efficacy of Medications for ADHD Using Meta-Analysis. Poster presented at the 159th Annual Meeting of the American Psychiatric Association, Toronto, Canada; May 24, 2006.