



Stimulants and Related Agents Therapeutic Class Review (TCR)

August 29, 2016

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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: Immediate-Release						
amphetamine sulfate (Evekeo™) ¹	Arbor	X	X	--	X	Exogenous obesity age ≥12 years
armodafinil (Nuvigil®) ²	generic, Cephalon	--	--	--	--	Excessive sleepiness associated with narcolepsy, OSA, and SWD for age ≥ 17 years
dexmethylphenidate IR (Focalin™) ³	generic, Novartis	--	X	--	--	--
dextroamphetamine IR (Zenzedi™) ⁴	generic, Arbor	X	X (≤ 16 years)	--	X	--
dextroamphetamine solution (ProCentra™) ⁵	generic	X	X (≤ 16 years)	--	X	--
methamphetamine (Desoxyn®) ⁶	generic	--	X	--	--	Exogenous obesity in adults and adolescents ≥ 12 years of age
methylphenidate IR (Methylin®, Ritalin®) ^{7,8}	generic, Shionogi	--	X	--	X	--
mixed amphetamine salts IR (Adderall®) ⁹	generic	X	X	--	X	--
modafinil (Provigil®) ¹⁰	generic, Cephalon	--	--	--	--	Excessive sleepiness associated with narcolepsy, OSA, and SWD for age ≥ 17 years
Stimulants: Extended-Release						
amphetamine ER (Adzenys XR-ODT™) ¹¹	Neos	--	X	X	--	--
amphetamine ER (Dyanavel™ XR) ¹²	Tris	--	X	X	--	--
dexmethylphenidate ER (Focalin XR™) ¹³	generic (5, 10, 15, 20, 30, 40 mg), Novartis	--	X	X	--	--
dextroamphetamine ER (Dexedrine®) ¹⁴	generic	X	X (≤ 16 years)	--	X	--
lisdexamfetamine dimesylate (Vyvanse™) ¹⁵	Shire	--	X	X	--	Moderate to severe binge eating disorder in adults
methylphenidate ER OROS (Concerta®) ¹⁶	generic, OMJPI	--	X	X	--	--

FDA-Approved Indications (continued)

Drug	Manufacturer	ADHD			Narcolepsy (age ≥6 years)	Other Indications
		Age 3–5 years	Age ≥ 6 years	Adults		
Stimulants: Extended-Release (continued)						
methylphenidate SR (Metadate ER®) ^{17,18}	generic	--	X	--	X	--
methylphenidate ER (Metadate CD®) ¹⁹	generic, UCB	--	X	--	--	--
methylphenidate ER (QuilliChew™ ER) ²⁰	Tris/Pfizer	--	X	X	--	--
methylphenidate ER (Quillivant XR®) ²¹	NextWave/Pfizer	--	X	X	--	--
methylphenidate ER (Ritalin LA®) ²²	generic, Novartis	--	X	--	--	--
methylphenidate ER (Aptensio XR®) ²³	Rhodes	--	X	X	--	--
methylphenidate transdermal (Daytrana™) ²⁴	Noven	--	X	--	--	--
mixed amphetamine salts ER (Adderall XR®) ²⁵	generic, Shire	--	X	X	--	--
Non-Stimulants						
atomoxetine (Strattera®) ²⁶	Eli Lilly	--	X	X	--	--
clonidine ER (Kapvay™) ²⁷	generic, Shionogi	--	X	--	--	Treatment of ADHD as adjunct to stimulants
guanfacine ER (Intuniv™) ²⁸	generic, Shire	--	X	--	--	Treatment of ADHD as adjunct to stimulants

OSA – obstructive sleep apnea; SWD – shift work disorder.

*In OSA, modafinil and armodafinil are indicated as an adjunct to standard treatment(s) (e.g., continuous positive airway pressure [CPAP]) for the underlying obstruction.

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.^{29,30,31,32,33,34} ADHD, which affects 4 to 12% of school-aged children and about 4% of adults, is a chronic condition with core symptoms of inattention, hyperactivity, and impulsivity.^{35,36,37} It may also be accompanied by internalized disorders, such as sadness and anxiety, as well as aggressive and oppositional disorders.^{38,39,40} The 3 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.^{41,42} 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. According to the 2011 ADHD guidelines formulated by a subcommittee of the American Academy of

Pediatrics (AAP), the primary care clinician should initiate an evaluation for ADHD for any child 4 through 18 years of age who is presented with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.⁴³ 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.

According to the 2011 ADHD guidelines in children and adolescents, the AAP recommends parent- and/or teacher-administered behavior therapy as first-line treatment for children 4 to 5 years of age.⁴⁴ Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate to severe continuing disturbance in the child's function. For children 6 to 11 years of age, the evidence is particularly strong for use of stimulant medications and sufficient, but less strong, for atomoxetine, extended-release guanfacine, and extended-release clonidine; medication therapy in addition to behavioral therapy is recommended. For patients 12 to 18 years of age, the AAP recommends FDA-approved medications with the assent of the adolescent and behavior therapy as treatment for ADHD, preferably both.

Although symptoms of ADHD tend to improve with age, this may be due in part to improved coping skills. The continuation of synaptogenesis and myelination into adolescence and young adulthood (especially in the frontal lobes) may also play a role in the improvement of symptoms with age. Sixty to 80% of children with ADHD will still require treatment throughout adolescence and into adulthood.^{45,46,47,48}

Studies have shown that 70 to 75% of patients respond to the first stimulant medication on which they are started.⁴⁹ Response increases to 90 to 95% 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 1 to 3 months to adequately establish the best dose and form of medication for any given patient. The AAP recommends that, if a trial with 1 drug compound group is ineffective or poorly tolerated, a trial on a medication from another group should be tried.⁵⁰

Treatment of ADHD in preschool children typically begins with a parent-training intervention. The Medical Letter suggests that school-age children begin with an oral stimulant, noting that none of these agents has been shown to be more effective than another.^{51,52} They indicate 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), a non-stimulant agent, 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. Extended-release formulations of guanfacine or clonidine may be helpful when used concurrently with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Mixing short- and long-acting stimulants can be helpful to achieve an early stimulant effect for early-morning school classes or for reducing rebound irritability or overactivity toward the end of the day, especially when studying in the evening.

Hypersomnolence

Excessive sleepiness, or hypersomnolence, is the primary and often debilitating symptom experienced by patients with narcolepsy, obstructive sleep apnea/hypopnea (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 OSA, the level of sleepiness does not always normalize.^{53,54,55,56,57,58} To address this residual daytime sleepiness, pharmacologic treatments may be beneficial in users of CPAP. Modafinil (Provigil) and armodafinil (Nuvigil) are relatively free of adverse cardiovascular effects and are FDA-approved for excessive daytime sleepiness associated with OSA/HS, as well as sleep problems resulting from circadian rhythm disruption (e.g., SWSD).^{59,60,61}

Modafinil (Provigil) and armodafinil (Nuvigil), along with CNS stimulants, such as dextroamphetamine (Dexedrine, ProCentra, Zenzedi), methylphenidate (Methylin, Ritalin, Metadate ER), mixed amphetamine salts (Adderall), and amphetamine sulfate (Evekeo), are used for narcolepsy. The potential for adverse cardiovascular events with CNS stimulant use may be of concern, especially in this overall high-risk patient population. Due to their lack of sympathomimetic activity, modafinil (Provigil) and armodafinil (Nuvigil) are relatively free of adverse cardiovascular effects.⁶²

Exogenous Obesity

Other CNS actions or metabolic effects may be involved, in addition to the appetite suppression caused by stimulants.⁶³ In relatively short-term clinical trials, adult subjects instructed in dietary management and treated with stimulants lost more weight on average than those treated with placebo and diet. However, the magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound per week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in subsequent weeks. Methamphetamine (Desoxyn) and amphetamine sulfate (Evekeo) are FDA-approved in adults for short-term adjunctive therapy in a weight reduction regimen based on caloric restriction for patients in whom obesity is refractory to alternative therapy.

Binge-Eating Disorder

Binge-eating disorder (BED) is characterized by uncontrolled eating occurring at least once every week for 3 months and 3 or more of the following behaviors: eating rapidly, eating until uncomfortably full, eating when not hungry, eating alone due to embarrassment, and/or feeling of guilt after eating. BED occurs in approximately 1 out of 35 adults in the U.S.⁶⁴ The 2006 Practice Guidelines for the Treatment of Patients with Eating Disorders suggest that serotonin reuptake inhibitor (SSRI) treatment is associated with at least a short-term reduction in BED symptoms, but not with considerable weight loss.⁶⁵ SSRIs are not FDA-approved for BED. Lisdexamfetamine dimesylate (Vyvanse) is the first and only FDA-approved product for moderate to severe BED in adults. Lisdexamfetamine dimesylate is not indicated for weight loss and it is not known if it is safe and effective for obesity treatment.

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 methylphenidate (MPH) causes the release of stored dopamine.⁶⁶ 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, Zenzedi, 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 (Adderall, Adderall XR), which contains d- and l-amphetamine in a 3:1 ratio, amphetamine sulfate (Evekeo), which contains d- and l- amphetamine in a 1:1 ratio, amphetamine extended-release (Dyanavel XR), which contains d- and l- amphetamine in a 3.2:1 ratio, or amphetamine extended-release (Adzenys XR-ODT), which contains d- and l- amphetamine in a 3:1 ratio.^{67,68,69} Mixed amphetamine salts tend to have fewer adrenergic side effects than MPH. MPH is a racemic mixture of d- and l-enantiomers, the former of which is more pharmacologically active.^{70,71} A product containing only the d-enantiomer, dexamethylphenidate (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.⁷² Lisdexamfetamine 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.⁷³

Compared to immediate-release dosage forms, extended-release preparations 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 than the more frequent dosing schedule of immediate-release dosage forms.⁷⁴ It is also important that extended-release dosage forms do not produce a flat plasma concentration of the stimulant, which could lead to acute tolerance.⁷⁵ There is increased experience with combining immediate- and extended-release 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.⁷⁶ It has minimal affinity for other monoamine transporters. Its mechanism of action suggests that atomoxetine is unlikely to have abuse potential or to cause motor tics.^{77,78} Atomoxetine has a slower onset of action than stimulants; therapeutic effects may not be seen until a week after the start of treatment. Atomoxetine has a longer duration of action than the stimulants with the possibility of symptom relief during the evening and early-morning hours.⁷⁹

Guanfacine ER (Intuniv) is a selective alpha-2A-adrenergic receptor agonist.⁸⁰ Clonidine (Kapvay) is a centrally acting alpha-2-adrenergic receptor agonist.⁸¹ These drugs reduce sympathetic nerve impulses to the heart and blood vessels leading to a decrease in blood pressure. This mechanism of action in the treatment of ADHD is not known.

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, then, may also work through other neurotransmitter systems. Armodafinil (Nuvigil) is the R-enantiomer of modafinil. Both armodafinil and modafinil have shown similar pharmacological properties.

PHARMACOKINETICS^{82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108}

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: Immediate-Release					
amphetamine sulfate (Evekeo)	--	--	--	--	--
armodafinil (Nuvigil)	2	--	15	--	--
dexmethylphenidate (Focalin)	1–1.5	30	2.2	4–6	--
dextroamphetamine IR (Zenzedi)	2–3	20–60	children: 6–8 adults: 10–12	4–6	--
dextroamphetamine solution (ProCentra)	--	--	11.75	--	--
methamphetamine (Desoxyn)	--	--	4–5	--	--
methylphenidate IR (Methylin, Ritalin) ¹⁰⁹	1.5–3	15–20	2–4	2–4	--
mixed amphetamine salts IR (Adderall)	3	30–60	children: 9–11 adults: 10–13	4–8	--
modafinil (Provigil)	2–4	--	15	--	--
Stimulants: Extended-Release					
amphetamine ER (Adzenys XR-ODT)	5 (d-amphetamine [d])/5.25 (l-amphetamine [l])	--	children: 9–10 (d)/ 10–11 (l) adults: 11 (d)/ 14 (l)	--	50% IR and 50% ER components
amphetamine ER (Dyanavel XR)	4	--	children: 10.43 (d)/12.14(l) adults: 12.36 (d)/15.12(l)	--	IR and ER components; ER component coated with pH-dependent polymer
dexmethylphenidate (Focalin XR)	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 ER (Dexedrine)	8–10	60–90	children: 6–8 adults: 10–12	6–10	initial dose delivered immediately with remaining medication released over 6–8 hours
lisdexamfetamine dimesylate (Vyvanse) ^{110,111}	dexamfetamine = 3.5* (prodrug = 1)	--	10–13 (prodrug <1)	~10	Active drug slowly released by rate-limited hydrolysis
methylphenidate SR (Metadate ER) ^{112,113}	1.5–4.7	30–180	2–4	3–8	Various
methylphenidate SR	4.7	--	--	--	--

Pharmacokinetics (continued)

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: Extended-Release (continued)					
methylphenidate ER OROS (Concerta) ¹¹⁴	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)	1–1.5, then 4–4.5	30–90	6.8	7–12	30% IR, 70% ER beads
methylphenidate ER (QuilliChew ER)	5	--	5.2	--	30% IR, 70% ER
methylphenidate ER (Quillivant XR)	5	45	5–5.2	12	extended-release oral suspension
methylphenidate ER (Ritalin LA)	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 ER (Aptensio XR)	2, then 8	60	5	12	multi-layer beads 40% IR, 60% ER
methylphenidate transdermal (Daytrana)	7.5–10.5	120	3-4	~3 following patch removal	concentrated drug cells in patch
mixed amphetamine salts ER (Adderall XR)	7**	30-60	children: 9–11 adults: 10–13	8–10	50% each of immediate- and delayed-release beads
Non-Stimulants					
atomoxetine (Strattera)	1–2	3–4 weeks	5.2	~24	--
clonidine ER (Kapvay)	6.5–6.8	--	12–16	--	extended-release tablet
guanfacine ER (Intuniv)	5–6	--	18 (adults)	--	matrix consisting of ionic polymers, enteric polymers, and organic acids

* 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

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 7 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 with the use of amphetamine sulfate (Evekeo), amphetamine extended-release (Dyanavel XR), amphetamine extended-release (Adzenys XR-ODT), and mixed amphetamine salts, if possible, to maintain consistent amounts of the active drug in the system.

Except for mixed amphetamine salts, stimulants are de-esterified in the liver to pharmacologically inactive metabolites. In contrast, mixed amphetamine salts 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 OROS (Concerta) and dexamethylphenidate ER (Focalin XR) have similar pharmacodynamic profiles, with the main difference being that the latter contains only dexamethylphenidate. The release profiles of Metadate CD and Ritalin LA, also extended-release formulations of MPH, are very similar to each other.

When opened and sprinkled on cold applesauce, the bioavailability of methylphenidate ER (Aptensio XR, Metadate CD, and Ritalin LA), dexamethylphenidate ER (Focalin XR), and mixed amphetamine salts ER (Adderall XR) are the same as the intact capsules. Dextroamphetamine SR (Dexedrine) 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 capsules are not to be opened as they are an ocular irritant. Quillivant XR is an extended-release suspension that is reconstituted with water and shaken for at least 10 seconds. **QuilliChew ER is an extended-release chewable tablet.**

Atomoxetine 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.¹¹⁵ Approximately 5 to 10% of patients are “slow metabolizers” in which the mean half-life of atomoxetine is 21.6 hours, over 4 times longer than in “rapid metabolizers.”¹¹⁶

Atomoxetine has a slower onset of action than the stimulants; onset of effect may take 1 week and full effect may not be seen for up to 4 weeks.^{117,118} The effects of atomoxetine appear to last longer than would be expected from its pharmacokinetic profile.¹¹⁹ 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.

Exposure to guanfacine ER (Intuniv) was higher in children (6 to 12 years of age) compared to adolescents (13 to 17 years of age) and adults, probably attributable to the lower body weight of children compared to adolescents and adults.¹²⁰ The pharmacokinetics of a single dose of guanfacine ER 4 mg was affected when administered with a high-fat breakfast. The mean exposure increased (C_{max} 75% and area under the curve [AUC] 40%) compared to dosing in a fasted state.

CONTRAINDICATIONS/WARNINGS^{121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141}

Contraindications

All products in this review, except clonidine ER (Kapvay) and guanfacine ER (Intuniv), are contraindicated during or within 14 days following administration of a monoamine oxidase inhibitor (MAOI). These drugs are also contraindicated in patients with glaucoma.

Stimulants are contraindicated in patients with marked anxiety or agitation as these symptoms may be aggravated.

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

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

Quillivant XR and QuilliChew ER are contraindicated with known hypersensitivity to methylphenidate or product components.

Atomoxetine (Strattera) is contraindicated in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate with clinically significant increases in blood pressure or heart rate. Increases in blood pressure and heart rate, orthostasis, and syncope have been reported. Atomoxetine should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

Clonidine ER and guanfacine ER are contraindicated in patients with a history of hypersensitivity to products containing those ingredients.

Modafinil (Provigil) and armodafinil (Nuvigil) are contraindicated in patients with known hypersensitivity to modafinil or armodafinil or their 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 of approved doses of methylphenidate (MPH) has 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 and dexamethylphenidate 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 and armodafinil have also been reported to induce mania, delusions, hallucinations, suicidal ideations, and aggression in patients with and without prior history of psychiatric illness. Two cases of suicide ideation were observed in clinical trials with armodafinil. Treatment-emergent psychotic or manic symptoms have been reported in 0.1% of patients receiving stimulants and 0.2% of patients receiving atomoxetine (Strattera).

Sudden death has been reported in association with stimulants and with atomoxetine at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Stimulants and atomoxetine generally should not be used in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects of atomoxetine. In addition, stimulants and atomoxetine can cause increased blood pressure and heart rate. Caution is indicated in treating patients with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia. Pulse and blood pressure should be monitored at baseline and during therapy.

Stimulants may cause long-term suppression of growth.

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

Stimulants have been associated with peripheral vasculopathy, including Raynaud's phenomenon.

Painful and prolonged penile erections and priapism have been reported with atomoxetine, mixed amphetamine salts, dextroamphetamine, methamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate products. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to a dosage increase. Priapism has also appeared during a period of drug withdrawal (e.g., drug holidays or during discontinuation). Immediate medical attention should be sought if signs or symptoms of painful or prolonged penile erections or priapism are observed.

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

Methylphenidate ER (QuilliChew ER) contains phenylalanine, which may be harmful to patients with phenylketonuria (PKU).

Use of MPH transdermal system (Daytrana) may lead to contact sensitization as evidenced by allergic contact dermatitis. MPH transdermal system should be discontinued if this occurs. Patients may develop systemic sensitization or other systemic reactions to MPH-containing products given via other routes. It is possible that some patients sensitized to MPH may not be able to take MPH in any form.

In June 2015, the FDA issued a warning that MPH transdermal system (Daytrana) use may result in permanent loss of skin color, or chemical leukoderma, in areas ranging up to 8 inches in diameter.¹⁴² A review of chemical leukoderma cases associated with the drug suggest that the skin condition's time to onset ranged from 2 months to 4 years after starting the MPH transdermal system. Patients and caregivers should watch for new areas of lightened skin, particularly in areas where the skin patch was rotated; however, skin color changes have been reported in other areas where the patch was never applied.

Limited reports of multi-organ hypersensitivity reactions have been reported after initiation of treatment between 4 to 33 days in patients taking modafinil. Some of the presenting signs and symptoms for the disorder were fever, rash, pruritus, asthenia, myocarditis, hepatitis, liver function test abnormalities, and dermatological abnormalities. A similar risk of multi-organ hypersensitivity reactions with armodafinil cannot be ruled out.

Rare cases of serious rash, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms, have occurred in patients taking modafinil and

armodafinil. The cases reported have occurred within 1 to 5 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, as well.

Atomoxetine has a boxed warning regarding the increased 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% of patients compared with no patients receiving placebo. All occurrences were reported during the first month of treatment in children 12 years and younger. Monitoring, including face-to-face contact with patients or caregivers, should occur weekly during the first 4 weeks of treatment, then every other week for 4 weeks, then again at 12 weeks.

Patients on atomoxetine should be monitored for the appearance or worsening of aggressive behavior or hostility.

Atomoxetine has a warning regarding severe liver injury; rare, but marked, elevations of hepatic enzymes and bilirubin have been reported. In 2 case reports, liver injury resolved after discontinuation of atomoxetine (with concomitant immunosuppressive therapy in 1 case).¹⁴³ The manufacturer warns to discontinue atomoxetine permanently in patients with any sign of jaundice or hepatic lab abnormality; other treatment options should be considered.

Dose-dependent decreases in blood pressure and heart rate have been seen in patients using clonidine ER or guanfacine ER. Heart rate and blood pressure should be measured prior to initiation of therapy, following dose increases, and periodically while on therapy. Use with caution in patients with a history of hypotension, heart block, bradycardia, cardiovascular disease, or syncope. The sympatholytic action of clonidine ER and guanfacine ER may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. Advise patients to avoid becoming dehydrated or overheated. Guanfacine ER should be titrated slowly in patients with history of hypotension or underlying conditions that may be worsened by hypotension and bradycardia, as well as patients with cardiac conduction abnormalities.¹⁴⁴

In 2011, the FDA published a safety communication based on studies that evaluated heart attacks and sudden deaths including children, adolescents, and adults treated with ADHD medications, and a study that assessed strokes in these adults.^{145,146} The FDA concluded that no increase in risk of serious adverse cardiovascular events in patients treated with ADHD medications was found. The medications studied included stimulants, atomoxetine, and pemoline (no longer marketed).

To avoid adverse effects on blood pressure when discontinuing therapy, the clonidine ER or guanfacine ER dose should generally be tapered off. Clonidine ER decrements should not exceed 0.1 mg every 3 to 7 days. For guanfacine ER, decrease in decrements of no more than 1 mg every 3 to 7 days.

All stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms generally improve after reduction in dose or discontinuation of the drug. Monitor for digital changes during treatment with ADHD stimulants.

Risk Evaluation and Mitigation Strategies (REMS)

The REMS requirements for armodafinil and modafinil were eliminated in 2012.

DRUG INTERACTIONS^{147,148,149,150,151,152,153,154,155,156,157,158}

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. Proton pump inhibitors reduce gastric acidity; patients who co-administer them with amphetamines should be monitored for changes in clinical effect due to the potential for decreases in the time to maximum concentration of amphetamine products. Amphetamine extended-release (Adzenys XR-ODT, Dyanavel XR) may enhance the effect of tricyclic antidepressants, including cardiac effects. Patients taking these agents concomitantly should have increased monitoring and dose adjustments as clinically indicated.

Effects can be additive when stimulants are used concurrently with other psychostimulants or sympathomimetics.¹⁵⁹ Due to the potential for excessive CNS or cardiovascular stimulation, combination use should be avoided unless necessary, and, if unavoidable, then used with caution.¹⁶⁰ In general, the concurrent use of methylphenidate (MPH; Aptensio XR, Methylin, Metadate ER, Metadate CD, Quillivant XR, Ritalin, Ritalin LA, Concerta, Daytrana) with amphetamines is not recommended. Since there are no clinical data regarding the concurrent use of MPH and atomoxetine (Strattera), concurrent use should be avoided.

Amphetamines 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.¹⁶¹ Melatonin may exacerbate the monoaminergic effects of amphetamine-related medications. Co-administration of melatonin with methamphetamine (Desoxyn) in animal studies resulted in increased dopaminergic and serotonergic stimulation.¹⁶²

Lithium may antagonize the central stimulating effects of amphetamines and should be avoided.¹⁶³ Likewise, MPH 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.¹⁶⁴ Haloperidol and chlorpromazine also inhibit the central stimulant effects of the amphetamines.

MPH and dexamethylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with MPH.

Like the monoamine oxidase inhibitors (MAOIs), stimulants and atomoxetine potentiate the effects of catecholamine neurotransmitters. MAOIs or drugs that possess MAOI 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.

Caution should be used when guanfacine ER (Intuniv) is administered to patients taking strong CYP3A4/5 inhibitors (e.g., ketoconazole), which can cause a substantial increase in rate and extent of guanfacine exposure (AUC) leading to an increased risk of adverse events such as hypotension, bradycardia, and sedation.

Concomitant use of guanfacine ER with a CYP3A4 inducer (e.g., rifampin) can cause a significant decrease in the rate and extent of guanfacine exposure (AUC). An increase in the dose of guanfacine ER within the recommended dose range may be considered.

Co-administration of guanfacine and valproic acid can result in increased concentrations of valproic acid. Adjustments in the dose of valproic acid may be required.

Somnolence and sedation with guanfacine ER and clonidine ER were commonly reported adverse reactions in clinical studies, especially during initial use. Caution should be used when operating heavy equipment or driving and use with other CNS depressants, including alcohol. Furthermore, alcohol should be avoided while taking methylphenidate.

Likewise, drugs affecting sinus node function or AV nodal conduction or antihypertensive drugs have the potential for additive effects when used with clonidine. Serious adverse events have been reported during concomitant use of MPH and clonidine; no causality has been established.

Use of modafinil (Provigil) with other psychostimulants has not been extensively studied, and concurrent use is not recommended. Co-administration of amphetamine and modafinil may increase stimulant-associated side effects.¹⁶⁵ Single-dose studies of MPH combined with modafinil showed that the rate of absorption of modafinil was delayed up to 1 hour in the presence of MPH. No changes occurred in the metabolism and extent of absorption of either medication.

Armodafinil (Nuvigil) and modafinil have not been evaluated for interactions with drugs with MAOI activity. Until more is known regarding the pharmacology of modafinil, it may be prudent to caution against the use of these agents in the presence of a MAOI.

Armodafinil and modafinil moderately induce CYP3A activity. Drugs that are substrates for CYP3A4/5, such as cyclosporine, may require dosage adjustment. Armodafinil and modafinil moderately inhibit CYP2C19 activity. Drugs that are substrates for CYP2C19, such as omeprazole, may require dosage reduction.

The effectiveness of steroidal contraceptive may be reduced with concurrent use of either armodafinil or modafinil and for 1 month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended and for 1 month after discontinuation of armodafinil or modafinil.

Where data specific to armodafinil drug interactions are not available, any available information on modafinil should be applicable to armodafinil, according to the prescribing information.

ADVERSE EFFECTS^{166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191}

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.¹⁹² They commonly subside spontaneously during the first 1 to 2 weeks of treatment.¹⁹³ 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.^{194,195}

In a double-blind study, investigators found that, based on parent assessment, only 2 adverse effects were more prevalent after initiation of stimulants than prior to initiation. These were insomnia (dextroamphetamine) and poor appetite (dextroamphetamine and MPH).¹⁹⁶ 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 released a policy statement indicating that adverse effects of stimulant medications are usually mild and of short duration, and there is no significant impairment of height in adult life. The guidelines state that stimulants used for ADHD do not require routine serologic, hematologic, or electrocardiogram monitoring.¹⁹⁷

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. If children are on too high of a dosage or are 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 extended-release formulations. There is no evidence to support statistically significant differences with respect to adverse effects of dextroamphetamine (Dexedrine, Zenzedi, ProCentra) and MPH (Aptensio XR, Methylin, Metadate ER, Metadate CD, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Concerta, Daytrana).

Adverse Effects in Children (*Adults Only)

Drug	Headache	Abdominal pain	Anorexia	Insomnia
Stimulants: Immediate-Release				
amphetamine sulfate (Evekeo)	reported	nr	reported	nr
armodafinil (Nuvigil)*	17 (9)	2 (1)	1 (0)	5 (1)
dexmethylphenidate (Focalin)	nr	15 (6)	6 (1)	nr
dextroamphetamine IR (Zenzedi)	reported	reported [†]	reported	reported
dextroamphetamine solution (ProCentra)	reported	nr	reported	reported
methamphetamine (Desoxyn)	reported	nr	nr	reported
methylphenidate IR (Methylin, Ritalin)	reported	reported	reported	reported
mixed salt amphetamines IR (Adderall)	reported	nr	reported	reported
modafinil (Provigil)*	34 (23)	1 (≥1)	4 (1)	5 (1)
Stimulants: Extended-Release				
amphetamine ER (Adzenys XR-ODT)	reported	11–14 (2–10)	22–36 (2)	12–17 (2–4)
amphetamine ER (Dyanavel XR)	nr	3.8 (0)	reported	nr
dexmethylphenidate (Focalin XR)	25 (11)	nr	30 (9)	reported
dextroamphetamine ER (Dexedrine)	reported	nr	reported	reported
lisdexamfetamine (Vyvanse)	reported	12 (6)	5 (0)	13–23 (3–4)
methylphenidate ER (Metadate ER)	reported	reported	reported	reported
methylphenidate ER (QuilliChew ER)	2.4 (0)	reported	2.4 (0)	reported
methylphenidate ER (Quillivant XR)	nr	reported	reported	reported
methylphenidate ER OROS (Concerta)	<1	6.2 (3.8)	<1	2.8 (0.3)
methylphenidate ER (Metadate CD)	12 (8)	7 (4)	9 (2)	5 (2)
methylphenidate ER (Ritalin LA)	>5 (nr)	>5 (nr)	>5 (nr)	>5 (nr)
methylphenidate ER (Aptensio XR)	>5 (nr)	>5 (nr)	>5 (nr)	>5 (nr)
methylphenidate transdermal (Daytrana)	12.4–15.3 (11.8–12.5)	4.8–7.1 (0–5.9)	4.8–5.1 (1.2–1.4)	6.2–13.3 (2.8–4.7)
mixed salt amphetamines (Adderall XR)	reported	11–14 (2–10)	22 (2)	12–17 (2–4)

Adverse Effects in Children (*Adults Only; continued)

Drug	Headache	Abdominal pain	Anorexia	Insomnia
Non-Stimulants				
atomoxetine (Strattera)	19 (15)	18 (10)	3 (1)	≥2 (nr)
clonidine ER (Kapvay)	19–29 (18)	13–20 (17)	nr	4–6 (1)
guanfacine ER (Intuniv)	21–24 (13–19)	10–11 (3–9)	5–7 (3–4)	12 (6)

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

* Adults only

† Zenedi adverse event reported as gastrointestinal disturbance

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

The majority of patients in the pivotal phase 3 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. However, use of MPH transdermal may lead to contact sensitization and should be discontinued if contact sensitization is suspected. Patients sensitized from use of MPH transdermal may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes (e.g., orally). The most common adverse reactions with the extended-release suspension (Quillivant XR) reported in the phase 3 controlled study conducted in 45 ADHD patients (ages 6 to 12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash. Other common adverse reactions with the extended-release methylphenidate (QuilliChew ER) not reported above but reported in a controlled study conducted in 90 ADHD patients (ages 6 to 12 years) were aggression, emotional poverty, nausea, and decreased weight.

Stimulants can cause unpredictable motor tics, which transiently occur in 15% to 30% 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 2 or 3 years before the tics appear. It is believed that stimulants do not cause Tourette's disorder, but simply unmask the disorder. Motor and verbal tics have not been associated with atomoxetine (Strattera).¹⁹⁸

Paresthesia (including formication) has been associated with treatment on mixed amphetamine salts (Adderall, Adderall XR).

Rhabdomyolysis has been identified as an adverse reaction during post-approval use of stimulants and atomoxetine (Strattera).

Effects on Growth

The 2011 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.¹⁹⁹ A temporary slowing in growth rate

(2 cm less growth in height and 2.7 kg less increase in weight over 3 years) has been noted in children starting treatment with MPH at ages 7 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 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.²⁰⁰

SPECIAL POPULATIONS^{201,202,203,204,205,206,207,208,209,210,211, 212,213,214,215,216,217,218}

Pediatrics

Methamphetamine (Desoxyn), methylphenidate (MPH; Aptensio XR, Concerta, Methylin, Metadate CD, Metadate ER, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Daytrana), d-MPH (Focalin, Focalin XR), amphetamine extended-release (Adzenys XR-ODT, Dyanavel XR), mixed amphetamine salts ER (Adderall XR), lisdexamfetamine (Vyvanse), and atomoxetine (Strattera) are indicated for children 6 years of age and older for the treatment of ADHD. Dextroamphetamine ER (Dexedrine) is indicated for children 3 to 16 years of age. Some of the immediate-release stimulants, dextroamphetamine IR tablets (Zenzedi), solution (ProCentra), amphetamine sulfate (Evekeo), and mixed amphetamine salts (Adderall), are indicated for children as young as 3 years. Dextroamphetamine IR tablets (Zenzedi) and solution (ProCentra) are approved through the age of 16 for ADHD. 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.

Agents approved for narcolepsy (amphetamine sulfate [Evekeo], dextroamphetamine IR [Zenzedi, ProCentra], methylphenidate IR [Methylin, Ritalin], mixed amphetamine salts IR [Adderall], dextroamphetamine ER [Dexedrine], and methylphenidate SR [Metadate ER]) are approved in pediatric patients ages 6 years and older. Amphetamine sulfate (Evekeo) also is approved for exogenous obesity in patients older than 12 years. For exogenous obesity, methamphetamine (Desoxyn) is indicated in patients 12 years and above. Safety and efficacy of lisdexamfetamine (Vyvanse) for the treatment of binge-eating disorder have not been established in pediatric patients.

The safety and efficacy of guanfacine ER (Intuniv) in pediatric patients less than 6 years of age have not been established. For children and adolescents 6 years and older, efficacy beyond 9 weeks and safety beyond 2 years of treatment have not been established.

The safety and efficacy of clonidine ER (Kapvay) in ADHD patients less than 6 years of age have not been established. Maintenance therapy beyond 5 weeks has not been evaluated; patients should be periodically re-evaluated to determine the long-term usefulness of clonidine ER.

Safety and effectiveness in patients below the age of 17 years for modafinil (Provigil) and armodafinil (Nuvigil) have not been established. Serious rash has been reported in pediatric patients receiving these agents.

Children under 3 years of age – Numerous studies indicate that stimulants are effective in the treatment of ADHD in preschool children.^{219,220} 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.²²¹ 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 and/or school placement are unavailable or unsuccessful. If medications are used, the AACAP suggests daily treatment without weekend holidays.

Pregnancy

Guanfacine ER is Pregnancy Category B. All other agents in this class are Pregnancy Category C. Amphetamine extended-release (Dyanavel XR) and extended-release methylphenidate (QuilliChew ER,

Quillivant XR) have not been assigned a Pregnancy Category based on the FDA's revised pregnancy risk formatting; data on use of amphetamines and methylphenidate in this population are limited.

Hepatic Impairment

For patients with moderate (Child-Pugh Class B) hepatic impairment, the initial and target doses of atomoxetine (Strattera) should be reduced by 50%. For patients with severe (Child-Pugh Class C) hepatic impairment, the initial and target doses should be reduced by 75%. For patients taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) or in patients who are known to be CYP2D6 poor metabolizers, atomoxetine should be started at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

For patients with severe hepatic impairment, the dosage of modafinil (Provigil) should be reduced by 50%. The bioavailability of the inactive metabolite, modafinil acid, is increased 9-fold in patients with severe renal impairment ($\text{CrCl} \leq 20$ mL/min); safety and efficacy of modafinil in this patient group have not been determined.

The dose of armodafinil (Nuvigil) should be reduced in patients with severe hepatic impairment. There is inadequate information to determine safety and efficacy of dosing in patients with severe renal impairment.

Renal Impairment

Patients with severe renal impairment taking lisdexamfetamine (Vyvanse) should not exceed a maximum dose of 50 mg/day. The recommended maximum dose of lisdexamfetamine in patients with end stage renal disease is 30 mg/day.

DOSAGES^{222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247}

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants: Immediate-Release				
amphetamine sulfate (Evekeo)	3–5 years	2.5 mg once daily	40 mg/day in 2 or 3 divided doses	Tablets: 5, 10 mg
	6–17 years	5 mg once or twice daily		
armodafinil (Nuvigil®)	≥17 years	150 mg to 250 mg once daily in the morning	250 mg/day	Tablets: 50, 150, 200, 250 mg
dexmethylphenidate (Focalin)	6–17 years	2.5 mg twice daily	10 mg twice daily	Tablets: 2.5, 5, 10 mg
dextroamphetamine IR (Zenzedi)	3–5 years	2.5 mg once daily	40 mg/day	Tablets: 5, 10 mg Tablets (Zenzedi): 2.5, 5, 7.5, 10, 15, 20, 30 mg
	6–16 years	5 mg once or twice daily	40 mg/day in 2 or 3 divided doses	
dextroamphetamine solution (ProCentra)	3–5 years	2.5 mg once daily	40 mg/day	Oral solution: 5 mg/5 mL
	6–16 years	5 mg once or twice daily	40 mg/day	
methamphetamine (Desoxyn)	6–17 years	5 mg once or twice daily	20-25 mg/day in 2 divided doses	Tablets: 5 mg
methylphenidate IR (Methylin, Ritalin)	6–17 years	5 mg twice daily	60 mg/day in 2 or 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

The above table represents doses used for the treatment of ADHD, except in the cases of Nuvigil (armodafinil) and Provigil (modafinil) which are only approved to treat shift work disorder, narcolepsy, and sleep apnea.

Dosages (continued)

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants: Immediate-Release (continued)				
mixed amphetamine salts IR (Adderall)	3–5 years	2.5 mg once daily	40 mg/day in 2 or 3 divided doses (60 mg/day for adolescents and adults)*	Tablets: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	6–17 years	5 mg 2 or 3 times daily		
modafinil (Provigil®)	≥17 years	200 mg once daily in the morning	400 mg/day	Tablets: 100, 200 mg
Stimulants: Extended-Release				
amphetamine ER (Adzenys XR-ODT)	6–17 years	6.3 mg once daily in the morning	6 to 12 years: 18.8 mg/day 13 to 17 years: 12.5 mg/day	Orally disintegrating tablets (ODT): 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg
	≥ 18 years (adults)	12.5 mg once daily in the morning	12.5 mg/day	
amphetamine ER (Dyanavel XR)	≥ 6 years	2.5–5 mg once daily	20 mg/day	Suspension: 1,160 mg/464 mL (2.5 mg/mL)
dexamethylphenidate ER (Focalin XR)	6–17 years	5 mg once daily	30 mg/day	Capsules: 5, 10, 15, 20, 25, 30, 35, 40 mg
	≥ 18 years (adults)	10 mg once daily	40 mg/day	
dextroamphetamine ER (Dexedrine)	3–5 years	2.5 mg once daily	not available	Capsules: 5, 10, 15 mg
	6–16 years	5 mg once daily	40 mg once daily	
lisdexamfetamine (Vyvanse)	≥ 6 years	30 mg daily in the morning	70 mg daily in the morning	Capsules: 10, 20, 30, 40, 50, 60, 70 mg
methylphenidate ER OROS (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)	6–17 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40, 50, 60 mg
methylphenidate ER (Metadate ER)	6–17 years	5 mg twice daily or equivalent (e.g., 10 mg once daily)	60 mg/day in 1 or 2 divided doses	Tablets: 10 mg (generic only), 20 mg
methylphenidate ER (QuilliChew ER)	≥ 6 years	20 mg once daily in the morning	60 mg/day	Chewable tablets: 20, 30, 40 mg (20 and 30 mg strengths are scored; 40 mg is not scored)
methylphenidate ER (Quillivant XR)	≥ 6 years	20 mg once daily	60 mg once daily	Suspension: 300 mg/60 mL, 600 mg/120 mL, 750 mg/150 mL, 900 mg/180 mL (5 mg/ mL)

The above table represents doses used for the treatment of ADHD, except in the cases of Nuvigil (armodafinil) and Provigil (modafinil) which are only approved to treat shift work disorder, narcolepsy, and sleep apnea.

* mixed amphetamine salts IR (Adderall)- maximum dose in narcolepsy is 60 mg/day in ages 6 years and older.

Dosages (continued)

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants: Extended-Release (continued)				
methylphenidate ER (Ritalin LA)	6–17 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40, 60 mg
methylphenidate ER (Aptensio XR)	≥ 6 years	10 mg once daily	60 mg once daily	Capsules: 10, 15, 20, 30, 40, 50, 60 mg
methylphenidate transdermal (Daytrana)	6–17 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 ER (Adderall XR)	6–17 years	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	
Non-Stimulants				
atomoxetine (Strattera)	≥ 6 years and <70 kg	0.5 mg/kg/day in 1 or 2 divided doses	1.4 mg/kg/day in 1 or 2 divided doses	Capsules: 10, 18, 25, 40, 60, 80, 100 mg
	≥ 6 years and >70 kg and adults	40 mg/day in 1 or 2 divided doses	100 mg/day given in 1 or 2 divided doses	
clonidine ER (Kapvay)	6–17 years	0.1 mg at bedtime	0.2 mg twice daily	Tablets: 0.1 mg
guanfacine ER (Intuniv)	6–17 years	1 mg once daily in the morning or evening	4 mg once daily in the morning or evening	Tablets: 1, 2, 3, 4 mg

The above table represents doses used for the treatment of ADHD, except in the cases of Nuvigil (armodafinil) and Provigil (modafinil) which are only approved to treat shift work disorder, narcolepsy, and sleep apnea.

The contents of lisdexamfetamine (Vyvanse) capsules can be emptied and mixed with yogurt, water, or orange juice. A spoon may be used to break apart any compacted powder in the water. The content should be stirred until completely dispersed. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass once the water is consumed.

MPH immediate-release (Methylin, Ritalin) should be administered 30 to 45 minutes before meals. Dexamethylphenidate (Focalin, Focalin XR) and MPH extended-release can be administered without regard to meals. The timing of the mid-day dose of MPH immediate-release and dexamethylphenidate immediate-release should be individualized based on patient response. The last daily dose of MPH extended-release should be given several hours before bedtime.

MPH transdermal patches (Daytrana) should be applied 2 hours prior to the desired onset of activity and should be worn for 9 hours. Wear time can be individualized based on patient response.

Clonidine ER (Kapvay) doses should be increased at a frequency of 0.1 mg per week. Tablets should not be chewed, crushed, or split. Do not substitute clonidine ER for immediate-release clonidine on a milligram-for-milligram basis.

The recommended target dose range for guanfacine ER (Intuniv), depending on tolerability and the clinical response of the patient, is 0.05–0.12 mg/kg/day. Doses above 4 mg/day have not been evaluated in children between 6 and 12 years of age and doses above 7 mg/day have not been evaluated in patients between 13 and 17 years of age. If switching from guanfacine IR to guanfacine ER (Intuniv), discontinue guanfacine IR and titrate with guanfacine ER according to the recommended dosing schedule. Prescribers should re-evaluate patients often and adjust weight-based dosage, as

needed. Patients may experience increases in blood pressure and heart rate after discontinuing guanfacine ER (Intuniv) treatment. Daily dose should be reduced in decrements no greater than 1 mg every 3 to 7 days to prevent rebound hypertension and patients should be closely monitored.

Amphetamine extended-release (Dyanavel XR) dosage may be increased by 2.5 to 10 mg per day every 4 to 7 days. Do not substitute for other amphetamine agents on an equal mg basis; they are not interchangeable.

Hypersomnolence

Armodafinil (Nuvigil 50, 150, 250 mg tablets) – 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 1 hour prior to the start of the work shift.

Dextroamphetamine (Zenzedi, ProCentra) – for adults and adolescents, 5 mg twice daily titrated to a maximum of 60 mg/day in 2 or 3 divided doses; for children 6 to 12 years, 5 mg once daily titrated to maximum of 60 mg/day in 2 or 3 divided doses. Once the dosage has been stabilized, patients can be converted to an equivalent dosage of dextroamphetamine extended-release (Dexedrine) given once daily.

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

Amphetamine sulfate (Evekeo) and mixed amphetamine salts (Adderall) – for the treatment of narcolepsy 5 mg to 60 mg per day in divided doses. The suggested initial dose for patients 6 to 12 years of age is 5 mg daily; dose may be titrated in increments of 5 mg per day at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily and may be titrated by 10 mg per day at weekly intervals until optimal response is obtained.

Modafinil (Provigil 100, 200 mg tablets) – 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 1 hour prior to work.

Exogenous Obesity

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

For exogenous obesity, the recommended dose of amphetamine sulfate (Evekeo) is up to 30 mg daily divided in doses of 5 to 10 mg given 30 to 60 minutes before meals. Use in children under 12 years is not recommended.

Binge Eating Disorder

The recommended dose of lisdexamfetamine dimesylate (Vyvanse) is 50 mg to 70 mg per day, following a starting dose of 30 mg every morning with a 20 mg weekly titration schedule.

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% 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of ADHD of less than 4 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% sensitive and 94% specific.
- **Swanson, Nolan, and Pelham scale (SNAP)** – The scale has been shown to have greater than 94% sensitivity and specificity in distinguishing hyperactive, inattentive, and impulsive children with ADHD from those without ADHD based on DSM-III-R criteria.
- **Swanson, Kotlin, Agler, M-Flynn, and Pelham scale (SKAMP)** – A validated rating scale that assesses ADHD manifestations in a classroom setting; specifically assesses context-bound behaviors critical to school settings.
- **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% sensitive and 49% specific; the teacher form is 72% sensitive and 86% specific.
- **Permanent Product Measure of Performance (PERMP)** – A skill adjusted math test; sum of the number of math problems attempted plus the number of math problems answered correctly in a 10-minute session.

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%.

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

atomoxetine (Strattera) versus MPH immediate-release

Two identical 12-week double-blind trials were conducted in 291 children (ages 7 to 13 years) with ADHD.²⁴⁸ Stimulant-naïve 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.²⁴⁹

atomoxetine (Strattera) versus MPH OROS (Concerta)

A randomized, double-blind, placebo-controlled study compared the response, as measured by the ADHD Rating Scale of atomoxetine, MPH OROS, and placebo.²⁵⁰ A total of 516 children ages 6 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 6 weeks. Patients who had previously had an inadequate response to stimulant treatment were excluded from the study. After 6 weeks, using double-blind conditions, the patients receiving MPH OROS were switched to atomoxetine. Response was determined by a 40% 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% response, MPH OROS resulting in a 56% response, and placebo resulting in a 24% 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%) responded after being switched to atomoxetine. Also, note that 69 patients did not respond to atomoxetine treatment, but 29 (42%) 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 MPH immediate-release

A randomized, double-blind, crossover trial compared the efficacy of atomoxetine and MPH for treating ADHD, as well as their effects on the sleep of children with ADHD.²⁵¹ 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 3 times daily MPH (mean dose 58.27 mg/day), each for approximately 7 weeks. Relative to baseline, actigraphy data indicated that MPH increased sleep latency significantly more than did atomoxetine (39.2 versus 12.1 minutes; $p < 0.001$); these results were consistent with polysomnography data. Compared with MPH, 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 MPH. Using the main measures of efficacy, the medications had similar efficacy for treatment of ADHD. Greater incidence of decreased appetite and insomnia with MPH were the only significant differences in treatment-emergent adverse events. Both medications decreased night time awakenings, but the decrease was greater for MPH.

clonidine ER (Kapvay) versus placebo

The efficacy of clonidine ER in the treatment of ADHD was established in 2 manufacturer approval trials in pediatric patients with ADHD ages 6 to 17 years.²⁵² Signs and symptoms of ADHD were evaluated using the ADHD RS-IV total score including hyperactive/impulsivity and inattentive subscales. Study 1 was a randomized, double-blind, placebo-controlled, study of 236 patients who were randomly assigned to clonidine ER 0.2 mg or 0.4 mg daily or placebo daily. At both doses, improvements in ADHD symptoms were statistically significantly superior in clonidine ER patients compared with placebo patients at the end of 5 weeks as measured by the ADHD RS-IV total score. Study 2 was a randomized, double-blind, placebo-controlled, study in 198 pediatric patients. Patients had previously been treated with methylphenidate or amphetamine for 4 weeks with inadequate response. Patients were randomly assigned to clonidine ER as adjunct to the stimulant or the previous stimulant alone. The clonidine ER dose was initiated at 0.1 mg daily and titrated upward, as clinically appropriate. ADHD symptoms were statistically significantly improved in clonidine ER plus stimulant group compared with the stimulant-alone group at the end of 5 weeks as measured by the ADHD RS-IV total score.

guanfacine ER (Intuniv) versus placebo

The efficacy of guanfacine ER in the treatment of ADHD was evaluated in 2 placebo-controlled trials in children and adolescents ages 6 to 17 years.²⁵³ Study 1 evaluated guanfacine ER 2, 3, or 4 mg dosed once daily in an 8-week, double-blind, placebo-controlled, parallel-group (n=345) trial. Study 2 evaluated guanfacine ER 1, 2, 3, or 4 mg dosed once daily in a 9-week, double-blind, placebo-controlled, parallel-group (n=324) trial. Doses were titrated in increments of up to 1 mg/week. The mean reductions in ADHD RS scores at endpoint were statistically significantly greater for guanfacine ER compared to placebo for both studies. Due to the relatively small proportion of adolescent patients (13–17 years of age) enrolled into these studies (approximately 25%), these data may not be sufficient to demonstrate efficacy in the adolescent subgroup. When evaluated regarding dose per body weight, clinically relevant improvements were observed beginning at doses in the range 0.05–0.08 mg/kg/day. In these studies, dosages were not optimized by body weight, and over half (55%) of the adolescent patients received doses of 0.01–0.04 mg/kg. The most commonly reported treatment-emergent adverse events were headache, somnolence, fatigue, upper abdominal pain, and sedation. Small to modest changes in blood pressure, pulse rate, and electrocardiogram parameters were observed but were not clinically meaningful.

mixed amphetamine salts ER (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.²⁵⁴ Adolescents (n=35, 19 males) with a diagnosis of ADHD completed 3 separate assessments (5:00 p.m., 8:00 p.m., 11:00 p.m.) on 3 different days and medications (mixed amphetamine salts ER, MPH OROS, 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.

dexmethylphenidate (Focalin), MPH immediate-release, and placebo

In a randomized, double-blind study, 132 subjects received dexmethylphenidate, MPH, or placebo twice daily for 4 weeks, with titration of the dose based on weekly clinic visits.²⁵⁵ 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 dexmethylphenidate (p=0.0004) or MPH immediate-release (p=0.0042) significantly improved Teacher SNAP ratings compared with placebo. The dexmethylphenidate 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 p.m. (p=0.0236). Improvement based on CGI-I occurred in 67% of patients on dexmethylphenidate and 49% of patients on MPH immediate-release. Both active treatments were well tolerated.

MPH immediate-release, MPH OROS (Concerta), and placebo

A double-blind, placebo-controlled, randomized, 5-period crossover study in 49 healthy subjects with a history of light (occasional) recreational stimulant use was performed to evaluate the abuse-related subjective effects of MPH OROS with comparable doses of MPH immediate-release.²⁵⁶ Patients were included in the study if they demonstrated a positive response to a 20 mg dose of dextroamphetamine 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 immediate-release. For each treatment, patients were observed for 24 hours to assess pharmacokinetics, pharmacodynamics, and safety. Both doses of MPH immediate-release produced statistically significant higher positive stimulant effects with respect to placebo for all measures (p<0.001). MPH OROS 108 mg 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 immediate-release, and the lowest MPH immediate-release doses produced more of an effect than the highest of MPH OROS doses, showing that formulation may help reduce abuse potential.

In a multicenter, double-blind trial, 282 children (ages 6 to 12 years) with ADHD were randomized to receive MPH immediate-release 5, 10, or 15 mg 3 times daily, MPH OROS 18, 36, or 54 mg once daily, or placebo for 28 days.²⁵⁷ Response, defined as >30% reduction from baseline IOWA Conners Oppositional/Defiance (O/D) score, occurred in 52, 59, and 26% of patients in the MPH immediate-release, 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%, respectively

($p < 0.0107$ for comparison of active treatments to placebo). The response rate for the 2 higher doses of MPH OROS (77%) was significantly higher than for MPH immediate-release based on parent ratings ($p < 0.05$). Forty-eight percent of the placebo group discontinued study drug early compared with 14% and 16% in the MPH and OROS MPH groups, respectively.

MPH extended-release (QuilliChew ER) and placebo

A 1-week, randomized, double-blind, placebo-controlled, parallel-group laboratory school study evaluated the efficacy of MPH extended-release chewable tablet in 90 subjects (ages 6 to 12 years; ITT population $n=85$) diagnosed with ADHD (based on DSM-IV criteria).²⁵⁸ Patients entered a 6-week open-label dose optimization period, followed by a 1-week period in which they were randomized to either placebo or the optimized dose (10 to 60 mg) of MPH extended-release chewable tablet. The primary outcome was the average of treatment effects (as measured by the SKAMP-combined score across all time points during the classroom day (0.75, 2, 4, 8, 10, 12, and 13 hours) as rated by teachers and raters. The placebo-subtracted difference in the average of treatment effect across all time points as measured by the SKAMP-combined score was -7 (95% CI, -10.9 to -3.1), demonstrating superiority of MPH extended-release chewable tablet over placebo.

MPH extended-release (Quillivant XR) and placebo

A total of 45 subjects (ages 6 to 12 years) were enrolled in this dose-optimized, randomized, double-blind, placebo-controlled, crossover laboratory school study. The purpose of this study was to determine the efficacy of extended-release (ER) suspension of MPH compared with placebo in the treatment of ADHD in children.²⁵⁹ Following a 4 to 6 week open-label dose optimization phase, subjects received 2 weeks of double-blind treatment, 1 week of MPH ER suspension, and 1 week of placebo. Efficacy measures included SKAMP Rating Scale-Combined and Permanent Product Measure of Performance (PERMP) mathematics tests measured at pre-dose and at 0.75, 2, 4, 8, 10, and 12 hours post-dose on each laboratory classroom day. MPH ER suspension resulted in significant ($p < 0.0001$) improvements in the SKAMP-Combined score at 4 hours post-dose (mean=7.12) as compared with placebo (mean=19.58) in the completers ($n=39$). Significant separation from placebo occurred at each time point tested with onset of action at 45 minutes post-dose and duration of efficacy extending to 12 hours post-dose. Adverse events and changes in vital signs following MPH ER suspension were generally mild and consistent with the known safety profile of MPH. MPH ER suspension effectively reduced symptoms of ADHD in children beginning at 45 minutes and continuing for 12 hours post-dose.

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

In a double-blind study, 270 children (ages 6 to 12 years) with ADHD were randomized to 1 of 3 treatment arms: MPH OROS + placebo patch, MPH transdermal + placebo capsule, or placebo capsule + placebo patch.²⁶⁰ The study consisted of a 5-week dose-optimization phase followed by a 2-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% was observed in 66, 78, and 29% 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 3, multicenter, randomized, double-blind, forced-dose, parallel-group study was conducted at 40 centers across the United States (U.S.).²⁶¹ 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 compared with placebo. The study included 290 randomized patients; 230 patients completed the study. Sixty patients did not 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 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 6:00 p.m. 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.

A multi-center, randomized, double-blind, placebo-controlled, crossover design, modified analog classroom study of lisdexamfetamine to simulate a workplace environment in 142 adults who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria for ADHD.²⁶² There was a 4-week open-label, dose optimization phase with lisdexamfetamine (30, 50, or 70 mg/day in the morning). Subjects were then randomized to 1 of 2 treatment regimens: an optimized dose of lisdexamfetamine followed by placebo, each for 1 week, or placebo followed by lisdexamfetamine, each for 1 week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. Lisdexamfetamine treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose.

amphetamine sulfate (Evekeo) versus placebo

A multicenter, dose-optimized, randomized, double-blind, placebo-controlled crossover laboratory classroom study was conducted to evaluate the safety and efficacy of amphetamine sulfate (Evekeo) in children with ADHD.²⁶³ After an 8-week open-label dose optimization period, 97 children between the ages of 6 and 12 were randomized to 2 weeks of treatment (amphetamine sulfate followed by placebo or placebo followed by amphetamine sulfate). Efficacy measures included the SKAMP rating scale and Permanent Product Measure of Performance (PERMP) which was administered before dose and at 0.75, 2, 4, 6, 8, and 10 hours after dose on 2 laboratory classroom days. Compared to placebo, a single daily dose of amphetamine sulfate significantly improved SKAMP-Combined scores at each time point during classroom days ($p < 0.0001$). Amphetamine sulfate also significantly improved PERMP number of problems attempted and correct ($p < 0.0001$).

methylphenidate extended-release (Aptensio XR) versus placebo

The efficacy of methylphenidate extended-release was evaluated in 2 studies; first in a randomized double-blind, placebo-controlled, flexible-dose, crossover trial in children ages 6 to 12 (n=26), secondly, in a randomized, double-blind multicenter, placebo-controlled, fixed-dose trial in patients ages 6 to 18 years (n=230).²⁶⁴

In Trial 1, patients received flexible dose methylphenidate extended-release (15 mg, 20 mg, 30 mg, or 40 mg once daily) in a 2 to 4 week optimization phase and were then randomized to continue their dose from the open-label phase or receive placebo. After 1 week, patients were evaluated over a period of 12 hours and then were given the opposite treatment for 1 week, followed by a second evaluation. Patients were assessed at various time points ranging from 1 to 12 hours post-dose using the SKAMP score. SKAMP total scores were significantly lower for methylphenidate extended-release than for placebo at test day average and all time points post-dose.

In Trial 2, patients were randomized to receive methylphenidate extended-release 10 mg, 15 mg, 20 mg, 40 mg, or placebo for 1 week, followed by an 11-week open label phase. The primary efficacy endpoint was the mean decrease from baseline to the end of Week 1 in the ADHD-RS-IV Total Score. Methylphenidate extended-release 20 mg/day and 40 mg/day doses were superior to placebo for the primary endpoint (p=0.0145 and p=0.0011, respectively).

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.²⁶⁵ This scale has a high level of internal consistency.²⁶⁶
- 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.²⁶⁷
- 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.²⁶⁸ 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 3 tests.^{269,270}

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 9 weeks.²⁷¹ The mean ESS score was significantly lower for each modafinil treatment group compared to placebo at weeks 3, 6, and 9. Subjective sleepiness ratings at each evaluation were reduced from baseline in all 3 groups. At baseline, 3% of the modafinil 400 mg group, 4% of the modafinil 200 mg group, and 3% of the placebo group were able to remain awake for at least 3 Maintenance of Wakefulness Tests (MWTs). At week 9, the percentage of subjects able to stay awake for at least 3 tests significantly increased to 20% for the modafinil 400 mg group and 14% 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 versus placebo in 157 patients with OSA-related daytime sleepiness despite CPAP for a total of 4 weeks.²⁷² Patients were randomized to receive modafinil (n=77) at an initial dose of 200 mg per day during week 1, then increasing over 3 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 1 and 4 ($p<0.001$), but not significantly different from placebo in MSLT at week 4 ($p<0.05$). The percentage of patients with normalized daytime sleepiness (ESS <10) was significantly higher with modafinil (51%) than with placebo (27%; $p<0.01$). There was no difference between groups in the percentage of patients with normalized MSLT (25 to 29%).

armodafinil (Nuvigil) versus placebo – OSAHS

The effectiveness of armodafinil in improving wakefulness in patients with excessive sleepiness associated with OSAHS was established in two 12-week studies of outpatients who met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are also consistent with the American Psychiatric Association DSM-IV criteria).²⁷³ In addition, all patients had excessive sleepiness per the ESS, despite treatment with continuous positive airway pressure (CPAP). In the first study, a total of 395 patients with OSAHS were randomized to receive armodafinil 150 mg/day, armodafinil 250 mg/day, or matching placebo every day for 12 weeks. In the second study, 263 patients with OSAHS were randomized to either armodafinil 150 mg/day or placebo. In both studies, patients treated with armodafinil showed improved wakefulness and overall clinical condition.

A 12-week, randomized, double-blind study evaluated armodafinil 150 mg/day compared to placebo as an adjunct treatment for residual excessive sleepiness in 259 patients with OSAHS who were otherwise well controlled with nCPAP.²⁷⁴ The authors assessed the ability of armodafinil to improve wakefulness and cognition and reduce fatigue in this population. Efficacy assessments were done at baseline and weeks 4, 8, and 12. At the final visit, mean Maintenance of Wakefulness Test (MWT) sleep latency increased from baseline with armodafinil and decreased in the placebo group ($p=0.0003$). Armodafinil improved Clinical Global Impression of Change compared to placebo ($p=0.0069$). Armodafinil significantly improved episodic secondary memory ($p=0.0102$) and patient-estimated wakefulness ($p<0.01$) and reduced fatigue ($p<0.05$) compared with placebo. Armodafinil did not adversely affect nCPAP use. The most common adverse event associated with armodafinil was headache.

armodafinil (Nuvigil) versus placebo – narcolepsy

Patients with excessive sleepiness, as documented by a mean sleep latency test (MSLT) with a sleep latency of 6 minutes or less and the absence of any other clinically significant active medical or psychiatric disorder, were enrolled in a 12-week study of outpatients who met the ICSD criteria for narcolepsy.²⁷⁵ A total of 196 patients were randomized to receive armodafinil 150 or 250 mg/day or matching placebo. Patients treated with armodafinil showed improved wakefulness and overall clinical condition.

armodafinil (Nuvigil) versus placebo – SWSD

The effectiveness of armodafinil in patients with excessive sleepiness associated with SWSD was demonstrated in a 12-week double-blind, placebo-controlled, parallel-group clinical trial. A total of 254 patients with chronic SWSD of moderate or greater severity were randomized to receive armodafinil 150 mg/day or placebo.^{276,277} Patients treated with armodafinil showed a statistically significant prolongation in the time to sleep onset, as measured by the nighttime MSLT at final visit (armodafinil MSLT at baseline=2.3, week 12=5.3; placebo at baseline=2.4, week 12=2.8; $p<0.001$), and improvement in overall clinical condition ratings were seen for armodafinil (79%) compared to placebo-treated patients (59%; $p=0.001$).

Binge Eating Disorder

lisdexamfetamine dimesylate (Vyvanse) versus placebo

The effectiveness of lisdexamfetamine dimesylate in patients with moderate to severe binge eating disorder (BED) was demonstrated in two 12-week double-blind, placebo-controlled, parallel-group clinical trials.²⁷⁸ A total of 724 patients aged 18 to 55 years who met DSV-IV criteria for BED were randomized to receive lisdexamfetamine dimesylate or placebo. The severity of BED was determined based on the patient having at least 3 binge days per week for 2 weeks prior to their baseline visit and on the patient having a Clinical Global Impression Severity (CGI-S) score of ≥ 4 at the baseline visit. The primary efficacy outcome for each study was the change from baseline at week 12 in the number of binge days per week. Each study consisted of a 4-week dose-optimization phase, followed by an 8-week dose-maintenance phase. In the dose-optimization phase, patients assigned to lisdexamfetamine dimesylate began treatment at 30 mg/day and titrated to either 50 mg/day or 70 mg/day, as tolerated. In both trials, patients treated with lisdexamfetamine dimesylate showed a statistically significant reduction from baseline in mean number of binge days per week compared to placebo (Trial 1: -3.87 versus -2.51, respectively; Trial 2: -3.92 versus -2.26, respectively; $p<0.001$ for both).

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.^{279,280,281,282,283} Research to date has not shown clear advantages of 1 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 1 medication will have a positive response to an alternative stimulant.²⁸⁴

A meta-analysis of 29 randomized, double-blind, placebo-controlled studies involving over 4,465 children (mean age 10 years) with ADHD showed that MPH and MAS are significantly more effective than non-stimulant medications used to treat ADHD (atomoxetine, bupropion, desipramine, and modafinil).²⁸⁵ Among stimulants, the meta-analysis found no difference in efficacy among MAS and MPH or among immediate-release or extended-release agents. The manufacturer of mixed amphetamine salts ER (Adderall XR) and MPH transdermal patch (Daytrana) funded this meta-analysis.

SUMMARY

The 2011 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. The guidelines state that, in many cases, the stimulants improve the child's ability to follow rules and decrease emotional overactivity, leading to improved relationships.

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.

Several medications have been shown to be effective in treating ADHD. Except for atomoxetine (Strattera), clonidine ER (Kapvay), and guanfacine ER (Intuniv), all of the drugs approved for treatment of ADHD by the FDA are stimulants and are classified as controlled substances. 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 comorbidities (e.g., coexistent tic disorders or Tourette's syndrome).

For school-age children, the once daily dosage forms of MPH enhance compliance and decrease the risk of diversion. Quillivant XR, an extended-release MPH suspension, and QuilliChew ER, an extended-release chewable tablet, are options for those patients who cannot swallow tablets or capsules and have failed treatment with other long-acting products that can be opened over applesauce. Amphetamine sulfate (Evekeo), mixed amphetamine salts (Adderall, Adderall XR), orally disintegrating extended-release amphetamine (Adzenys XR-ODT), and amphetamine extended-release suspension (Dyanavel XR) provide alternatives for patients who cannot tolerate MPH. Clinical trials of dextroamphetamine (Dexedrine, Zenzedi, ProCentra) are generally of poor quality and are somewhat dated. Additionally, dextroamphetamine has a greater potential for diversion and misuse than the other drugs used for ADHD. 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, 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. Lisdexamfetamine dimesylate (Vyvanse) is also the first and only FDA-approved treatment for moderate to severe binge eating disorder in adults.

Atomoxetine, clonidine ER, and guanfacine ER are non-stimulants that should not be addictive and are not scheduled drugs. However, atomoxetine has some of the same adverse effects as the stimulants, including increased heart rate, blood pressure, and potential growth retardation. Children treated with atomoxetine have also exhibited modest decreases in weight from baseline. Atomoxetine may be a useful agent in patients with a comorbid diagnosis, such as anxiety and tic disorders. Clonidine ER and guanfacine ER also have cardiac adverse events as well as sedative properties. None of these products have shown increased effectiveness relative to other drugs in this class in comparative trials.

Modafinil (Provigil) and armodafinil (Nuvigil) may provide a slightly different profile of adverse effects than the stimulant medications traditionally used for the treatment of narcolepsy. Methamphetamine (Desoxyn) and amphetamine sulfate (Evekeo) are FDA-approved in adults for short-term adjunctive

therapy in a weight reduction regimen based on caloric restriction for patients in whom obesity is refractory to alternative therapy.

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