Stimulants and Related Agents Review

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Stimulants and Related Agents Review

Overview

Stimulants are used to treat several disorders of attention, including those due to lack of appropriate sleep or motivation, medication side effects, psychiatric disorders and cognitive disorders.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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

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

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

Studies have shown that 70 to 75 percent of patients respond to the first stimulant medication on which they are started.[19] This number increases to 90 to 95 percent when a second stimulant is tried. Treatment failures with stimulants are often due to improper doses rather than ineffectiveness of the medication. It may take one to three months to adequately establish the best dose and form of medication for any given patient.

The American Academy of Pediatrics (AAP) recommends that, if one or two stimulants are ineffective or poorly tolerated, a third stimulant might be tried prior to initiation of a second line treatment. The AAP also recommends the use of behavior therapy in addition to stimulants.[20] Evidence indicates that behavioral or cognitive therapy alone is not as effective as when these treatment strategies are used concomitantly with the stimulants.[21] There remains some question, however, as to whether these non-pharmacological treatments may be just as effective in patients with less severe disease and/or medication-naive patients.[22]

Clinical trials have identified several medications that may be used as alone as second-line treatment or in combination with first-line agents depending upon the ADHD type or comorbidity profile. Tricyclic antidepressants have been shown to be effective as monotherapy for ADHD, but

their use is limited by their adverse event profile. Alpha-2 agonists (e.g., clonidine) may be especially useful in patients with predominant hyperactivity or impulsivity. Bupropion is effective for patients (over eight years of age) with comorbid depression. Risperidone (Risperdal®) may be used for patients with overly aggressive behavior.

The stimulants most commonly used to enhance attention in ADHD are amphetamines and methylphenidate (MPH). Although effective, methamphetamine is not routinely used due to its potential for abuse. Atomoxetine, a non-stimulant medication, is also approved for the treatment of ADHD.

HYPRESOMNOLENCE

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

While CPAP has been shown to improve daytime sleepiness in patients with OSA, the level of sleepiness does not always normalize.[23,24,25,26,27,28] To address this residual daytime sleepiness, pharmacologic treatments may be beneficial in users of CPAP. While CNS stimulants, such as dextroamphetamine, have been used for this purpose, the potential for adverse cardiovascular events may be of concern, especially in this overall high-risk patient population.[29] Due to its lack of sympathomimetic activity, modafinil is relatively free of adverse cardiovascular effects and may be preferable to the stimulants for the treatment of excessive daytime sleepiness resulting from OSA.[30]

Pharmacology

Stimulants act by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space. Amphetamines appear to release newly synthesized dopamine while MPH causes the release of stored dopamine.[31] 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, has much less of an effect on norepinephrine release than the l-enantiomer. Thus, the combination of the two isomers of amphetamine may provide additional benefit over dextroamphetamine in some patients. This combination is available as mixed amphetamine salts (MAS), which contains d- and l-amphetamine in a 3:1 ratio. Mixed amphetamine salts tends to have fewer adrenergic side effects than MPH. Methylphenidate is a racemic mixture of d- and l-enantiomers, the former of which is more pharmacologically active.[32,33] A product containing only the d-enantiomer, dexmethylphenidate (d-MPH, Focalin™, Focalin XR), is available.

Compared to short-acting dosage forms, extended-release preparations and longer acting stimulants offer the advantages of less fluctuation in effect and removal of the need for dose administration in school. Their prolonged action, however, may be less intense and their use forfeits the advantages of flexibility and control of titrating that more frequent doses allow.[34] It is also important that longer-acting dosage forms do not produce a flat plasma concentration of stimulant that could lead to acute tolerance.[35] There is increased experience with combining slow release and fast acting preparations to produce optimal symptom control throughout the day.

Atomoxetine (Strattera®) is a selective inhibitor of the presynaptic norepinephrine transporter. It increases norepinephrine and dopamine levels, especially in the prefrontal cortex.[36] It has minimal affinity for other monoamine transporters. This mechanism of action suggests that atomoxetine is unlikely to have abuse potential or to cause motor tics.[37,38] Atomoxetine has a slower onset of action than do 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 after once daily dosing with the possibility of symptom relief during the evening and early-morning hours.[39]

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.

FDA-Approved Indications

Drug	Manufacturer	ADHD		Narcolepsy (age ≥6 years)	Exogenous Obesity (in adults)	Excessive sleepiness associated with narcolepsy, OSA/HS and SWSD (age ≥16 years)
		age 3-5 years	age ≥6 years			
Stimulants						
dextroamphetamine IR	generic	X	X	X		
dextroamphetamine ER	generic		X	X		
methamphetamine (Desoxyn®)	Ovation		X		X	
mixed amphetamine salts IR	generic	X	X	X		
mixed amphetamine salts ER (Adderall XR®)	Shire		X			
methylphenidate IR	generic		X	X		
methylphenidate SR	generic		X	X		
methylphenidate ER (Concerta®)	McNeil		X			
methylphenidate ER (Metadate® CD)	UCB		X			
methylphenidate ER (Ritalin LA®)	Novartis		X			
methylphenidate transdermal (Daytrana™)	Shire		X			
dexmethylphenidate IR (Focalin)	Novartis		X			
dexmethylphenidate ER (Focalin XR™)	Novartis		X			
Non-Stimulants						
atomoxetine (Strattera)	Eli Lilly		X			
modafinil (Provigil)	Cephalon					X

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

Pharmacokinetics

Drug	Time(s) to Peak Concentration(s) (hours)	Onset of Action (minutes)	Half-Life (mean, in hours)	Duration of Action (hours)	Extended-Release Delivery System (where applicable)
Stimulants					
dextroamphetamine IR[40]	2-3	20-60	children: 6-8 adults: 10-12	4-6	--
dextroamphetamine ER[41]	8-10	60-90		6-10	initial dose delivered immediately with remaining medication released over 6-8 hours
methamphetamine (Desoxyn)[42]	--		4-5		--
mixed amphetamine salts IR[43]	3	30-60	children: 9-11 adults: 10-13	4-8	--
mixed amphetamine salts ER (Adderall XR)[44]	7*	30-60		8-10	50% each of immediate- and delayed-release beads
methylphenidate IR[45,46]	1.5-3	20-30	2-4	3-6	--
methylphenidate SR[47,48,49,50]	1.5-4.7	30-180		3-8	various
methylphenidate ER (Concerta)[51,52]	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)[53]	1-1.5, then 4-4.5	30-90	6.8	7-12	30% IR, 70% ER beads
methylphenidate ER (Ritalin LA)[54]	1-3, then 4-8	30-110	2.5-3.5	7-12	50% dose IR beads, 50% dose enteric–coated, delayed release beads
methylphenidate transdermal (Daytrana)[55]	7-10.5	120	3-4	approximately 3 hours after patch removal	concentrated drug cells in patch
dexmethylphenidate (Focalin)[56]	1-1.5	30	2.2	3-6	--
dexmethylphenidate (Focalin XR)[57]	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
Non-Stimulants					
atomoxetine (Strattera)[58]	1-2	slow	5.2	~24	--
modafinil (Provigil)[59]	2-4		15		--

* Food prolongs the Tmax of mixed amphetamine salts ER by 2.5 hours

The half-life of amphetamine is directly related to urinary pH, increasing with higher pH and decreasing with lower pH. For every unit increase in pH, the half-life of mixed amphetamine salts increases by an average of seven hours.

Except for MAS, the stimulants are de-esterified in the liver to pharmacologically inactive metabolites. In contrast, MAS are metabolized in the liver by hydroxylation, dealkylation and deamination. Urinary excretion accounts for nearly all of the elimination of the stimulants and atomoxetine, as well as their metabolites.

Atomoxetine is metabolized in most patients primarily by the CYP2D6 enzymatic pathway. Medications that inhibit this enzyme system (such as paroxetine) increase the bioavailability of atomoxetine. Atomoxetine does not appear to induce or inhibit the CYP2D6 enzyme system.[60] Approximately five to ten percent of patients are "slow metabolizers" in which the mean half-life of atomoxetine is 21.6 hours, over four times longer than in "rapid metabolizers."[61] These differences do not require a change in dose or dose schedule, nor does it change the drug's side effect profile.[62]

Concerta and Focalin XR have similar pharmacodynamic profiles, with the main difference being that the latter contains only d-MPH. Similarly, the release profiles of Metadate CD and Ritalin LA are very similar to each other.

As a result of the shorter half-life of the amphetamines in children, they have, at an equivalent weight based dose, approximately 30 percent less systemic exposure when compared to adults.

When opened and sprinkled on cold applesauce, the bioequivalence of Metadate CD, Ritalin LA, dexmethylphenidate ER and mixed amphetamine salts ER are the same as the intact capsules. Dextroamphetamine SR capsules can also be opened and sprinkled on food.

Atomoxetine has a slower onset of action than the stimulants; the onset of effect may take one week and full effect may not be seen for up to four weeks.[63,64] The effects of atomoxetine appear to last longer than would be expected from its pharmacokinetic profile.[65] 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 transported.

Clinical Trials

A search of PubMed and the IFPMA Clinical Trials Portal was conducted for English language randomized clinical trials in humans directly comparing two or more drugs in this class. Additionally, clinical data were requested from pharmaceutical manufacturers of drugs in this class. All clinical data were evaluated for bias, validity and relevance to the patient population being studied. In cases where there was insufficient data from active-control studies, placebo-controlled studies meeting the criteria were included. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers. While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

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

stimulants available at that time in treating the symptoms of ADHD. These studies have been discussed in numerous review articles to which the reader is referred for further information.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Rating Scales

Specific

- Conners' Parent Rating Scale (CPRS) – This scale provides the parents' or caregivers' perspective on a child's behavior. This scale is 92 percent sensitive and 94 percent specific.

- Swanson, Nolan and Pelham scale (SNAP) – This scale has been shown to have greater than 94 percent sensitivity and specificity in distinguishing hyperactive, inattentive and impulsive children with ADHD from those without ADHD based on DSM-III-R criteria.

- ADHD Rating Scale-IV (ADHD RS) – This scale, which can be completed by a parent, teacher or clinician, is less effective than the SNAP in differentiating children with ADHD from those without ADHD. It has been shown to have good internal consistency and test-retest reliability. The parent form is 84 percent sensitive and 49 percent specific; the teacher form is 72 percent sensitive and 86 percent specific.

Global

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

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

CLINICAL TRIALS

atomoxetine (Strattera) and MPH IR

Two identical 12-week double-blind trials were conducted in 291 children (ages seven to 13 years) with ADHD.[66] 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.[67]

atomoxetine (Strattera) and MPH OROS (Concerta)

An unpublished, placebo-controlled study compared atomoxetine with MPH OROS during acute treatment for six weeks.[68] A total of 516 children ages six to 16 years with ADHD were randomized in double-blind fashion to atomoxetine, MPH OROS or placebo. Patients who had previously had an inadequate response to stimulant treatment were excluded from the study. Response (≥40 percent reduction in ADHD RS from baseline) occurred in 56 percent of MPH patients, 45 percent of atomoxetine patients and 24 percent of placebo patients. The response

rates for both active treatments were significantly higher than placebo; the response rate for MPH OROS was significantly higher than atomoxetine (p=0.016).

d-MPH (Focalin), MPH IR and placebo

In a randomized, double-blind study, 132 subjects received d-MPH, MPH or placebo twice daily for four weeks, with titration of the dose based on weekly clinic visits.[69] The primary efficacy variable was change from baseline of Teacher SNAP to last study visit. Secondary efficacy measures included the change on Parent SNAP, CGI-I and Math Test performance. Treatment with either d-MPH (p=0.0004) or MPH IR (p=0.0042) significantly improved Teacher SNAP ratings compared with placebo. The d-MPH group showed significant improvements compared with placebo on the afternoon Parent SNAP (p=0.0003) and on the Math Test scores obtained at 6:00 p.m. (p=0.0236). Improvement based on CGI-I occurred in 67 percent of patients on d-MPH and 49 percent of patients on MPH IR. Both active treatments were well tolerated.

MPH IR, MPH OROS (Concerta) and placebo

In a multicenter, double-blind trial, 282 children (ages six to 12 years) with ADHD were randomized to receive MPH IR 5, 10 or 15 mg three times daily, MPH OROS 18, 36 or 54 mg once daily or placebo for 28 days.[70] Response, defined as >30 percent reduction from baseline IOWA Conners Oppositional/Defiance (O/D) score, occurred in 52, 59 and 26 percent of patients in the MPH IR, MPH OROS and placebo groups, respectively, as rated by parents (p<0.0001 for comparison of both active treatments to placebo). Teacher-rated response rates were 63, 68 and 43 percent, respectively (p<0.0107 for comparison of active treatments to placebo). The response rate for the two higher doses of MPH OROS (77 percent) was significantly higher than for MPH IR based on parent ratings (p<0.05). Forty-eight percent of the placebo group discontinued study drug early compared with 14 percent and 16 percent in the MPH and OROS MPH groups, respectively.

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

In a double-blind study, 270 children (ages six to 12 years) with ADHD were randomized to one of three treatment arms: MPH OROS + placebo patch, MPH transdermal + placebo capsule or placebo capsule + placebo patch.[71] This study consisted of a five-week dose-optimization phase followed by a two-week maintenance phase. At the conclusion of the study, the mean daily doses were 43.4 and 22.9 mg for the oral and transdermal dosage forms, respectively. The primary endpoint was the change in ADHD RS from baseline. A reduction in ADHD RS of at least 30 percent was observed in 66, 78 and 29 percent of patients receiving MPH OROS, MPH transdermal and placebo, respectively (p=NS for comparison of active treatments; p<0.05 for comparison of each active treatment to placebo). Reductions from baseline in both the hyperactivity/impulsivity and the inattentiveness subscales were similar in both active treatment groups and were significantly greater than in the placebo group. The manufacturers of MPH transdermal funded this study.

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.[72] This scale has a high level of internal consistency.[73]

- Maintenance of Wakefulness Test (MWT) – In this test, the subject sits in bed, resting against pillows, in a quite dimly lit room, attempting to stay awake for 20 (or 40) minutes while under scrutiny and with electrodes and wires attached.[74]

- Multiple Sleep Latency Test (MSLT) – This 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.[75] This test is considered by many to be the gold standard for measuring daytime sleepiness, although analysis has recently shown it to be the least accurate of the three tests.[76,77]

modafinil (Provigil) and placebo - narcolepsy

A total of 285 subjects between the ages of 18 to 68 years with a diagnosis of narcolepsy were enrolled in a randomized trial to receive modafinil 200 mg, modafinil 400 mg or placebo once daily for nine weeks.[78] The mean ESS score was significantly lower for each modafinil treatment group compared to placebo at weeks three, six and nine. Subjective sleepiness ratings at each evaluation were reduced from baseline in all three groups. At baseline, three percent of the modafinil 400 mg group, four percent of the modafinil 200 mg group and three percent in the placebo group were able to remain awake for at least three MWTs. At week nine, the percentage of subjects able to stay awake for at least three tests significantly increased to 20 percent for the modafinil 400 mg group and 14 percent of 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) and placebo – OSA related daytime sleepiness

In a double-blind, parallel group study, investigators randomized 157 patients with OSA-related daytime sleepiness despite CPAP to receive modafinil or placebo once daily for four weeks.[79] Modafinil significantly improved daytime sleepiness, with significantly greater mean changes from baseline in ESS scores at weeks one and four ($p<0.001$) and in MSLT at week four ($p<0.05$). The percentage of patients with normalized daytime sleepiness (ESS <10) was significantly higher with modafinil (51 percent) than with placebo (27 percent; $p<0.01$). There was no difference between groups in the percentage of patients with normalized MSLT (25 to 29 percent).

Pediatrics

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

Children under three years of age – Numerous studies indicate that stimulants are effective in the treatment of ADHD in preschoolers.[80,81] There is concern on the part of some, however, that the use of neuropsychiatric drugs in children in this age group could have long term effects on neurotransmitters in the brain.[82] The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines recommend initial parent training and a structured preschool setting that may progress to low dose medication with frequent monitoring. Behavior modification therapy may be useful if implemented consistently. The AACAP suggests medication use only in the

most severe cases, or where parent training/school placement are unavailable or unsuccessful. If medications are used, the AACAP suggests daily treatment without weekend holidays.

Children under six years of age - Although not indicated for children under six years of age, six small controlled studies have reported on the use of MPH in 187 children (ages 1.8 to 5.9 years) with ADHD. In these trials, doses ranged from 0.15 mg/kg twice daily up to 0.6 mg/kg three times daily.[83,84,85,86,87] Other studies have not used weight-based dosing, with total doses ranging from 2.5 to 30 mg/day.[88] In general, only MPH IR should be used in children less than six years with children under 25 kg receiving no more than 45 mg/day. The National Institute of Mental Health's ongoing Preschool ADHD Treatment Study (PATS) is expected to provide clinical guidance for children with ADHD three to five years of age. In this study, the initial dose of MPH IR is 1.25 mg three times daily.

Special Populations

Pregnancy - All of the agents in this Therapeutic Drug Class are FDA pregnancy risk category C.

Bipolar disorder – ADHD coexists with bipolar disorder in 29 to 98 percent of pediatric patients with this mood disorder. For children and adolescents with ADHD and bipolar disorder, mixed amphetamine salts has been shown to be effective after mood stabilization with divalproex.[89] Stimulants and atomoxetine should be used with caution in patients with bipolar disorder as they may induce mixed/manic episodes.

Oppositional Defiant Disorder (ODD) - In a preliminary report of a phase III, randomized, double-blind, placebo-controlled study, mixed amphetamine salts ER has also been shown to be efficacious and safe for the short-term treatment of children and adolescents with ODD.[90]

Autism - Recent studies have shown that at least some stimulants may be effective for treating autistic children with symptoms of hyperactivity.[91] In a pilot crossover study of 16 children, ages five to 15 years, with autism spectrum disorders, atomoxetine was superior to placebo in terms of the primary endpoint, effect on the Hyperactivity subscale of the Aberrant Behavior Checklist ($p=0.043$).[92] Nine patients responded to atomoxetine, while four responded to placebo.

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

Multiple Sclerosis (MS) – Modafinil was shown in a single blind, uncontrolled study to reduce fatigue in patients with MS.[93]

Cerebral Palsy (CP) – Data from a retrospective review indicate that modafinil may improve tone and ambulation in spastic diplegic CP.[94] In this study, 29 of 59 pediatric patients given modafinil for CP, were noted to have an improving gait on modafinil. By contrast, only three of 61 patients who did not receive modafinil showed such improvement.

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

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

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

Warnings/Contraindications

WARNINGS

Stimulants have boxed warnings regarding their 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. Patients should be carefully supervised during withdrawal from MPH and d-MPH as it may result in depression and/or unmasking of symptoms.

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

Stimulants should be used with caution in patients with pre-existing psychosis, bipolar disorder or aggression as these conditions may be exacerbated. Treatment emergent psychotic or manic symptoms have been reported in 0.1 percent of patients receiving stimulants and 0.2 percent of patients receiving atomoxetine.

Stimulants may cause long-term suppression of growth.

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

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

Atomoxetine has a warning regarding severe liver injury; rare, but marked, elevations of hepatic enzymes and bilirubin have been reported. In two case reports, liver injury resolved after discontinuation of atomoxetine (with concomitant immunosuppressive therapy in one case).[95]

CONTRAINDICATIONS

The stimulants and atomoxetine are contraindicated during or within 14 days following administration of an MAO inhibitor (MAOI). These drugs are also contraindicated in patients with glaucoma.

Stimulants are contraindicated in agitated patients.

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

Methylphenidate and dexmethylphenidate are contraindicated in patients with anxiety, tension, tics or a diagnosis or family history of Tourette's syndrome.

Drug Interactions

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

Effects can be additive when stimulants are used concurrently with other psychostimulants or with sympathomimetics.[96,97,98] Due to the potential for excessive CNS or cardiovascular stimulation, such combinations should be used with caution, if at all.[99] In general, the concurrent use of MPH with amphetamines is not recommended.[100] Since there are no clinical data regarding the concurrent use of MPH and atomoxetine, concurrent use should be avoided.[101]

The use of modafinil with other psychostimulants has not been extensively studied and concurrent use is not recommended. Coadministration of amphetamine and modafinil may increase stimulant-associated side effects.[102,103] Single-dose studies of MPH combined with modafinil showed that the rate of absorption of modafinil was delayed up to one hour in the presence of MPH. No changes occurred in the metabolism and extent of absorption of either medication.

Amphetamine may stimulate the release of serotonin in the CNS and thus may interact with other serotonergic agents, such as the serotonin-receptor agonists. These interactions could lead to serotonin excess and, potentially, the 'serotonin syndrome'.[104] Melatonin may exacerbate the monoaminergic effects of amphetamine-related medications. Coadministration of melatonin with methamphetamine in animal studies resulted in increased dopaminergic and serotonergic stimulation.[105]

Like the MAOIs, stimulants and atomoxetine potentiate the effects of catecholamine neurotransmitters.[106] Monoamine oxidase inhibitors or drugs that possess MAO-inhibiting activity, such as procarbazine, can prolong and intensify the cardiac stimulation and vasopressor effects of the stimulants. Stimulants and atomoxetine should not be administered during or within 14 days following the use of MAOIs or drugs with MAO-inhibiting activity.[107,108,109] Selegiline, an inhibitor of MAO type B, may also predispose to this reaction and should be avoided in patients receiving stimulants or atomoxetine.[110]

Modafinil has not been evaluated for drug interactions with MAOIs, including drugs with MAO-inhibiting activity (such as procarbazine).[111] Until more is known regarding the pharmacology of modafinil, it may be prudent to caution against the use of modafinil in the presence of a MAOI. Lithium may antagonize the central simulating effects of amphetamines and should be avoided.[112,113] 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.[114,115] Haloperidol and chlorpromazine also inhibit the central stimulant effects of the amphetamines.

Serious adverse events have been reported during concomitant use of MPH and clonidine; no causality has been established.

Adverse Drug Reactions

For the most part, side effects of stimulant medication are dose-dependent, mild to moderate in severity, and diminish with alteration of medication dose or timing.[116] They commonly subside spontaneously during the first one to two weeks of treatment.[117] 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.[118,119]

In a double-blind study, investigators found that, based on parent assessment, only two side effects were more prevalent after initiation of stimulants than before the start of treatment – insomnia (dextroamphetamine) and poor appetite (dextroamphetamine and MPH).[120] These investigators also found that the severity of several side effects (insomnia, irritability, crying, anxiousness, sadness/unhappiness, and nightmares) was higher on dextroamphetamine than on MPH; there were no side effects with higher severity on MPH than on dextroamphetamine.

The American Academy of Pediatrics has released a policy statement that states that side effects of stimulant medications are usually "mild and short lived" and that there is "no significant impairment of height attained" in adult life. These guidelines state that stimulants used for ADHD do not require routine "serologic, hematologic or electrocardiogram monitoring."[121]

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

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

In general, a review of the evidence shows no statistically significant differences in the incidence of adverse effects between immediate-release and modified-release formulation. There is no evidence to support statistically significant differences with respect to adverse effects of dextroamphetamine and MPH.

The following table includes those adverse drug reactions most commonly reported with the drugs in this class when used in children. The rate of each adverse reaction is indicated in percentage of occurrence for the drug.

Drug	Headache	Abdominal pain	Anorexia	Insomnia
Stimulants				
dexmethylphenidate (Focalin)[122]	--	15	6	--
dexmethylphenidate (Focalin XR)[123]	25	--	*	*
dextroamphetamine[124]	*	--	*	*
methamphetamine (Desoxyn)	*	--	--	*
methylphenidate ER (Concerta)[125]	14	7	4	4
methylphenidate ER (Metadate CD)[126]	12	7	9	5
methylphenidate ER (Ritalin LA)[127]	>5	>5	>5	>5
methylphenidate IR and ER (Methylin ER, Ritalin-SR)[128,129]	*	*	*	*
methylphenidate transdermal (Daytrana)[130]	--	--	5	13
mixed salt amphetamines IR[131]	*	--	*	*
mixed salt amphetamines (Adderall XR)[132]	*	14	22	17
Non-Stimulants				
atomoxetine (Strattera)[133]	27	20	14	2
modafinil (Provigil)[134]	34	1	4	5

*reported

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

The majority of patients in the pivotal phase III clinical trial of MPH transdermal had minimal to definite erythema. This erythema general caused little, if any, discomfort and did not usually result in discontinuation from treatment.

Stimulants can cause unpredictable effects on motor tics, which transiently occur in 15 to 30 percent of children taking them. Tics may appear in some patients when they are on stimulant medication and disappear with discontinuation of the medication. Rare patients may appear to develop Tourettes disorder when on stimulants; however, in actuality, 50 percent of patients with Tourettes Disorder also have ADHD which may present two to three years before the tics appear. It is believed that stimulants do not cause Tourettes (an inherited disorder), but simply unmask the disorder. Motor and verbal tics have not been associated with atomoxetine.[135]

Cardiovascular side effects of atomoxetine occurring in clinical trials at a rate greater than placebo include increased systolic blood pressure (2.0 mm Hg increase vs. 0.7 mm Hg

decrease), increased heart rate (6.8 bpm increase vs. 1.2 bpm decrease) and weight loss (0.9 kg loss vs. 0.8 kg gain).[136] In a meta-analysis of 13 studies that included 272 children, ages six to seven years, 24 months of treatment with atomoxetine resulted in statistically significant increases in pulse and blood pressure, as well as decreases in cardiac PR interval; these changes were deemed by the investigators not to be clinically significant.[137]

Effects on Growth

The American Academy of Pediatrics Clinical Practice Guideline for the School Aged Child with ADHD acknowledges that appetite suppression and weight loss are common side effects of stimulants but that studies of stimulant use have found little or no decrease in expected height, with any decrease in growth early in treatment compensated for later on.[138] A temporary slowing in growth rate (2 cm less growth in height and 2.7 kg less growth in weight over three years) has been noted in children starting treatment with MPH at ages seven through 10 years.

With stimulants, delayed growth may be a concern through mid-adolescent 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.[139]

Dosages

ADHD

Drug	Ages	Usual Initial Dosage	Maximum Dosage	Dosage Forms
Stimulants				
dextroamphetamine IR	3-5 years	2.5 mg once daily	0.5 mg/kg/day in 2-3 divided doses	Tablets: 5, 10 mg
	≥6 years	5 mg two or three times daily	40 mg/day in 2-3 divided doses	
dextroamphetamine ER	5-11 years	Total daily IR dosage given once daily	45 mg once daily	Capsules: 5, 10, 15 mg
	≥6 years	Total daily IR dosage given once daily	60 mg once daily	
methamphetamine (Desoxyn)	≥6 years	5 mg once or twice daily	20-25 mg/day in two divided doses	Tablets: 5 mg SR Tablets: 5, 10 mg
mixed amphetamine salts IR	3-5 years	2.5 mg once daily	40 mg/day in 2-3 divided doses	Tablets: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	≥6 years	5 mg two or three times daily		
mixed amphetamine salts ER (Adderall XR)	6-17 years	5-10 mg once daily	30 mg once daily	Capsules: 5, 10, 15, 20, 25, 30 mg
	≥18 years	20 mg once daily	20 mg once daily	
methylphenidate IR	≥6 years	5 mg twice daily	60 mg/day in 2-3 divided doses	Tablets: 5, 10, 20 mg Chewable tablets: 2.5, 5, 10 mg Oral solution: 5 mg/5 ml, 10 mg/5 ml
methylphenidate ER	≥6 years	20-60 mg/day in 1-2 divided doses	60 mg/day in 1-2 divided doses	Tablets: 10, 20 mg
methylphenidate ER (Concerta)	6-12 years	18 mg once daily	54 mg once daily	Tablets: 18, 27, 36, 54 mg
	13-17 years	18 mg once daily	72 mg once daily (≤2 mg/kg/day)	
methylphenidate ER (Metadate CD)	≥6 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40, 50, 60 mg
methylphenidate ER (Ritalin LA)	≥6 years	20 mg once daily	60 mg once daily	Capsules: 10, 20, 30, 40 mg
methylphenidate transdermal (Daytrana)[140]	≥6 years	10 mg patch worn 9 hours daily	30 mg patch worn 9 hours daily	Patches: 10, 15, 20, 30 mg per 9 hours
dexmethylphenidate (Focalin)[141,142]	≥6 years	2.5 mg twice daily	10 mg twice daily	Tablets: 2.5, 5, 10 mg
dexmethylphenidate ER (Focalin XR)[143]	6-17 years	5 mg once daily	20 mg once daily	Capsules: 5, 10, 15, 20 mg
	≥18 years	10 mg once daily		
Non-Stimulants				
atomoxetine (Strattera)[144]	≥6 years and ≤70 kg	0.5 mg/kg/day in 1-2 divided doses	1.2 mg/kg/day in 1-2 divided doses	Capsules: 10, 18, 25, 40, 60, 80, 100 mg
	≥6 years and ≥70 kg	40 mg/day in 1-2 divided doses	100 mg/day given in 1-2 divided doses	

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

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

For patients with moderate (Child-Pugh Class B) hepatic insufficiency, the initial and target doses of atomoxetine should be reduced by 50 percent. For patients with severe (Child-Pugh Class C) hepatic insufficiency, the initial and target doses should be reduced by 75 percent. For patients taking strong CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine), the daily dose of atomoxetine should not exceed 80 mg.[145]

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

HYPERSOMNOLENCE

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

Methylphenidate – the dosages for the treatment narcolepsy are the same as those for ADHD.

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

OBESITY

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

Summary

Several medications have been shown to be effective in treating ADHD. While there are differences between the stimulants and the non-stimulant, as well as among the various stimulants, the effectiveness of all of these agents is related to attenuation, either direct or indirect, of dopamine and norepinephrine transmission.[146]

The American Academy of Pediatrics Clinical Practice Guideline for the School Aged Child with ADHD recommends stimulant medication and/or behavioral therapy for the treatment of ADHD in children.[147] They state that, in many cases, the stimulants improve the child's ability to follow rules and decrease "emotional overactivity, thereby leading to improved relationships with peers and parents."[148]

Treatment Guidelines from The Medical Letter suggest that treatment of ADHD begin with an oral stimulant, noting that none of these agents has been shown to be more effective than another. This group indicates that short-acting stimulants may be useful in small children to demonstrate effectiveness or in instances where there is not an appropriately low dose of a long-acting agent. The methylphenidate patch is recommended for use when oral administration is problematic. Atomoxetine 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.[149]

Several meta-analyses and reviews support the short-term efficacy of stimulant medications in reducing the core symptoms of ADHD, inattention, hyperactivity and impulsivity.[150,151,152,153,154] Research to date has not shown clear advantages of one stimulant medication over another or between dosage forms of a given agent. In their policy statement, the AAP states that, based on a review and analysis of the clinical evidence, the stimulants are equally effective for this purpose. Many children who fail to respond to one medication will have a positive response to an alternative stimulant.[155]

A meta-analysis of 29 randomized, double-blind, placebo-controlled studies involving over 4,465 children (mean age 10 years) with ADHD showed that the stimulants MPH and MAS are significantly more effective than non-stimulant ADHD medications (atomoxetine, bupropion, desipramine and modafinil) in the treatment of ADHD.[156] Among stimulants, this meta-analysis found no difference in efficacy among MAS and MPH or among immediate-acting or long-acting agents. The manufacturer of MAS ER and MPH transdermal funded this meta-analysis.

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 (i.e., coexistent tic disorders or Tourette's syndrome). 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. In some circumstances, however, limited dosage strengths available in the once-daily dosage forms may make an immediate-release formulation preferable.

The most commonly prescribed stimulant for the treatment of ADHD is MPH. For school-age children, the once daily dosage forms of MPH enhance compliance and decrease the risk of diversion. Mixed amphetamine salts provide an alternative for patients who can not tolerate MPH. Clinical trials of dextroamphetamine are generally of poor quality and are somewhat dated. Additionally, it has a greater potential for diversion and misuse than the other drugs used for ADHD. It is probably less likely, then, to be used as first-line therapy for the majority of children and adolescents with ADHD.

Behavioral therapy helps normalize behavior, which is particularly important for times when stimulants are not active (i.e., later in the day). Behavioral management can help the five to 20 percent of children who do not respond to psychostimulants and may allow for lower medication doses in those patients who are on stimulants.

Atomoxetine is a non-stimulant that should not be addictive and is not a scheduled drug. It may be a useful agent in patients with a co-morbid diagnosis such as anxiety and tic disorders. Atomoxetine has some adverse effects in common with the stimulants, including increased heart rate and blood pressure and potential growth retardation. Children treated with atomoxetine

have also exhibited modest decreases in weight from baseline. Atomoxetine has a boxed warning regarding an increased risk of suicidal ideation in children treated with the drug.

Regardless of the agent used for the treatment of ADHD, careful consideration must be given towards the various warnings and contraindications that these drugs have.

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

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