Drug Class Review

Central Nervous System Stimulants used in the Treatment of Attention Deficit Disorder

28:20.04 Amphetamines
28:20.32 Respiratory and CNS Stimulants

Amphetamine (Adzenys® XR-ODT; Dyanavel® XR; Evekeo®)
Dexmethylphenidate (Focalin®, Focalin® XR)
Dextroamphetamine (Dexedrine®, ProCentra®, Zenzedi®)
Dextroamphetamine-Amphetamine Mixed Salts (Adderall®, Adderall® XR)
Lisdexamfetamine (Vyvanse®)
Methamphetamine (Desoxyn®)
Methylphenidate (Aptensio® XR, Concerta®, Daytrana®, Metadate® CD, Metadate® ER, Methylin®, QuilliChew® ER, Quillivant® XR, Ritalin®, Ritalin® LA)

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Executive Summary

Introduction: The central nervous system (CNS) stimulant agents are indicated in the treatment of attention-Deficit/Hyperactivity Disorder (ADHD) and may also be used in the treatment of exogenous obesity or narcolepsy. All of the CNS stimulants are available in oral capsule or tablet formulations and many of the agents are available in extended-release, orally disintegrating and liquid formulations which may be helpful to improve compliance or patient preference. Clinical guidelines for the treatment of ADHD recommend behavioral therapy for preschool-aged children with ADHD, both medication and behavioral therapy for school-aged children with ADHD and medication therapy alone in adults with ADHD. The stimulant medications have demonstrated efficacy in the treatment of ADHD and are recommended as first-line treatment options in patients requiring medication therapy.

Attention-Deficit/Hyperactivity Disorder is a common mental health disorder diagnosed in childhood which may continue into adulthood. ADHD is characterized by symptoms of hyperactivity, impulsivity and/or inattention. Untreated ADHD may lead to delinquent behavior, substance abuse or other comorbidities. The full pathophysiology of ADHD is not well understood but may be tied to inadequate production of norepinephrine and dopamine in the prefrontal cortex. The stimulants work by increasing the availability of these catecholamines, resulting in reduced symptoms. The stimulants may be divided into three categories based on chemical structure: amphetamine (dextro-amphetamine and levo-amphetamine), methamphetamine and methylphenidate (dextro-methylphenidate and levo-methylphenidate). The isomers of each of the stimulant moieties are combined in varying ratios to increase desired pharmacologic effects and reduce adverse effects.

Clinical Efficacy: Clinical experience with the stimulant agents in treating patients with ADHD is extensive. The majority of comparative evidence evaluated in this report comes from the Oregon Report (369 clinical studies) published in 2009 and 10 additional systematic reviews and clinical trials published after 2009. In general, clinical studies of stimulant medications in the treatment of ADHD are inconsistent and provide limited information with respect to comparative efficacy. Most clinical trials are limited by small sample sizes and short study durations. Based on the available evidence, it appears that all agents are similarly effective for treating ADHD.

Adverse Drug Reactions: The most common adverse events reported with the stimulants include headache, insomnia, increased blood pressure, abdominal pain and decreased appetite. Weight loss and growth suppression are reported with the agents and discontinuing treatment usually results in resumption of normal growth. According to clinical evidence summarized in the Oregon Report, the most serious adverse reaction associated with stimulant therapy is sudden cardiac death which is very rare, estimated at less than one event per 1 million prescriptions. The stimulant agents are Schedule II controlled substances due to high potential for abuse and should be avoided in patients with a history of substance abuse or in patients with high risk of misuse.

Summary: Overall, the CNS stimulant agents are effective treatment options for ADHD. When compared in clinical trials, the agents demonstrate similar rates of safety and efficacy. The stimulants are available in many dosage forms, varying potencies and differing durations of action. Treatment management must be individualized for each patient and include careful evaluation of patient age, comorbidities and medical history.

Introduction

Currently, over 20 different stimulant agents consisting of eight different chemical moieties are available for use in the United States. The eight different chemical moieties include: amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methamphetamine, methylphenidate and modafinil/armodafinil. Modafinil and armodafinil are indicated in the treatment of narcolepsy, obstructive sleep apnea and shift work sleep disorder. With the exception of modafinil and armodafinil, all of the other moieties are indicated in the treatment of attention deficit hyperactivity disorder (ADHD). This report will focus on the safety and efficacy of the stimulant agents indicated in the treatment of ADHD and will not include data on modafinil and armodafinil.

All of the central nervous system (CNS) stimulant agents are available in oral tablet or capsule formulations.[1,2] Methamphetamine is only available in an immediate-release tablet formulation and lisdexamfetamine is only available in an extended- release capsule formulation; all other agents are available in both immediate-release and extended-release formulations. Three stimulant moieties are available in oral solution/suspension formulations: amphetamine, dextroamphetamine and methylphenidate. Amphetamine is available as an orally disintegrating tablet and methylphenidate is available as a chewable tablet and transdermal patch. Four of the stimulants are labeled for use in the treatment of narcolepsy: amphetamine, dextroamphetamine, mixed amphetamine salts and methylphenidate. Two of the stimulants are labeled for use in the treatment of exogenous obesity: amphetamine and methamphetamine. Lisdexamfetamine is labeled for use in the treatment of binge eating. This report will focus on use of the agents in the treatment of ADHD.[3]

Table 1. Comparison of the Central Nervous System Stimulant Agents[1,2]

Agent	Preparations	Labeled Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Amphetamine (Adzenys® XR-ODT; Dyanavel® XR; Evekeo®)	Oral suspension, extended release (Dyanavel XR): 2.5 mg/mL (464 mL) Oral tablet (Evekeo): 5 mg, 10 mg Oral tablet, extended release, dispersible (Adzenys XR-ODT): 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg	Attention-deficit/hyperactivity disorder : Treatment of ADHD Exogenous obesity (IR tablet only): Short-term treatment of exogenous obesity as an adjunct to caloric restriction for patients refractory to alternative therapy Narcolepsy (IR tablet only): Treatment of narcolepsy	ADHD: Adzenys XR-ODT: 12.5 mg once daily. Dyanavel XR: 2.5-5 mg once daily; may increase 2.5-10 mg/day every 4-7 days until optimal response is obtained; max: 20 mg/day **Do not substitute extended-release formulation for other amphetamine products on a mg-per-mg basis since base composition & pharmacokinetic profiles are not similar Exogenous obesity: Evekeo: Up to 30 mg daily in divided doses (5-10 mg per dose) Narcolepsy: Evekeo: 5-60 mg daily in divided doses; titrate in 10 mg increments at weekly intervals until optimal response	ADHD: Adzenys XR-ODT: Children ≥6 years: 6.3 mg once daily; may increase 3.1-6.3 mg/day every week until optimal response (max: 6-12 years 18.8 mg/day) Adolescents: 6.3 mg once daily; may increase 3.1-6.3 mg/day every week until optimal response (max: 12.5 mg/day) Dyanavel XR: Children ≥6 years & Adolescents: Refer to adult dosing Evekeo: Children 3-5 years: 2.5 mg once daily; may increase 2.5 mg/day every week until optimal response Children ≥6 years & Adolescents: 5 mg once or twice daily; may increase 5 mg/day every week until optimal response Exogenous obesity: Evekeo: Children ≥12 years & Adolescents: Up to 30 mg daily in divided doses Narcolepsy: Evekeo: Children 6-12 years: 5-60 mg daily in divided doses; may increase 5 mg/day every week until optimal response Children ≥12 years & Adolescents: 5-60 mg daily in divided doses; may increase 10 mg/day every week until optimal response	No

Agent	Preparations	Labeled Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Dexmethylphenidate (Focalin®, Focalin® XR)	Oral capsule, extended release: 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg Oral tablet: 2.5 mg, 5 mg, 10 mg	Attention-deficit/hyperactivity disorder: Treatment of ADHD in patients ≥6 years	IR: 2.5 mg twice daily; may increase 2.5-5 mg/day each week; max: 20 mg/day ER: 10 mg once daily; may increase 10 mg/day each week; max: 40 mg/day **Dose reductions and discontinuation: Reduce dose or discontinue in patients with paradoxical aggravation of symptoms; Discontinue if no improvement is seen after one month of treatment	Children ≥6 years & Adolescents: IR: 2.5 mg twice daily; may increase 2.5-5 mg/day each week; max: 20 mg/day ER: 5 mg once daily; may increase 5 mg/day each week; max: 30 mg/day	Yes
Dextroamphetamine (Dexedrine®, ProCentra®, Zenzedi®)	Oral capsule, extended release: 5 mg, 10 mg, 15 mg Oral solution: 5 mg/5 mL (473 mL) Oral tablet: 5 mg, 10 mg Oral tablet (Zenzedi): 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg	Attention-deficit/hyperactivity disorder: Treatment of ADHD as part of a total treatment program that typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children 3 to 16 years of age Narcolepsy: Treatment of narcolepsy	Narcolepsy: 5-60 mg daily in divided doses; may increase 10 mg/day each week until optimal response	<u>ADHD</u>: Children 3-5 years: IR tablets and oral solution: 2.5 once daily; may increase 2.5 mg/day each week until optimal response; max: 40 mg daily Children ≥6 years and Adolescents: IR tablets and oral solution: 5 mg once or twice daily; may increase 5 mg/day each week until optimal response; max: 40 mg daily ER capsules: 5 mg once or twice daily; may increase 5 mg/day each week until optimal response; max: 40 mg daily <u>Narcolepsy</u>: Children 6-12 years: 5-60 mg daily in divided doses; may increase 5 mg/day each week until optimal response Children >12 years & Adolescents: Refer to adult dosing	Yes

Agent	Preparations	Labeled Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Dextroamphetamine-Amphetamine Mixed Salts (Adderall®, Adderall® XR)	Oral capsule, extended release: 5 mg [dextroamphetamine sulfate 1.25 mg, dextroamphetamine saccharate 1.25 mg, amphetamine aspartate monohydrate 1.25 mg, amphetamine sulfate 1.25 mg (equivalent to amphetamine base 3.1 mg)]; 10 mg [2.5 mg, 2.5 mg, 2.5 mg, 2.5 mg (base 6.3 mg)]; 15 mg [3.75 mg, 3.75 mg, 3.75 mg, 3.75 mg (base 9.4 mg)]; 20 mg [5 mg, 5 mg, 5 mg, 5 mg (base 12.5 mg)]; 25 mg [6.25 mg, 6.25 mg, 6.25 mg, 6.25 mg (base 15.6 mg)]; 30 mg [7.5 mg, 7.5 mg, 7.5 mg, 7.5 mg (base 18.8 mg)] Oral tablet: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg	Attention-deficit/hyperactivity disorder: Treatment of ADHD Narcolepsy: Treatment of narcolepsy	ADHD: IR: 5 mg once or twice daily; may increase 5 mg/day each week until optimal response; max: 40 mg daily in divided doses ER: 20 mg once daily in the morning Narcolepsy: IR: 10 mg daily; may increase 10 mg/day each week until optimal response; max: 40 mg daily in divided doses	ADHD: Children <3 years: Not recommended Children 3-5 years: IR: 2.5 mg once daily; may increase 2.5 mg/day each week until optimal response; max: 40 mg daily in divided doses Children 6-12 years: IR: 5 mg once or twice daily; may increase 5 mg/day each week until optimal response; max: 40 mg daily in divided doses ER: 5-10 mg once daily in the morning; may increase 5-10 mg each week; max: 30 mg daily Narcolepsy: Children 6-12 years: IR: 5 mg once or twice daily; may increase 5 mg/day each week until optimal response; max: 60 mg daily in divided doses Children >12 years: Refer to adult dosing	Yes

Agent	Preparations	Labeled Indications	Dosing, Adult	Dosing, pediatric	Generic Available
Lisdexamfetamine (Vyvanse®)	Oral Capsule (Vyvanse): 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	Attention-deficit/hyperactivity disorder: Treatment of ADHD Binge eating disorder: Treatment of moderate to severe binge eating disorder	ADHD: 30 mg once daily in the morning; may increase 10-20 mg/day each week until optimal response; max: 70 mg/day Binge eating disorder: 50-70 mg once daily in the morning; may increase 20 mg/day each week until optimal response; max: 70 mg/day	ADHD: Children ≥6 years & Adolescents: Oral: Refer to adult dosing **Prior to treatment, assess for presence of cardiac disease and assess for risk of abuse	No
Methamphetamine (Desoxyn®)	Oral tablet: 5 mg	Attention-deficit/hyperactivity disorder: For a stabilizing effect in children >6 years with moderate-severe distractibility, short attention span, hyperactivity, emotional lability & impulsivity Exogenous obesity: Short-term adjunct in a regimen of weight reduction based on caloric restriction in treatment-resistance Off-Label: Narcolepsy	Exogenous obesity: 5 mg given 30 minutes before each meal; treatment duration should not exceed a few weeks	ADHD: Children ≥6 years: 20-25 mg daily in 1 or 2 divided doses; may increase 5 mg/day each week until optimum response Exogenous obesity: Children ≥12 years: Refer to adult dosing	Yes
Methylphenidate (Aptensio® XR, Concerta®, Daytrana®, Metadate® CD, Metadate® ER, Methylin®, QuilliChew® ER, Quillivant® XR, Ritalin®, Ritalin® LA)	Oral capsule, extended release: Metadate (generic): 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg Oral capsule, 24-hour extended release:	Attention-deficit/hyperactivity disorder: Treatment of ADHD Narcolepsy: Symptomatic management of narcolepsy (oral solution, oral ER/IR tablet)	ADHD: IR products (tablets, chewable tablets & solution): 5 mg twice daily, before breakfast and lunch; increase 5-10 mg daily at weekly intervals; max: 60 mg daily in 2 to 3 divided doses ER & SR products (capsules, tablets, chewable tablets and suspension): 10 to 36 mg once	ADHD: IR products (tablets, chewable tablets & solution): Children ≥6 years and Adolescents: 5 mg twice daily, before breakfast and lunch; increase 5-10 mg daily at weekly intervals; max: 60 mg daily in 2 to 3 divided doses ER & SR products (capsules, tablets, chewable tablets and suspension):	Product dependent

Agent	Preparations	Labeled Indications	Dosing, Adult	Dosing, pediatric	Generic Available
	Aptensio XR: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg Ritalin LA (generic): 10 mg, 20 mg, 30, mg, 40 mg, 50 mg, 60 mg Oral solution: 5 mg/5 mL; 10 mg/5 mL Oral suspension (Quillivant XR): 25 mg/5 mL Oral tablet: 5 mg, 10 mg, 20 mg Oral tablet, chewable: 2.5 mg, 5 mg, 10 mg Oral tablet, chewable extended release (QuilliChew ER): 20 mg, 30 mg, 40 mg Oral tablet, extended release: 10 mg, 18 mg, 20 mg, 27 mg, 36 mg, 54 mg Transdermal patch (Daytrana): 10 mg, 15 mg, 20 mg, 30 mg	Off-Label: Depression, Fatigue in adult cancer survivors	every morning; max: 60-72 mg/day Aptensio XR: 10 mg once daily; max: 60 mg daily QuilliChew ER: 20 mg once daily in the morning; increase 10, 15 or 20 mg at weekly intervals; max: 60 mg daily <u>Narcolepsy</u>: IR products (Methylin, Ritalin): 5 mg twice daily, before breakfast and lunch; increase 5-10 mg daily at weekly intervals; max: 60 mg daily in 2 to 3 divided doses ER & SR products (Metadate ER, Ritalin-SR): max: 60 mg daily	Children ≥6 years & Adolescents <18 years: 10 mg, 18 mg, 20 mg once every morning; max: 54-60 mg/day Aptensio XR: 10 mg once daily; max: 60 mg daily QuilliChew ER: 20 mg once daily in the morning; increase 10, 15 or 20 mg at weekly intervals; max: 60 mg daily Transdermal (Daytrana): Children ≥6 years & Adolescents <18 years: 10 mg patch once daily; remove up to 9 hours after application <u>Narcolepsy</u>: Children ≥6 years & Adolescents: Refer to adult dosing	

Key: DSC = discontinued, IR = immediate release, XR/ER = extended release, ADHD = attention-deficit/hyperactivity disorder, SR = sustained release

Table 2. Conversion of Stimulant Agents to Different Moieties or Formulations[1,2]

Conversion	Recommendations
Adderall XR to Adzenys XR-ODT	Should be determined by the current dose of Adderall XR as follows: Current Adderall XR dose of 5 mg once daily: Initial Adzenys XR-ODT dose of 3.1 mg once daily Current Adderall XR dose of 10 mg once daily: Initial Adzenys XR-ODT dose of 6.3 mg once daily Current Adderall XR dose of 15 mg once daily: Initial Adzenys XR-ODT dose of 9.4 mg once daily Current Adderall XR dose of 20 mg once daily: Initial Adzenys XR-ODT dose of 12.5 mg once daily Current Adderall XR dose of 25 mg once daily: Initial Adzenys XR-ODT dose of 15.7 mg once daily Current Adderall XR dose of 30 mg once daily: Initial Adzenys XR-ODT dose of 18.8 mg once daily
Converting from all other amphetamine formulations (excluding Adderall XR) to Adzenys XR-ODT	Discontinue that treatment and titrate Adzenys XR-ODT as per the recommended dosing schedule available in Table 1; Do not substitute extended-release formulation for other amphetamine formulations on a mg-per-mg basis
Converting to dexmethylphenidate from methylphenidate	Immediate release and extended release: Initial: One-half the total daily dose of racemic methylphenidate
Conversion from dexmethylphenidate immediate release to dexmethylphenidate extended release	Patients currently using dexmethylphenidate immediate-release may be switched to the same daily dose of dexmethylphenidate extended-release
Conversion from immediate release to extended release Adderall formulations	Patients may be switched from the immediate release formulation to the extended release formulation using the same total daily dose once daily
Conversion from immediate release (IR) to extended release (ER) methylphenidate formulation	Patients taking IR methylphenidate 5 mg 2 to 3 times daily: 18 mg ER once every morning Patients taking IR methylphenidate 10 mg 2 to 3 times daily: 36 mg ER once every morning Patients taking IR methylphenidate 15 mg 2 to 3 times daily: 54 mg ER once every morning Patients taking IR methylphenidate 20 mg 2 to 3 times daily: 72 mg ER once every morning
Conversion from other methylphenidate formulations to QuilliChew ER	Discontinue previous formulation and titrate using schedule outlined in Table 1; do not substitute on a milligram-per-milligram basis
Conversion from immediate release or sustained release methylphenidate formulation to Ritalin LA	Use equivalent total daily dose administered once daily

Disease Overview

Mental illness is defined as any diagnosable mental disorder with sustained abnormalities in behavior, mood or thinking which result in impaired functioning and distress.[4] Diagnosable mental disorders may include anxiety disorders, mood disorders, personality disorders, attention deficit disorders, schizophrenia, addiction disorders and feeding/eating disorders.[5] The most commonly reported mental illnesses in adults in the United States (US) are anxiety and mood disorders, including depression and bipolar disorder.[4] The most commonly reported mental illnesses in adolescents in the US are depression and attention deficit disorders.[6] All mental illnesses can cause severe disruptions in activities of daily living and result in premature death. According to the World Health Organization (WHO), mental health disorders cause more patient disability than cancer, heart disease or any other illness.[4] In addition, mental health disorders are associated with increased rates of comorbid chronic diseases (including cardiovascular disease, diabetes, obesity, asthma, epilepsy and cancer), inappropriate use of medical care (including treatment nonadherence and increased emergency department visits), use of tobacco products, abuse of alcohol and other substances, increased rates of intentional and unintentional injuries and an overall increase in adverse health outcomes.[4] According to the Centers for Disease Prevention and Control (CDC), approximately 25% of all adults currently have a mental illness and up to 50% of adults will report a mental illness during their lifetime resulting in an economic burden of nearly $300 billion in the US (2002).[4] Increased access to mental health treatment services results in successful management of the mental health disorder, reduced rates of mortality and morbidity and improved health outcomes for comorbid chronic diseases.[4]

Attention Deficit Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by inattention, hyperactivity and impulsivity. ADHD is most often a disorder of childhood which may continue into adulthood. According to a National Survey of Children's Health (2010-2012), over 10% (~6.4 million) of US school-aged children have a diagnosis for ADHD and this number continues to rise with an increase of 42% reported between 2003 and 2011. In general, ADHD is diagnosed more frequently in school-aged boys (1 in 5) than in school-aged girls (1 in 11) and the average age of first onset of the disease is 7 years. The prevalence of ADHD in US adults is estimated to be 4.1%. The economic burden of ADHD in the US (reaching $52 billion in 2005) results from the combined costs associated with the treatment of patients and lost productivity for patients and family members.[7-9] In addition, ADHD frequently occurs in combination with other mental health disorders (up to ~50%) including aggression-related disorders (Oppositional Defiant Disorder or Conduct Disorder), learning ability disorders, depression and anxiety, which may further contribute to increased costs and morbidity. Increasing mental health disorder education and screening can help to improve patient outcomes and reduce overall costs.[10]

Attention-deficit/hyperactivity disorder is defined as a mental disorder with inattention (difficulty sustaining focus and disorganized not due to incomprehension), hyperactivity (restlessness and excessive movement/talking) and/or impulsivity (hasty actions with high potential for harm and/or inability to delay gratification) which result in difficulty functioning at school and at home. ADHD may be divided into three different types: predominantly inattentive,

predominantly hyperactive-impulsive or combined presentation with symptoms of both types equally exhibited.[11] There is no single test to diagnose ADHD. In general, diagnosis requires six or more symptoms of inattention &/or hyperactivity-impulsivity for children (< 16) or five or more symptoms for adolescents (> 17) and adults which have persisted for at least 6 months. Symptoms of inattention may include: failure to pay close attention to details, make careless mistakes, trouble maintaining attention on a single task, inability to listen, failure to finish duties, trouble organizing tasks, avoids tasks that require mental effort over a long period of time, often loses things and is easily distracted or forgetful. Symptoms of hyperactivity-impulsivity may include: fidgets, trouble remaining seated, feels restless (may run or climb), trouble participating in quiet activities, "on the go," talks excessively, speaks out of turn, trouble waiting turn and often interrupts or intrudes. For diagnosis, symptoms should be present before age 12, present in two or more settings and reduce the quality of school/work and social functioning.[12]

Treatment of ADHD should include a combination of behavior therapy and medication therapy. For preschool-aged children, behavior therapy alone is recommended as first line.[11] Behavioral therapies include teaching the child new behaviors to replace ones which cause disruptions to activities of daily living in addition to instructing the child's parents to teach and enforce skills to help the child manage their behavior. Medication therapy may include stimulant and nonstimulant agents. Stimulants, including amphetamine and methylphenidate agents, are the most widely used ADHD treatments, are fast-acting and are efficacious in reducing ADHD symptoms. Nonstimulant agents, including atomoxetine (Strattera®), guanfacine and clonidine, are not as fast-acting but are long-acting and may be associated with fewer adverse effects. Often it requires multiple trials of different medications at various doses to find the optimal drug therapy in children with ADHD.[13] Effective treatment plans should include both behavioral and medication therapy, close monitoring and frequent follow-ups.[11,14-16]

Clinical guidelines for the treatment of attention-deficit/hyperactivity disorder include the American Academy of Child and Adolescent Psychiatry guidelines on Attention-Deficit/Hyperactivity Disorder (2007)[17], the American Academy of Pediatrics guidelines on Attention-Deficit/Hyperactivity Disorder (2011)[18] and the National Collaborating Centre for Mental Health NICE guidelines on Attention Deficit Hyperactivity Disorder (2008).[19] See Table 3 for a summary of the most current guideline recommendations. In general, the guidelines recommend treatment with medication and behavioral therapy in children and adolescents with ADHD. In preschool-aged children, guidelines recommend behavioral therapy alone as first-line treatment of ADHD. In adults, guidelines recommend medication therapy alone as first-line treatment of ADHD. In general, evidence suggests stimulants are more efficacious than non-stimulants in the treatment of ADHD. Choice of medication therapy usually includes a methylphenidate agent as first-line, atomoxetine in patients with underlying anxiety disorder or risk for substance abuse and an amphetamine agent in patients with methylphenidate-resistant disease. Some evidence suggests clonazepam in addition to a stimulant agent may be helpful in children with only a partial response to stimulant monotherapy. [20] All patients should receive a well-thought out treatment plan with close follow-up and appropriate titration of medication therapy.

Table 3. Current Clinical Treatment Practice Guidelines for Attention Deficit Disorder

Guideline	Recommendations
American Academy of Child and Adolescent Psychiatry guidelines on Attention-Deficit/Hyperactivity Disorder (2007)[17]	Initial medication therapy should be with a trial of an agent with a labeled indication for the treatment of ADHD by the FDA: dextroamphetamine, methylphenidate, mixed salts amphetamine or atomoxetine: • Stimulants are highly efficacious • Methylphenidate and amphetamine agents are equally efficacious in the treatment of ADH • Long-acting formulations are equally efficacious as immediate-release agents but may be more convenient In patients with treatment-refractory disease, Behavior Therapy and/or the use of medications not approved by the FDA for the treatment of ADHD (bupropion or tricyclic antidepressants) should be considered All patient should be monitored for treatment-emergent side effects and assessed periodically for treatment efficacy • Patients treated with medication for ADHD should have height and weight monitored throughout treatment • Treatment of ADHD should continue as long as symptoms remain present and cause impairment
American Academy of Pediatrics guidelines on Attention-Deficit/Hyperactivity Disorder (2011)[18]	Recommendations vary depending on the patient's age: Preschool-aged children (4–5 years of age) • Evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment • Methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in functioning Elementary school–aged children (6–11 years of age) • FDA–approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as, preferably both o Evidence is strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine and extended-release clonidine (in that order) Adolescents (12–18 years of age) • FDA–approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as, preferably both Medication therapy in all patient age groups should titrated to achieve maximum benefit with minimum adverse effects

Guideline	Recommendations
National Collaborating Centre for Mental Health NICE guidelines on Attention Deficit Hyperactivity Disorder (2008)[19]	Treatment for children and young people • Parent-training/education programs are first-line for pre-school children; drug treatment is not recommended for pre-school children • Group-based parent-training/education programs are first-line for school-age children and young people with moderate impairment • Medication therapy is usually first-line for school-age children and young people with severe symptoms and impairment or for those with moderate impairment who have not responded to parent-training/education programs or group psychological treatment o Drug treatment should only be initiated by an ADHD specialist o Drug therapy includes: methylphenidate, atomoxetine and dexamphetamine ▪ Methylphenidate for ADHD without significant comorbidity ▪ Methylphenidate for ADHD with comorbid conduct disorder ▪ Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present ▪ Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses ▪ Dexamphetamine in children and young people unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine o Extended-release preparations should be considered: for convenience, improving adherence, reducing stigma, in schools with rules against storing and administering controlled drugs o Immediate-release preparations should be considered: for more flexible dosing regimens, during initial titration o Overall, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed Treatment for adults • Medication therapy is the first-line treatment for adults with moderate or severe levels of impairment o Methylphenidate is the first-line drug o Psychological interventions without medication may be effective for some adults with moderate impairment o Atomoxetine or dexamphetamine are recommended in patients who did not respond to methylphenidate treatment o There is potential for drug misuse and diversion in adults with ADHD receiving stimulants
Institute for Clinical Systems Improvement: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2012)[21]	Medication therapy • Use FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants • Decision to initiate medication therapy should be made in conjunction with parents and discussion of expected benefits and potential risks • Age, disease severity and presence of comorbidities should be considered • Optimal medication management alone is superior to other modalities for the core symptoms of ADHD • If patient does not respond to initial medication choice, a second or third trial with other stimulants is recommended • Atomoxetine is recommended in patients with comorbid anxiety, sleep initiation disorder, substance abuse or tics • Extended-release guanfacine and extended-release clonidine have a labeled indication as adjunctive therapy with stimulant medications • Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a nontricyclic antidepressant (bupropion) or immediate-release guanfacine

Pharmacology

Three types of stimulants, amphetamine (dextro-amphetamine and levo-amphetamine), methamphetamine and methylphenidate (dextro-methylphenidate and levo-methylphenidate), may be used for treatment of attention deficit/hyperactivity disorder (ADHD), management of narcolepsy or weight reduction.[22] Many different formulations exist, ranging from immediate release to extended release formulations.[1,2] The full pathophysiology of ADHD is not well understood, however evidence suggests that ADHD may be due to inadequate production of norepinephrine and dopamine in the prefrontal cortex.[23-25] As a result, amphetamines, methylphenidate and methamphetamine are used to increase the availability of catecholamines which helps to alleviate symptoms. In addition, the various isomers of these agents are commonly combined in differing ratios to exert desired pharmacologic effects and reduce adverse effects. Of note, individual patient genetic variations can result in differences in efficacy between the agents; for example, patients with a 9/9 genotype (SLC6A3/DAT1) may require higher doses of stimulant medications in order to achieve adequate symptom control.[26]

Amphetamines, which belong to the class of β-phenylethlyamines, are potent noncatecholamine sympathomimetic amines which increase the availability of catecholamines such as dopamine or norepinephrine via increased release or reuptake inhibition.[1,2,22] Increased availability of catecholamines results in stimulation of the peripheral systems in addition to the central nervous system resulting in increased blood pressure and bronchodilation. The alerting and anorectic effects of amphetamines are thought to be largely due to norepinephrine release in central noradrenergic neurons. Amphetamine is composed of two active isomers, dextro-amphetamine and levo-amphetamine, which have different actions in the body. Dextro-amphetamine is approximately 3-4 times more potent than levo-amphetamine in producing central nervous system (CNS) stimulation, while levo-amphetamine has slightly more potent cardiovascular effects, including increased systolic and diastolic pressure and the presence of cardiac arrhythmias at high doses. As a result, amphetamine agents (Adzenys® 3:1, Dyanavel® 3.2:1) and mixed amphetamine salts (Adderall® 3:1) utilize higher ratios of dextro-amphetamine to levo-amphetamine to reduce the risk of unwanted cardiovascular effects. Dextroamphetamine (Dexedrine®) and lisdexamfetamine (an inactive prodrug which is converted to dextro-amphetamine, Vyvanse®) are not mixed-isomer agents and have pharmacological effects solely due to dextro-amphetamine.[1,2,22]

Methamphetamine has a similar chemical structure to amphetamine, with the only difference being the addition of a methyl group at the N position. Methamphetamine works by increasing the availability of catecholamines, enhancing release from storage sites, inhibiting reuptake through monoamine transporters and decreasing metabolism by inhibiting oxidases. The central effects of methamphetamine tend to be more prominent than that of amphetamine.[1,2,22] Desoxyn® is an oral tablet methamphetamine agent indicated in the treatment of ADHD and exogenous obesity. Methylphenidate is also structurally related to amphetamines, with the addition of a piperidine group. Methylphenidate (Concerta®, Ritalin®, others) is composed of two active isomers, d-methylphenidate, which is more potent, and l-methylphenidate. Dexmethylphenidate (Focalin®) is made up of only the active d-methylphenidate isomer. Methylphenidate works by decreasing dopamine and norepinephrine reuptake and, overall, exhibits similar pharmacological properties as amphetamines.[1,2,22]

Table 4. Pharmacokinetic Properties of the Central Nervous System Stimulant Agents[1,2,22]

Agent	Onset/Duration/Tmax	Half-life	Bioavailability	Distribution	Metabolism	Excretion
Amphetamine (Adzenys® XR-ODT; Dyanavel® XR; Evekeo®)	Amphetamine Sulfate Onset: 1-3 hours Duration (Single Dose): up to 10 hours Tmax: 4 hours Amphetamine Onset: Not Reported Duration: 24 hours Tmax: 4 hours	Amphetamine Sulfate $t_{1/2}$: 7-34 hours depending on urine pH Amphetamine D-amphetamine $t_{1/2}$: 12.36 hours L-amphetamine T1/2: 15.12 hours	Amphetamine Sulfate Well absorbed, Alkaline gastrointestinal pH increases absorption Amphetamine D-amphetamine: 106% compared to equal dose IR amphetamine salts L-amphetamine: 111% compared to equal dose IR amphetamine salts	Amphetamine Sulfate Protein binding: 20% Vd: 3.5-6.11 L/kg CSF levels: 80% of plasma levels Amphetamine Protein binding: 16% Vd: 3-4 L/kg	Amphetamine Sulfate Hepatic: Linear pharmacokinetic one-compartment open model Amphetamine Hepatic: Extensive, oxidation, deamination, CYP2D6	Amphetamine Sulfate Renal: 67%-73% excreted unchanged with urine pH <6.6 Amphetamine Renal: 30%-40% excreted unchanged with normal urine pH
Dexmethylphenidate (Focalin®, Focalin® XR)	Immediate Release Onset: 1-2 hours Duration: 3-5 hours Tmax: 1-1.5 hours Extended Release Onset: 1-2 hours Duration: 9-12 hours Tmax: First peak-1.5 hours, second peak-6.5 hours	IR/ER $t_{1/2}$: 2-4.5 hours	Mean absolute bioavailability: 22-25%	Protein binding: 12%-15% Vd: 2.65 L/kg	Hepatic: Extensive, de-esterification	Renal: 90% excreted as inactive metabolite, 0.5% excreted unchanged (after IV dose)

Agent	Onset/Duration/Tmax	Half-life	Bioavailability	Distribution	Metabolism	Excretion
Dextroamphetamine (Dexedrine®, ProCentra®, Zenzedi®)	Immediate Release Onset: 2-3 hours Duration: 4-6 hours Tmax: 60-180 minutes Extended Release Onset: 2-3 hours Duration: 4-24 hours Tmax: ~8 hours	IR/ER $t_{1/2}$: 10-12 hours	Well-absorbed; The bioavailability of ER capsule is similar to IR capsule	Vd: 6.11 L/kg CSF levels: 80% of plasma levels	Hepatic: Extensive, CYP deamination, hydroxylation	Renal: 17%-73% excreted unchanged depending on urine pH
Dextroamphetamine-Amphetamine Mixed Salts (Adderall®, Adderall® XR)	Immediate Release Onset: Not reported Duration: Not reported Tmax: 3 hours Extended Release Onset: Not reported Duration: Not reported Tmax: 7 hours	IR/ER $t_{1/2}$: 10-13 hours	Well-absorbed	Not Reported	Hepatic: Variable, depends on renal excretion, oxidation, CYP2D6	Renal: 30%-40% excreted unchanged depending on urine pH
Lisdexamfetamine (Vyvanse®)	Onset: Not reported Duration: Not reported Tmax: 1 hour lisdexamfetamine, 3.5 hours dextroamphetamine	$t_{1/2}$: ~1 hour lisdexamfetamine, 10-13 hours dextroamphetamine	Rapidly absorbed	Dextroamphetamine Vd: 3.5-4.6 L/kg Dextroamphetamine CSF levels: 80% of plasma levels	Lisdexamfetamine hydrolyzed to dextroamphetamine and L-lysine in the blood. Dextroamphetamine Hepatic: Extensive, CYP deamination, hydroxylation	Renal: 2% excreted unchanged as lisdexamfetamine Feces: 0.3% excreted
Methamphetamine (Desoxyn®)	Onset: Not reported Duration: Not reported Tmax: Not reported	$t_{1/2}$: 4-5 hours	Rapidly absorbed from GI tract	Not reported	Hepatic: aromatic hydroxylation, N-dealkylation/deamination	Renal: ~33% excreted unchanged depending on urine pH

Agent	Onset/Duration/Tmax	Half-life	Bioavailability	Distribution	Metabolism	Excretion
Methylphenidate (Aptensio® XR, Concerta®, Daytrana®, Metadate® CD, Metadate® ER, Methylin®, QuilliChew® ER, Quillivant® XR, Ritalin®, Ritalin® LA)	<u>Immediate Release</u> Onset: 20-60 minutes Duration: 3-5 hours Tmax: 1-2 hours <u>Extended Release</u> Onset: 20-60 minutes Duration: 6-12 hours Tmax: 1.5-6.6 hours <u>Sustained Release</u> Onset: 60-180 minutes Duration: 2-6 hours Tmax: 4.7 hours <u>Transdermal</u> Onset: 1 hour Duration: 11-12 hours Tmax: 7.5-10 hours	IR $t_{1/2}$: 3 hours CR $t_{1/2}$: 2.1-2.4 hours ER $t_{1/2}$: 2.45-6.8 hours SR $t_{1/2}$: 3.4 hours	Oral: Readily absorbed Transdermal: Less first-pass effect, Absorption increased when exposed to heat or inflamed skin, absorption continues for 9 hours after application	Protein binding: 10%-33% D-methylphenidate Vd: 2.65 L/kg L-methylphenidate Vd: 1.8 L/kg	Hepatic/other tissues: De-esterification via carboxylesterase CES1A1	Renal: 78%-97% excreted, <1% excreted unchanged in urine

Key: Tmax: time to max concentration; $t_{1/2}$: half-life; BA: bioavailability; Pb: protein binding; Vd: volume of distribution; IM: intramuscular; ER: extended release; IR: immediate release

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE, evaluating efficacy of the central nervous system stimulant agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Non-comparative and placebo-controlled trials and trials comparing monotherapy with combination regimens are excluded.[27-48] The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as: pharmacologic characteristics[26,49-55], memory[56-58], adverse effects[59-63], toxicity[64,65] or abuse.[66-72]
- Individual trials comparing the CNS stimulants in dose-finding studies or in healthy volunteers.[51,53,54,73-79]
- Individual clinical trials evaluating formulations or indications not currently approved in the US or clinical trials without access to the full article.[37,80-83]

Clinical Efficacy

An Oregon Health and Science University Drug Class Review on Pharmacological Treatments for Attention Deficit Hyperactivity Disorder was published in October 2009.[3] The drug class review includes a summary of the guideline recommendations, systematic reviews and comparative clinical trials evaluating the safety and efficacy of the agents. A summary of the clinical evidence is provided below. For this report, a PubMed and Cochrane Library literature search for systematic reviews and randomized controlled trials (RCTs) was conducted for trials published 1/2009-4/2016. The Agency for Healthcare Research and Quality (AHRQ), the FDA website (including product labeled information), Micromedex and Lexicomp were also searched for safety information, systematic reviews, clinical trials and guidelines. A summary of this evidence can be found in evidence tables in the appendix of this document as well as in the second half of the clinical efficacy section of this report.

Summary of the Oregon Health and Science University Pharmacological Treatments for Attention Deficit Hyperactivity Disorder Drug Class Review, October 2009[3]

Clinical studies of stimulant medications in the treatment of ADHD have generally been flawed and provide limited information with respect to comparative efficacy. The clinical efficacy and effectiveness of the stimulants and atomoxetine were evaluated in 369 studies in patients with ADHD. These include 69 head-to-head trials, 12 active control trials, 169 placebo controlled trials, 86 observational studies, 15 systematic reviews/meta-analyses and 18 other studies (pooled analyses, uncontrolled, open label studies, erratum, etc). According to the Oregon Report, "the evidence for comparative efficacy and adverse events of drugs for treating ADHD is severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring symptom control vary

significantly across studies. A crossover design was frequently used, with few analyzing the effect of order of administration of drugs. Those that did found a significant effect related to order of administration. No head-to-head efficacy trial was [of] good quality." Based on the available evidence, it appears that all agents are similarly effective for treating ADHD with some differences in the duration of treatment before discontinuing a drug (persistence) between immediate release and extended release formulations.

When evaluating treatments for ADHD, it is important to consider both patient age and dosage form. The Oregon Review evaluated studies in children, adolescents and adults. The report also evaluated both immediate release and extended release formulations of the stimulant agents. There are few head to head comparisons. Studies in children favor efficacy compared to placebo with fair evidence for stimulant drugs and poor evidence for atomoxetine. Comparative studies between immediate release drugs indicate little or no difference in efficacy with good evidence to support these findings. Studies comparing immediate release and extended release drugs show differences in efficacy that are time dependent as would be expected, but the evidence is poor. Among extended release formulations, very few comparisons have been made and the evidence supporting the superiority of one agent over another is poor. Atomoxetine was compared to both immediate release and extended release stimulants. The evidence weakly suggests that atomoxetine is comparable in efficacy to immediate release stimulants and inferior to extended release formulations. Fewer studies have been done in adolescents than in younger children. The level of evidence in these studies is poor, but the efficacy of different agents appears to follow the same trends as in children. In adults, modafinil was compared to dextroamphetamine extended release and similar rates of efficacy were reported between treatment groups. Indirect comparisons tend to favor the efficacy of immediate release stimulants compared to extended release stimulants in adults. The efficacy of atomoxetine was not consistently superior to placebo in adults.

Summary of the Comparative Clinical Evidence Not Included in the Oregon Report

A total of four systematic reviews & meta-analyses and six comparative clinical trials published 2009-2016 were identified for evaluation in this report.

One meta-analysis of 15 randomized, controlled trials of 1,172 patients with ADHD evaluating the duration of efficacy of the long-acting stimulants (amphetamine n=378 and methylphenidate n=794) was published in 2010.[84] According to the evidence, long-acting stimulants improved ADHD symptoms in both children and adults. Most agents improved outcomes for up to 12 hours (measured by performance on mathematics tests) however differences in time to peak effect, maintenance of peak effect and magnitude of effect may vary between the agents. A systematic review of 5 randomized controlled trials and 10 open-label extension studies of 3,176 patients with ADHD was published in 2012.[85] Methylphenidate agents, amphetamine agents and atomoxetine were all found to be more efficacious than placebo but no differences in efficacy were reported between treatment groups. Methylphenidate was associated with increased rates of decreased appetite and mucosal dryness compared to placebo, both methylphenidate and amphetamine were associated with increased rates of cardiovascular changes compared to placebo and lisdexamfetamine was associated with higher rates of upper respiratory infections than both other stimulant agents and placebo. Roskell et al[86] published a

systematic review and meta-analysis of 32 randomized controlled trials evaluating the efficacy of methylphenidate, dexamphetamine and atomoxetine in children with ADHD (2014). According to the analysis, lisdexamfetamine therapy may be more effective in reducing ADHD symptoms but may also be associated with increased adverse-event discontinuation rates when compared to the methylphenidate therapy. Another large meta-analysis of 28 randomized, controlled trials evaluating the efficacy of ADHD treatments in pediatric patients was published in 2015.[87] According to this analysis, lisdexamfetamine therapy was associated with increased rates of efficacy (reducing symptoms) compared to methylphenidate therapy while methylphenidate therapy demonstrated reduced treatment discontinuation rates compared to the other treatment groups. Overall, both methylphenidate agents and amphetamine agents are more effective than placebo in the treatment of ADHD. According to the limited evidence, lisdexamfetamine may be more effective in reducing ADHD symptoms but may also be associated with increased adverse events.

Four randomized, controlled trials not included in the systematic reviews and meta-analyses above are available for evaluation. Coghill et al[88] conducted a double-blind, parallel group study of lisdexamfetamine, methylphenidate and placebo in 336 pediatric patients with ADHD. At the end of the 7-week study period, treatment discontinuation rate was lowest in the lisdexamfetamine treatment group (9.75%) compared to both the methylphenidate treatment group (19.6%) and placebo treatment group (48.6%, no p value reported). Both active treatment groups demonstrated higher investigator-related symptom improvement rates compared to placebo. Treatment-emergent adverse event rates varied between treatment groups: lisdexamfetamine (72.1%), methylphenidate (64.9%) and placebo (57.3%, no p value reported). Spencer et al[89] compared methylphenidate-extended release to methylphenidate immediate-release in a single-blind study of 53 adult patients with ADHD. At the end of the 6-week study period, no differences in efficacy, adverse effects or patient preference were reported between treatment groups. A small difference in the number of missed doses was reported between treatment groups, with a higher rate reported in the methylphenidate immediate-release treatment group ($p = 0.02$). Two small cross-over studies were identified for evaluation. Martin et al[90] evaluated the efficacy of lisdexamfetamine, mixed amphetamine salts and placebo in adult patients with ADHD. Both lisdexamfetamine and mixed amphetamine salts were associated with higher rates of efficacy, decreased appetite and mucosal dryness compared to placebo. No differences in safety or efficacy were reported between treatment groups. Stein et al[91] evaluated the efficacy of extended-release dexmethylphenidate and extended-release mixed amphetamine salts in 56 children with ADHD. At the end of the 8 week study period, no differences in reduction of ADHD symptoms or adverse events (including reduced appetite and insomnia) were reported between treatment groups. Of note, higher doses of either stimulant were associated with increased rates of efficacy (defined as reduced ADHD symptoms) compared to lower doses of stimulant therapy.

A large retrospective analysis of over 60,000 patients with a diagnosis for ADHD, receiving treatment with a stimulant or nonstimulant medication was published in 2010.[92] According to the analysis, patients receiving medication therapy with a stimulant stayed on the medication longer (persistence) and appeared to be more adherent to their medication therapy (adherence). In addition, those receiving an amphetamine agent (compared to a methylphenidate agent) and/or an extended release product (compared to an immediate-release product) were

more likely to demonstrate increased rates of persistence and adherence. Of note, dose changes occurred less frequently in patients receiving nonstimulant medication therapy compared to stimulant medication therapy. No safety data was reported. A second retrospective database analysis evaluating the efficacy of lisdexamfetamine compared to other FDA-approved stimulant and nonstimulant medications was published in 2013.[93] According to the analysis, treatment adherence rates varied by patient population. In treatment-naïve pediatric patients long-acting methylphenidate was associated with higher rates of adherence. In adult patients long-acting amphetamine agents were associated with higher rates of adherence. And in most other patient populations, lisdexamfetamine therapy was associated with higher rates of adherence.

Safety

Central nervous system (CNS) stimulants such as amphetamine, methylphenidate and methamphetamine exert their effects via increasing the availability of catecholamines in the synaptic cleft.[1,2] As a result, side effects tend to be similar across the drug class. The most common adverse events (based on events occurring in ≥10% of patients) include headache, insomnia, increased blood pressure, abdominal pain and decreased appetite. Less common adverse events reported with the CNS stimulants include restlessness, anxiety, dizziness, weight loss, growth suppression in children and adolescents, changes in libido, dry mouth, nausea, vomiting and diarrhea.[1,2] Amphetamines, methylphenidate and methamphetamine also carry black box warnings for high dependence and abuse potential.[1,2] Close monitoring and caution should be exercised when prescribing to patients with a known history of drug abuse or dependence. Some of the more serious, but rare, adverse effects reported with the CNS stimulants include psychosis, sudden death, cardiac arrhythmias, stroke, myocardial infarctions, priapism, anaphylaxis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Permanent luekoderma has been reported with methylphenidate (Daytrana®) transdermal patches.[1,2] See tables 5 and 6 for a summary of the contraindications, warnings and adverse effects reported with the agents, based on package labeling.

Most studies evaluating the difference in adverse events between the stimulant agents are of fair quality and show mixed or inconsistent results.[3] According to clinical evidence summarized in the Oregon Report, the most serious adverse reaction associated with stimulant therapy is sudden cardiac death. Large scale population studies show that this serious adverse drug event (ADE) is very rare, estimated at less than one event per 1 million prescriptions.[62] Atomoxetine therapy demonstrates similar results. Rates of sudden cardiac death with these agents are greater than controls by a statistically significant margin but not by a clinically significant margin.[94] Cardiovascular adverse events may be related to less serious increases in blood pressure and ECG changes seen in 0.7-4% of patients. Methylphenidate and amphetamine agents may also be associated with weight loss (or reduced weight gain compared to control) and delayed growth in children. No differences in these adverse events are reported between methylphenidate and amphetamine therapy and discontinuing treatment results in resumption of normal growth.[63] In clinical trials, insomnia, decreased appetite and headaches have been observed at similar rates among most stimulants however immediate-release methylphenidate and atomoxetine showed a lower incidence than amphetamines or long-acting methylphenidate. Tics are reported with both methylphenidate and amphetamine agents although studies show mixed results when comparing agents to each other or placebo.[3]

A Cochrane Review published in 2011 reported greater treatment dropout rate for adults with mixed amphetamine salts compared to dextroamphetamine and lisdexamfetamine in subgroup analyses due to adverse effects.[23] A second Cochrane Review evaluating the CNS stimulants in adolescents did not reveal significant differences among adverse events of amphetamine and its derivatives in subgroup analyses.[25] In a short-term, placebo-controlled clinical trial evaluating the rate of treatment-emergent adverse events in children and adults, lisdexamfetamine treatment was associated with similar rates of adverse events compared to other stimulant agents.[95] A retrospective cohort study used Florida Medicaid fee-for-service claims data of over 2 million children aged 3-20 years with a diagnosis of ADHD receiving methylphenidate or amphetamine salts to evaluate the potential for cardiovascular effects with stimulant use. Overall, the agents demonstrated similar rates of cardiac-related emergency room visits. There is some concern regarding the potential for development of serious heart disease after long-term use and differences in rates of effects depending on stimulant dose.[61] Overall, most adverse events reported in clinical trials were manageable and did not require treatment discontinuation.[59]

A growing concern with stimulant therapy is the increasing rate of stimulant abuse which occurs among the caretakers of children receiving the medication and youth without diagnoses of ADHD in addition to the patients themselves. In youth without an ADHD diagnosis, the most frequently reported reason for abuse is improved academic achievement.[66] Along with the increased rates of abuse come increased rates of overdose. Stimulant medications have a low therapeutic index, with toxicity occurring at levels just above recommended doses. In general, acute ingestion of more than 1 mg/kg of dextroamphetamine (or equivalent) may be life-threatening; although, the development of tolerance can occur after repeated stimulant use. Acute signs of stimulant overdose include restlessness, agitation, psychosis, seizures, coma and hypertension potentially resulting in myocardial infarction or intracranial hemorrhage. Other peripheral signs and symptoms may include sweating, tremor or rigidity. Death may occur as a result of ventricular arrhythmia, status epilepticus or hyperthermia. Effects associated with chronic amphetamine abuse include cardiomyopathy, dental changes, paranoid psychosis, pulmonary hypertension and weight loss.[96] The National Poison Data System published a retrospective observational case series of non-therapeutic stimulant exposures from 2007 to 2012. According to the report, the majority of patients were referred to health care facilities, most patients reported no effects or only minor toxicity, serious adverse effects occurred in approximately 20-25% of reported cases and toxic effects were similar across all stimulant agents.[64] A randomized, controlled trial reported similar outcomes with methamphetamine and dextroamphetamine agents demonstrating equivalence for abuse potential.[68]

Table 5. Warnings and Precautions for the Central Nervous System Stimulant Agents[1,2]

Agent	US Black Box Warnings and Contraindications
Amphetamine	**Misuse may cause serious cardiovascular events including sudden death.** **Potential for drug abuse and dependency exists; prolonged use may lead to drug dependency and must be avoided. Assess the risk for abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Consider the possibility of patients obtaining amphetamines for non-therapeutic use or distribution to others; prescribe sparingly.** Contraindications: advanced arteriosclerosis; symptomatic cardiovascular disease; moderate to severe hypertension; hyperthyroidism; agitated states; history of drug abuse; use during or within 14 days following MAO inhibitor
Dexmethylphenidate	**Use with caution in patients with a history of alcohol or drug dependence. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviors. Frank psychotic episodes can occur, especially with parenteral abuse.** Contraindications: marked anxiety, tension, and agitation; glaucoma; motor tics; family history or diagnosis of Tourette syndrome; concurrent use with or within 14 days following discontinuation with MAO therapy
Dextroamphetamine	**Use has been associated with serious cardiovascular events including sudden death in patients with preexisting structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults).** **Potential for drug dependency exists; prolonged use may lead to drug dependency.** Contraindications: advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-to-severe hypertension; hyperthyroidism; glaucoma; agitated states; patients with a history of drug abuse; during or within 14 days following MAO inhibitor therapy **Although FDA approved, current guidelines do not recommend use of dextroamphetamine in children ≤5 years due to insufficient evidence. Precautions: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates
Dextroamphetamine-Amphetamine Mixed Salts	**Use has been associated with serious cardiovascular events including sudden death in patients with preexisting structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults).** **Potential for drug dependency exists; prolonged use may lead to drug dependency.** Contraindications: advanced arteriosclerosis; symptomatic cardiovascular disease; moderate-to-severe hypertension; hyperthyroidism; hypersensitivity or idiosyncrasy to the sympathomimetic amines; glaucoma; agitated states; patients with a history of drug abuse; during or within 14 days following MAO inhibitor

Agent	US Black Box Warnings and Contraindications
Lisdexamfetamine	**CNS stimulants (including lisdexamfetamine) have a high potential for abuse and dependence; assess for abuse potential prior to use and monitor for signs of abuse and dependence while on therapy.** Contraindications: concurrent use of MAO inhibitor, or within 14 days of the last MAO inhibitor dose
Methamphetamine	**Potential for drug dependency and abuse exists.** **Use in weight reduction programs only when alternative therapy has been ineffective. Avoid prolonged treatment durations due to potential for drug dependence.** Contraindications: during or within 14 days following MAO inhibitors; glaucoma; advanced arteriosclerosis; symptomatic cardiovascular disease; moderate to severe hypertension; hyperthyroidism; hypersensitivity or idiosyncrasy to sympathomimetic amines; agitated state; patients with a history of drug abuse
Methylphenidate	**Potential for drug dependency exists; avoid abrupt discontinuation in patients who have received for prolonged periods.** Contraindications: use during or within 14 days following MAO inhibitor therapy; marked anxiety, tension, and agitation; glaucoma; family history or diagnosis of Tourette syndrome or tics; severe hypertension, heart failure, arrhythmia, hyperthyroidism or thyrotoxicosis, recent MI or angina; concomitant use of halogenated anesthetics; patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency Precautions: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; some dosage forms may contain lactose or sucrose or phenylalanine; prolonged and painful erections (priapism), sometimes requiring surgical intervention, have been reported (rarely) with methylphenidate and atomoxetine use in pediatric and adult patients

Key: MAO = monoamine oxidase inhibitor

Table 6. Adverse Events Reported with the Central Nervous System Stimulant Agents[1,2]

	Amphetamine	Dexmethylphenidate	Dextroamphet-amine	Dextroamphetamine Mixed Salts	Lisdexamfetamine	Methamphetamine	Methylphenidate
Central Nervous System	Dizziness, dysphoria, euphoria, exacerbation of Tourette's syndrome, tics, headache, insomnia, restlessness	Headache (25%-39%), insomnia (children 5%-17%), restlessness (adults 12%), anxiety (5%-11%), Dizziness (adults 6%), fever (children 5%), irritability (children ≤5%), depression (children ≤3%), mood swings (children ≤3%),	Aggressive behavior, dizziness, dysphoria, euphoria, exacerbation of tics, Tourette's syndrome, headache, insomnia, mania, overstimulation, psychosis, restlessness	Insomnia (extended release: 12%-27%), headache (ER; adults: ≤26%), emotional lability (ER: 2%-9%), anxiety (ER; adults: 8%), agitation (ER; adults: ≤8%), dizziness (ER: 2%-7%), nervousness (ER: 6%), drowsiness (2%-4%), speech disturbance (ER: 2%-4%), twitching ((ER: 2%-4%), aggressive behavior, depression, dysphoria, euphoria, exacerbation of vocal tics, formication, paresthesia, overstimulation, psychosis, restlessness, talkativeness	Insomnia (13%-27%), irritability (children: 10%), anxiety (adults: 5%-6%), jitteriness (adults: 4%-6%), dizziness (children: 5%), agitation (adults: 3%), emotional lability (children: 3%), restlessness (adults: 2%-3%), drowsiness (children: 2%), increased energy (adults: 2%), nightmares (adults: 2%), paresthesia (adults: 2%), tics (children 2%)	Dizziness, drug dependence, dysphoria, euphoria, exacerbation of tics (motor, vocal, Tourette's), headache, insomnia, overstimulation, psychotic symptoms, restlessness	Headache (transdermal; adults: 22%), insomnia (children: 3%-5%; adults: 12%), irritability (6%-11%), emotional lability (children: 6%-9%; adults: 1%), anxiety (8%), tics (oral; adolescents: 7%; TD; children: 2%), dizziness (adolescents: 2%-7%), depressed mood (4%), initial insomnia (≤4%), nervousness (3%), restlessness (3%), aggressive behavior (2%), agitation (2%), depression (2%), hypertonia (2%), vertigo (2%), confusion (1%), paresthesia (1%), sedation (1%), tension headache (1%), drowsiness, fatigue, Tourette's, hypervigilance, toxic psychosis, outbursts of anger, lethargy

Cardiovascular	Increased blood pressure, tachycardia, arrhythmias (at larger doses), stroke, MI	Increased blood pressure	Cardiomyopathy, hypertension, palpitations, tachycardia	Systolic hypertension (ER; adolescents: 12%-35%, transient), tachycardia (ER; adults: ≤6%), palpitations (ER: 2%-4%), MI, Raynaud's	Increased heart rate (adults: 2%-7%), increased blood pressure (adults: 3%)	Hypertension, increased blood pressure, palpitations, tachycardia	Tachycardia (5%; transdermal; children: ≤1%), palpitations (3%), angina pectoris, cardiac arrhythmias, cerebrovascular accident, decreased pulse, hypertension, increased pulse, myocardial infarction, necrotizing angitis, Raynaud's phenomenon
Dermatologic	Stevens-Johnson syndrome, Urticaria	Pruritis (children ≤3%)	Urticaria	Diaphoresis (ER: 2%-4%), skin photosensitivity (ER: 2%-4%), alopecia, dermatillomania, skin rash, urticaria	Hyperhidrosis (adults: 3%-4%), skin rash (children: 3%), pruritis (adults: 2%)	Urticaria	Hyperhidrosis (5%), excoriation (children: 4%), skin rash (children: 2%), alopecia, erythema multiforme, exfoliative dermatitis, urticaria
Endocrine and Metabolic	Change in Libido	Growth suppression	Change in libido, weight loss, growth suppression	Weight loss (ER: 4%-10%), decreased libido (ER: 2%-4%), dysmenorrhea (ER: 2%-4%), growth suppression	Weight loss (children: 9%; adults: 3%-4%), decreased libido (adults: <2%), growth suppression	Change in libido, growth suppression (children)	Weight loss (6%-9%), decreased libido (2%), growth suppression
Gastrointestinal	Upper abdominal pain (children: 4%), anorexia, constipation, diarrhea, dysguesia, GI distress, weight loss, xerostomia	Decreased appetite (children 30%), xerostomia (adults 7%-20%), abdominal pain (children 15%), nausea (children 9%), dyspepsia (5%-9%), vomiting (children 2%-9%), anorexia (children 5%-7%), pharyngolaryngeal pain (adults 4%-7%)	Anorexia, constipation, diarrhea, unpleasant taste, xerostomia	Decreased appetite (ER: 22%-36%), xerostomia (ER: 2%-4%), abdominal pain (ER: 11%-14%), nausea (ER: 2%-8%), vomiting (ER: 2%-7%), diarrhea (ER: 2%-6%), constipation (ER: 2%-4%), dyspepsia (ER: 2-4%), teeth clenching (ER: ≤4%), tooth infection (ER: ≤4%), anorexia (ER: 2%), bruxism, unpleasant taste	Decreased appetite (children: 34%-39%; adults: 8%-27%), xerostomia (children: 4%-5%; adults: 26%-36%), upper abdominal pain (children: 12%; adults: 2%), vomiting (children: 9%; adults: 2%), diarrhea (adults: 7%), nausea (6%-7%), constipation (adults: 6%), anorexia (adults: 5%), gastroenteritis (adults: 2%)	Constipation, diarrhea, gastrointestinal distress, unpleasant taste, xerostomia	Decreased appetite (≤26%), xerostomia (14%), nausea (10%-13%), vomiting (2%-10%), anorexia (transdermal: 2%-9%), abdominal pain (children: 5%-7%), bruxism (2%), dyspepsia (2%), motion sickness (children 2%), constipation (1%), diarrhea

Genitourinary	Impotence, erectile dysfunction	Priapism	Frequent erections, impotence, prolonged erection	Urinary tract infection (ER: 5%), impotence (ER 2%-4%), frequent/prolonged erections	Erectile dysfunction (adults: 3%)	Frequent erections, prolonged erections, impotence	Erectile dysfunction
Neuromuscular and Skeletal	Dyskenesia, tremor	Rhabdomyolysis	Dyskinesia, rhabdomyolysis, tremor	Dyskenesia, rhabdomyolysis, tremor	Tremor (adults: 2%)	Rhabdomyolysis, tremor	Tremor (3%), arthralgia, dyskinesia
Respiratory	Allergic rhinitis (children: 4%), epistaxis (children: 4%)	Nasal congestion (children ≤5%)	N/A	Dyspnea (ER: 2%-4%)	Dyspnea (adults: 2%), oropharyngeal pain (2%)	N/A	Nasopharyngitis (children 3%), cough (children 2%), upper respiratory tract infection (2%), oropharyngeal pain (1%-2%), dyspnea, pharyngitis, rhinitis, sunusitis
Miscellaneous	Dysmenorrhea, dyspnea, hyperhidrosis, growth suppression in children with long-term use, tooth disorder	Fever (children 5%)	Accommodation disturbances, blurred vision,	Blurred vision, mydriasis, fever (ER: 5%)	Fever (children 2%)	N/A	Fever (2%), accidental injury, increased serum bilirubin, immune thrombocytopenia, leukopenia, pancytopenia, application site reaction (transdermal)

<1%, Postmarketing	Aggression, alopecia, anaphylactic reaction, angioedema, blurred vision, bruxism, cardiomyopathy, constipation, Raynaud's phenomenon, peripheral vascular disease	Accommodation difficulties, anaphylaxis, Raynaud phenomenon, angioedema, blurred vision, hypersensitivity reactions	N/A	Cardiomyopathy, cerebrovascular accident, Tourette's exacerbation, exacerbation of vocal tics, peripheral vascular disease, seizure, SJS, TEN	Accommodation disturbance, aggressive behavior, anaphylaxis, blurred vision, bruxism, cardiomyopathy, decreased skeletal growth, frequent erections, depression, dyskinesia, diplopia, euphoria, dysphoria, hallucinations, hepatitis, hypersensitivity, prolonged erections, Raynaud's, SJS, TEN, peripheral vascular insufficiency	N/A	Hypersensitivity, abnormal behavior, abdominal distress, anaphylaxis, leukoderma (transdermal), tonic-clonic seizures, visual disturbances, weakness, chest pain, change in libido, hallucination, heart murmur, hot flash, muscle twitching

Summary

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common mental health disorder diagnosed in childhood which may continue into adulthood. ADHD is characterized by symptoms of hyperactivity, impulsivity and/or inattention. Untreated ADHD may lead to delinquent behavior, substance abuse or other comorbidities. The central nervous system (CNS) stimulant agents are indicated in the treatment of ADHD and may also be used in the treatment of exogenous obesity or narcolepsy. All of the CNS stimulants are available in oral capsule or tablet formulations and many of the agents are also available in extended-release, orally disintegrating and liquid formulations which may be helpful to improve compliance or patient preference. Clinical guidelines for the treatment of ADHD recommend behavioral therapy for preschool-aged children with ADHD, both medication and behavioral therapy for school-aged children with ADHD and medication therapy alone in adults with ADHD. The stimulant medications have demonstrated efficacy in the treatment of ADHD and are recommended as first-line treatment options in patients requiring medication therapy. The NICE guidelines (2008) recommend a methylphenidate agent as first-line, atomoxetine in patients with tics/Tourette's syndrome/anxiety disorder and dextroamphetamine in patients without an adequate response to methylphenidate or atomoxetine.

Clinical experience with the stimulant agents in treating patients with ADHD is extensive. The majority of comparative evidence evaluated in this report comes from the Oregon Report (including 369 studies) published in 2009 and 10 additional systematic reviews and clinical trials published after 2009. In general, clinical studies of stimulant medications in the treatment of ADHD are inconsistent and provide limited information with respect to comparative efficacy. Most clinical trials are limited by small sample sizes and short study durations. Based on the available evidence, it appears that all agents are similarly effective for treating ADHD. Studies evaluating differences in adverse event rates between the stimulant agents are also of fair quality and show mixed or inconsistent results. The most common adverse events reported with the stimulants include headache, insomnia, increased blood pressure, abdominal pain and decreased appetite. Weight loss and growth suppression are also reported with the agents; no differences in these adverse events are reported between methylphenidate and amphetamine therapy and discontinuing treatment results in resumption of normal growth. According to clinical evidence summarized in the Oregon Report, the most serious adverse reaction associated with stimulant therapy is sudden cardiac death which is very rare, estimated at less than one event per 1 million prescriptions. The stimulant agents are Schedule II controlled substances due to high potential for abuse and should be avoided in patients with a history of substance abuse or in patients with high risk of misuse.

Overall, the CNS stimulant agents are effective treatment options for ADHD. When compared in clinical trials, the agents demonstrate similar rates of safety and efficacy. The stimulants are available in many dosage forms, varying potencies and differing durations of action. Treatment management must be individualized for each patient and include careful evaluation of patient age, comorbidities and medical history.

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Appendix: Evidence Tables

Evidence Table 1. Systematic Reviews Evaluating the Central Nervous System Stimulant Agents

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Brams et al, 2010[84] 15 randomized, controlled trials 378 patients (five trials) were treated with long-acting amphetamine formulations; 794 patients (10 trials) were treated with long-acting methylphenidate formulations	1172	Patients with ADHD	Long-acting stimulants: • Lisdexamfetamine dimesylate • Mixed amphetamine salts extended release • Dextroamphetamine extended release • Long-acting methylphenidate • Methylphenidate extended release • Dexmethylphenidate extended release	Duration of efficacy • Lisdexamfetamine dimesylate: up to 14 hours (3 trials) • Mixed amphetamine salts: up to 12 hours (2 trials) • Dextroamphetamine: 4 hours (1 trial) • Methylphenidate; osmotically controlled-release oral delivery system: up to 12 hours (4 trials) • Methylphenidate; spheroidal oral drug absorption system: up to 12 hours (2 trials) • Methylphenidate; extended release: up to 7.5 hours (1 trial) • Dexmethylphenidate: up to 12 hours (5 trials)	Not reported
Fredriksen et al, 2012[85] Systematic review of 5 randomized controlled trials, 10 open-label extension studies, 18 naturalistic longitudinal, cross-sectional studies	3176	Patients with ADHD	Methylphenidate Amphetamine Atomoxetine	Efficacy • Methylphenidate > placebo • Amphetamine > placebo • Atomoxetine > placebo "Observational studies also showed positive correlations between early recognition of the disorder, stimulant treatment during childhood and favorable long-term outcome in adult ADHD patients."	Decreased appetite • Methylphenidate > placebo Mucosal dryness • Methylphenidate > placebo Changes in cardiovascular parameters • Methylphenidate > placebo • Amphetamine > placebo Upper respiratory infections • Lisdexamfetamine > other stimulants = placebo

Reference/ Study Design	N	Patient Population	Treatment Interventions	Results	Safety
Roskell et al, 2014[86] Systematic review and meta-analysis of 32 randomized, controlled clinical trials	NR	Children and adolescents with attention deficit hyperactivity disorder (ADHD)	Methylphenidate Dexamphetamine Atomoxetine	Treatment response • Lisdexamfetamine > Methylphenidate	Adverse event withdrawal rate • Lisdexamfetamine > Methylphenidate
Stuhec at al, 2015[87] Meta-analysis of 28 double-blind, placebo-controlled, non-crossover studies	NR	Children and adolescents with attention deficit hyperactivity disorder (ADHD)	Atomoxetine Bupropion Lisdexamfetamine Methylphenidate	Reducing ADHD symptoms • Lisdexamfetamine > Methylphenidate = Atomoxetine > Bupropion $\geq$ Placebo Treatment discontinuation rate • Methylphenidate < Placebo; $p < 0.05$ • Lisdexamfetamine = Placebo	Not reported

Key: NR = not reported

Evidence Table 2. Clinical Trials Evaluating the Central Nervous System Stimulant Agents

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Christensen et al, 2010[92] Retrospective claims-based analysis	60,010	Patients with at least one claim with a diagnosis code for ADHD and a filled prescription for ADHD medication	Stimulant and non-stimulant medications	Persistence • Stimulants > Nonstimulants, p < 0.0001 • Amphetamines > Methylphenidates, p < 0.0001 • Long-acting > Short- and Intermediate-acting; p < 0.0001 Adherence rates • Stimulants > Nonstimulants, p < 0.0001 • Amphetamines > Methylphenidates, p < 0.0001 • Long-acting > Short- and Intermediate-acting; p < 0.0001 Dose changes • Nonstimulant < Stimulants; p < 0.0001 • Methylphenidates < Amphetamines; p < 0.0001 • Intermediate-acting drugs < Short- and Long-acting drugs; p < 0.0001	Not reported
Spencer et al, 2011[89] Randomized, single-blind, controlled trial	53	Adults with ADHD	Methylphenidate extended-release Methylphenidate immediate-release Duration: 6 weeks	Reduced symptoms • Methylphenidate ER = Methylphenidate IR Patient preference • Methylphenidate ER = Methylphenidate IR Missed doses • Methylphenidate ER < Methylphenidate IR; p = 0.02	Adverse Effects • Methylphenidate ER = Methylphenidate IR

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Stein et al, 2011[91] Randomized double-blind, crossover study	56	Children and adolescents with ADHD	Dexmethylphenidate, long-acting extended-release Mixed amphetamine salts, extended-release Duration: 8 weeks	Reduction of ADHD symptoms • dexmethylphenidate = mixed amphetamine salts • higher dose > lower dose	Reduced appetite • dexmethylphenidate = mixed amphetamine salts Insomnia • dexmethylphenidate = mixed amphetamine salts
Coghill et al, 2013[88,97] Randomized, double-blind, parallel-group, dose-optimized, controlled study	336	Children (6–12 years old) and adolescents (13–17 years old)	Lisdexamfetamine (n = 113) Osmotic-release oral system methylphenidate (n = 112) Placebo (n = 111) Duration: 7 weeks	Lack of efficacy discontinuation rate: • Lisdexamfetamine: 11/113 (9.7%) • Methylphenidate: 22/112 (19.6%) • Placebo: 54/111 (48.6%) Investigator-rated ADHD-RS-IV total score • Lisdexamfetamine < Placebo • Methylphenidate < Placebo	Treatment emergent adverse effects • Lisdexamfetamine: 80/111 (72.1%) • Methylphenidate: 72/111 (64.9%) • Placebo: 63/110 (57.3%)
Martin et al, 2013[90] Randomized, Double-Blind, Placebo-Controlled, Crossover Study	18	Adults with Attention-Deficit/ Hyperactivity Disorder	Lisdexamfetamine dimesylate (LDX) 50mg/day Mixed amphetamine salts, immediate release 20 mg/day Placebo	Improvement in Cognitive Drug Research Computerized Battery of Tests • Lisdexamfetamine > Placebo • Mixed amphetamine salts > Placebo	Decreased appetite • Lisdexamfetamine > Placebo • Mixed amphetamine salts > Placebo Mucosal dryness • Lisdexamfetamine > Placebo • Mixed amphetamine salts > Placebo

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Results	Safety
Setyawan et al, 2013[93] Retrospective database analysis	NR	Patients with Attention-Deficit/ Hyperactivity Disorder	Lisdexamfetamine (LDX) Other FDA-approved stimulants and non-stimulant medications (atomoxetine (ATX), osmotic release methylphenidate hydrochloride long acting (OROS MPH), other methylphenidate/ dexmethylphenidate long acting (MPH LA) and short acting (MPH SA), and amphetamine/ dextroamphetamine short acting (AMPH SA) and long acting (AMPH LA))	Treatment adherence • Lisdexamfetamine > Other stimulants (exceptions below) Treatment adherence in treatment-naïve children and adolescents • OROS MPH > LDX Treatment adherence in adults • AMPH LA > LDX	Not reported

Key: NS = not significant; NR = not reported