ADHD Diagnosis & Treatment: A Review for Pharmacists

Objectives: After completing this activity, participants should be able to:

1. Recognize the signs and symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD).
2. Describe the clinical practice guideline changes for diagnosing and treating ADHD.
3. Explain the role of pharmacologic treatments, including mechanisms of action, dosing, side effects, and drug interactions.
4. Identify and recommend pharmacologic and nonpharmacologic treatment interventions for patients with ADHD.

Data sources: Recently published articles in Medline and PsychInfo, reviews in the Cochrane Database, and resources on various government, proprietary, and pharmaceutical manufacturer websites, identified using search terms such as ADHD, attention deficit hyperactivity disorder, pharmacotherapy, and the names of specific drugs and drug classes, as well as bibliographies of gathered articles.

Summary: ADHD is a common disruptive behavioral disorder that presents in childhood and frequently persists into adolescence. It is one of the most prevalent psychiatric disorders and is now understood to be a lifelong condition for most individuals, with many more adults being diagnosed today. An increase in the prescribing of ADHD medications has also become more prevalent, with the use of stimulant medications on the rise. As a practicing South Carolina pharmacist, one must become well-informed about the many treatment options for ADHD and apply the most recent clinical guideline updates for managing ADHD in children and adolescents to current practice.

Conclusion: Although it is one of the most common behavioral disorders in childhood, ADHD often progresses into adolescence and even adulthood and may cause significant distress in a person’s life. The criteria for diagnosing ADHD are listed in the DSM-IV-TR, with changes to the subtypes in the upcoming DSM-5 (scheduled for May 2013), and include symptoms of hyperactivity, impulsivity, and inattention. Upon completion of this learning activity, one will be able to identify the signs and symptoms of ADHD, understand the diagnostic criteria and various subtypes, and make treatment recommendations to prescribers to include pharmacologic and nonpharmacologic therapy with an overall goal of improving the quality of life of the patient. Updates to clinical practice guidelines for the diagnosis, evaluation, and treatment of ADHD in children and adolescents will also be reviewed.

Keywords: ADHD, attention-deficit/hyperactivity disorder, adult, pediatric, adolescent, stimulants, alpha adrenergic agonists, norepinephrine reuptake inhibitor

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), sometimes referred to as Attention Deficit Disorder (ADD), is the most common neurobehavioral disorder of childhood.\(^1\) ADHD can make it difficult for children to do well in school, in their ability to make and keep friends, and in their ability to function in society. Boys are four times more likely to receive a diagnosis of ADHD than girls as they usually present with more disruptive behaviors. ADHD is a lifespan condition not only affecting children and adolescents, but also adults of all ages.\(^2\) According to data from the National Health and Nutrition Examination Survey (NHANES) in 2009, the prevalence of ADHD in children and adolescents was almost nine percent with symptoms persisting into adulthood in approximately four percent of adults.\(^3\) To appreciate where South Carolina compares to the national average of ADHD prevalence, the community-based Project to Learn About ADHD in Youth (PLAY) study found the ADHD prevalence in SC school-aged children to be 8.7% and the prevalence of ADHD medication use was 10.1%.\(^4\) The PLAY study also reported that only 39.5% of patients medicated in SC met the case definition of an ADHD diagnosis.\(^4\) Pharmacists, as medication experts, can fulfill the need for accurate
counseling on pharmacotherapy used to manage ADHD and provide assistance to patients with ADHD and their parents or caregivers as well as assist practitioners in appropriate medication selection.

DIAGNOSIS OF ADHD

There is no single diagnostic test for ADHD. A thorough diagnostic evaluation uses medical, psychological, educational, and social resources. A complete history and evaluation of the patient are critical in determining a diagnosis of ADHD. The criteria for diagnosing ADHD are described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). One must have at least six (or more) symptoms of inattention OR at least six (or more) symptoms of hyperactivity/impulsivity that are present for at least six months. Table 1 categorizes symptom descriptions. The symptoms must be present before seven years of age, although new ADHD clinical practice guidelines will extend the age to 12 years. The symptoms must interfere with or reduce the quality of social, academic, or occupational functioning. Also, the symptoms should be witnessed in two or more settings (e.g., at school and at home) in order to meet the criteria for ADHD diagnosis. These symptoms cannot be due to another psychiatric disorder (e.g., mood disorder or personality disorder). Several ADHD subtypes exist, with classification determined by the specific presentation of symptoms. Table 2 classifies ADHD subtypes.

Table 1: ADHD Symptoms (Adapted from DSM-IV-TR)

<table>
<thead>
<tr>
<th>Inattention:</th>
<th>Hyperactivity:</th>
<th>Impulsivity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carelessness</td>
<td>Fidgets with hands/feet or squirms in seat</td>
<td>Difficulty waiting for turn</td>
</tr>
<tr>
<td>Reduced attention</td>
<td>Inability to remain seated in class</td>
<td>Inturrupts or intrudes on others</td>
</tr>
<tr>
<td>Poor listening skills</td>
<td>Uncontrolled restlessness</td>
<td>Difficulty playing or engaging in leisure activities quietly</td>
</tr>
<tr>
<td>Failure to complete tasks or follow instructions</td>
<td>Difficulty organizing</td>
<td>Often “on the go”</td>
</tr>
<tr>
<td>Difficulty organizing</td>
<td>Avoidance of chores/homework</td>
<td>Excessive talking</td>
</tr>
<tr>
<td>Avoidance of chores/homework</td>
<td>Loses items frequently (i.e., books, homework, tools)</td>
<td>Difficulty waiting for turn</td>
</tr>
<tr>
<td>Easily distracted by extraneous stimuli</td>
<td>Often “on the go”</td>
<td>Inturrupts or intrudes on others</td>
</tr>
<tr>
<td>Forgetful in daily activities</td>
<td>Excessive talking</td>
<td>Difficulty playing or engaging in leisure activities quietly</td>
</tr>
</tbody>
</table>

Table 2: ADHD Subtypes

<table>
<thead>
<tr>
<th>ADHD Subtype</th>
<th>Symptom Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined</strong></td>
<td>6 or more symptoms present for past 6 months from each category (hyperactivity/impulsivity &amp; inattention)</td>
</tr>
<tr>
<td><strong>Predominately Inattentive</strong></td>
<td>6 or more symptoms of inattention met and 3 or more hyperactivity/impulsivity symptoms present for past 6 months</td>
</tr>
<tr>
<td><strong>Inattentive Restrictive</strong>*</td>
<td>6 or more symptoms of inattention met but no more than 2 hyperactivity/impulsivity symptoms present for past 6 months</td>
</tr>
<tr>
<td><strong>Predominately Hyperactive/Impulsive</strong></td>
<td>6 or more symptoms of hyperactivity/impulsivity present but symptoms of inattention not met for past 6 months</td>
</tr>
</tbody>
</table>

*Designates new subtype in upcoming DSM-5
ADHD is a chronic condition and data collected from multiple prospective longitudinal studies of ADHD children followed 10 to 20 years into adulthood have shown that up to 65% of these children will continue to have persistent ADHD symptoms that cause impairment. Medical conditions that may mimic adult ADHD such as hyperthyroidism, seizure disorders, hearing deficits, lead toxicity, and sleep apnea should be ruled out as potential causes. High rates of psychiatric comorbidities including oppositional defiant disorder, conduct disorder, bipolar disorder, major depressive disorder, and anxiety disorders add complexity to the diagnosis and are fairly prevalent across the lifespan of patients with ADHD. Comorbid conditions such as substance abuse and anxiety disorders are present in 30% to 50% of adult patients with ADHD. Although treatment of patients with comorbid psychiatric disorders is often convoluted, typically the symptom-predominant disorder is treated first.

ADHD ETIOLOGY AND PATHOPHYSIOLOGY

The specific cause of ADHD is unknown, but it appears to be multifaceted. Twin studies have shown the heritability of ADHD to be about 90%, although no single gene has been identified. A positive family history for ADHD is a risk factor, and children with a first-degree relative with the diagnosis have up to eight times an increase in the chance of developing ADHD versus the general population. Other risk factors for the development of ADHD include maternal smoking, alcohol exposure during pregnancy, perinatal stress, low birth weight, exposure to lead, severe traumatic brain injury, and early social deprivation.

The neurobiology and pathophysiology of ADHD is complex in nature and is not completely understood. Imbalances in dopaminergic and noradrenergic systems are implicated in the core ADHD symptoms and support the dysfunctional catecholamine neurotransmission theory. ADHD is primarily viewed as a disorder where norepinephrine and dopamine signals in the cerebral cortex are weak, resulting in inefficient processing of information and difficulty sustaining attention, resulting in ADHD symptoms. Increasing the activity of dopamine at the postsynaptic D1 receptor and norepinephrine at the postsynaptic alpha2A receptor has shown to help alleviate the symptoms associated with ADHD. However, overstimulation at these receptors may result in deterioration of symptom control and also lead to symptoms of poor attention and impulsivity. Therefore, the primary goal of ADHD symptom control involves maintaining an adequate equilibrium of catecholamine neurotransmission in the prefrontal cortex.

PHARMACOTHERAPY

Currently available Food and Drug Administration (FDA) approved medications for treating ADHD target catecholamine neurotransmission in the central nervous system. Most of the agents work by blocking the presynaptic reuptake of dopamine, norepinephrine, or both in the prefrontal cortex. Other agents target postsynaptic alpha2A receptors, acting as agonists, and mimic the action of norepinephrine. To date, no FDA-approved agents exist that specifically act as agonists at D1 receptors. Pharmacotherapy is an important component of treatment, with stimulants serving as first-line treatment options in the majority of patients. According to the American Academy of Pediatrics 2011 clinical practice guidelines for the treatment of ADHD in children and adolescents, new recommendations allow for evaluating and treating children and adolescents in the 4-year to 18-year range as opposed to the much more limited 6-year to 12-year range previously. FDA-approved medications for ADHD are recommended as first-line interventions for children ages six to 11 years of age as well as adolescents (12 to 18 years of age). Careful dosage titration to FDA-approved dose ranges should occur in order to achieve the desired effect while minimizing side effects.

Treatment recommendations for preschool children, ages four to five years, have also been revised. Behavioral therapy is recommended as first-line treatment, and may include parent training, classroom management, and peer interventions. Treatment with methylphenidate is recommended in children who do not respond to behavioral techniques. Currently there are no FDA-approved methylphenidate preparations for use in children under six years of age, thus stimulant treatment in this patient population remains controversial, and
should be carefully reviewed. Some believe that preschoolers should only be treated with medication in special circumstances by expert clinicians in the field of ADHD in order to ensure the diagnosis is indeed correct. Parents should be counseled on the overall benefits and risks of using stimulants as their preference is critical in determining the overall treatment plan for the child.

Stimulants

Stimulants are considered a first-line intervention for ADHD, unless there are comorbidities or safety issues that preclude their use. The two categories of stimulants used in the treatment of ADHD are methylphenidate and amphetamines. Both classes of medications work by blocking the reuptake of dopamine and norepinephrine in the prefrontal cortex, and amphetamines additionally cause the release of catecholamines from vesicular storage sites. Methylphenidate and amphetamines are equally effective in controlling ADHD symptoms, with efficacy rates ranging from 70% to 90%. Treatment failure is defined by lack of satisfactory improvement in core symptoms of ADHD while on the maximum dose or the occurrence of intolerable side effects. When a patient experiences treatment failure, a switch between stimulant classes is recommended (e.g., if a patient failed treatment with an amphetamine product, then switch to a methylphenidate product and vice versa).

Stimulants are available in many different formulations including short-acting, intermediate-acting, and long-acting preparations. Various delivery devices such as the wax-matrix systems, beaded delivery systems, osmotic release oral system (OROS), and transdermal patches exist among the intermediate- and long-acting preparations. Another unique delivery device is the prodrug lisdexamfetamine which has a lysine residue attached to its amphetamine structure. Once ingested, the lysine residue is cleaved via enzymatic hydrolysis and transformed into an active amphetamine. The enzymatic process results in lisdexamfetamine’s long half-life, and the novel delivery system is thought to have lower abuse potential compared to immediate-release stimulants. See Table 3 for detailed descriptions of currently available stimulants in the U.S.

Although short-acting agents exist, treatment may begin with long-acting preparations of stimulants in order to improve adherence, allow for ease of once-daily administration, and provide overall benefit. It is not necessary to initiate treatment with short-acting products and transition to long-acting products. Long-acting formulations also prevent children in school from having to receive mid-day doses of immediate-release stimulants, and may decrease the stigma of the disorder in this population. Because pharmacists are aware of the mechanisms of side effects and are easily accessible healthcare professionals, they can assist in guiding patients and caregivers in appropriate treatment selection by discussing the overall risks and comparing the benefits of treatment.

Table 3: Stimulant Medications Approved by FDA for ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval</th>
<th>Available Formulations</th>
<th>Dose</th>
<th>Length of Action (h)</th>
<th>Patient Counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylphenidate preparations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPH IR (Ritalin®, Methylin®)</td>
<td>Age ≥ 6 years</td>
<td>5, 10, 20 mg tablets (Ritalin®); 2.5, 5, 10 mg chewable tablets &amp; 5 mg/5 mL &amp; 10 mg/5 mL oral solution (Methylin®)</td>
<td>5 mg BID; max 60 mg/day</td>
<td>3-4</td>
<td>May be crushed; dose up to TID; give chew tabs with at least 8 ounces of fluid</td>
</tr>
<tr>
<td>Dex-MPH</td>
<td>Age ≥ 6</td>
<td>2.5, 5, 10 mg tablets</td>
<td>2.5 mg BID;</td>
<td>5</td>
<td>Active enantiomer of</td>
</tr>
<tr>
<td>Focalin®</td>
<td>years</td>
<td>max 20 mg/day</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---------</td>
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<td></td>
</tr>
</tbody>
</table>
| MPH; twice as potent as MPH

### Intermediate-acting

<table>
<thead>
<tr>
<th>Metadate ER®, Ritalin SR®</th>
<th>Age ≥ 6 years</th>
<th>20 mg tablets</th>
<th>20 mg QAM, max 60 mg/day</th>
<th>8</th>
<th>May dose up to BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metadate CD®</td>
<td>Age ≥ 6 years</td>
<td>10, 20, 30, 40, 50, 60 mg capsules</td>
<td>20 mg QAM, max 60 mg/day</td>
<td>8-9</td>
<td>May open &amp; sprinkle on soft food</td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>Age ≥ 6 years</td>
<td>10, 20, 30, 40 mg capsules</td>
<td>20 mg QAM, max 60 mg/day</td>
<td>7-9</td>
<td>May open &amp; sprinkle on soft food</td>
</tr>
</tbody>
</table>

### Long-acting

<table>
<thead>
<tr>
<th>Concerta®</th>
<th>Age ≥ 6 years</th>
<th>18, 27, 36, 54 mg tablets</th>
<th>18 mg QAM, max 54 mg/day (6-12y), max 72 mg/day (≥13y)</th>
<th>12</th>
<th>Oral osmotic controlled-release (OROS) delivery system; must take with fluid; tablet shell may appear in stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytrana®</td>
<td>Age 6-17 years</td>
<td>10, 15, 20, 30 mg/9 hr transdermal patches</td>
<td>10 mg applied QAM, max 30 mg</td>
<td>12</td>
<td>Alternate placement daily to hip; apply 2 hours before desired effect; do not exceed 9 hour total wear time</td>
</tr>
<tr>
<td>Focalin XR®</td>
<td>Age ≥ 6 years</td>
<td>5, 10, 15, 20, 25, 30, 35, 40 mg capsules</td>
<td>5 mg QAM, max 30 mg/day (children); 10 mg QAM, max 40 mg/day (adults)</td>
<td>12</td>
<td>May open and sprinkle on soft food</td>
</tr>
</tbody>
</table>

### Amphetamine Preparations

#### Short-acting

<table>
<thead>
<tr>
<th>Mixed AMP salts (Adderall®)</th>
<th>Age ≥ 3 years</th>
<th>5, 7.5, 10, 12.5, 15, 20, 30 mg tablets</th>
<th>2.5 mg QAM (3-5 y); 5 mg QD – BID (≥ 6 y); max 40 mg/day</th>
<th>4</th>
<th>Racemic mixture of D- and L-enantiomers; dosed 2-3 times daily; higher doses in adults (max 60 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextro-AMP (Dextrostat®, Dexedrine®, ProCentra®/Liquadd®)</td>
<td>Age ≥ 3 years</td>
<td>2.5, 5, 10 mg tablets (Dextrostat®); 5, 10 mg capsules (Dexedrine®); 5 mg/5 mL oral solution (ProCentra®/Liquadd®)</td>
<td>2.5 mg QAM (3-5 y); 5 mg QD - BID (≥ 6 y); max 40 mg/day</td>
<td>4</td>
<td>Short-acting stimulants often used in small children (&lt;16 kg) initially, dosed BID-TID to control symptoms throughout day</td>
</tr>
</tbody>
</table>
### Long-acting

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Age Range</th>
<th>Dosage</th>
<th>Route</th>
<th>Training</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixed AMP salts, extended release (Adderall XR®)</strong></td>
<td>≥ 6 years</td>
<td>5, 10, 15, 20, 25, 30 mg capsules</td>
<td>5-10 mg QAM, max 30 mg/day (6-12 y); 10-20 mg QAM, max 60 mg/day (≥ 13 y)</td>
<td>12</td>
</tr>
<tr>
<td><strong>Dextro-AMP, sustained release (Dexedrine Spansule®)</strong></td>
<td>≥ 6 years</td>
<td>5, 10, 15 mg capsules</td>
<td>5-10 mg QD-BID, max 40 mg/day</td>
<td>12</td>
</tr>
<tr>
<td><strong>Lisdex-amfetamine (Vyvanse®)</strong></td>
<td>≥ 6 years</td>
<td>20, 30, 40, 50, 60, 70 mg capsules</td>
<td>30 mg QAM, max 70 mg/day</td>
<td>13</td>
</tr>
</tbody>
</table>

*Abbreviations: MPH = methylphenidate; AMP = amphetamine; QD = once daily; BID = twice daily; QAM = once daily every morning; TID = three times daily*

### Adverse Effects - Stimulants

The stimulant medications are fairly well tolerated. The primary adverse effects reported include insomnia, appetite suppression, weight loss, headache, stomach upset, and slight increases in blood pressure and pulse. These adverse effects typically subside over time as patients become tolerant, but options are available to minimize them. Pharmacists may counsel patients to take their medicine with a meal if gastrointestinal upset persists, although the time to effect may be delayed. Insomnia is more noticeable with long-acting preparations, especially the long-acting amphetamine products. Pharmacists may advise patients to try nonpharmacological strategies for controlling insomnia secondary to stimulants (e.g., do not watch TV in bed, do not exercise right before bedtime, bedroom should only be used for sleep, etc). Other possible pharmacist recommendations include moving the dose to an earlier time in the day or reducing the total daily dose of the stimulant. If insomnia persists despite interventions, then a switch to an immediate-release formulation may occur. Adjunctive agents may be used if nonpharmacological treatment strategies fail. Adjunctive treatment options include melatonin, diphenhydramine, cyproheptadine, clonidine, and guanfacine.

Appetite suppression is an adverse effect that can be challenging for caregivers and patients alike. A recommendation to patients by pharmacists should include eating their highest calorie containing meal of the day at breakfast, before taking the medication. High calorie drinks or snacks may also be used throughout the day when the stimulant has worn off if weight loss is an issue. If weight loss continues to be problematic and is impacting growth, then a switch to another stimulant or nonstimulant medication is indicated. Frequent monitoring of height and weight is recommended in children and adolescents during treatment, and an interruption in therapy may be necessary if a patient is not gaining adequate weight or growing.

Patients may express concern about the potential cardiovascular effects associated with stimulant use. In patients with underlying structural heart abnormalities, or cardiomyopathies, sudden cardiac death has occurred. Stimulant therapy should be avoided in patients with underlying cardiac problems. A complete patient and family history should be assessed prior to stimulant initiation. An EKG should also be performed if high-risk conditions are suspected based on the patient’s history or clinical findings. Blood pressure and pulse should be monitored routinely at each follow-up, especially if dizziness is present.
Because stimulants have a high potential for abuse, a black-box warning for drug dependence is listed under each amphetamine and methylphenidate preparation. Stimulants should be prescribed cautiously to patients with a history of drug dependence. Particular attention should be paid to the possibility of subjects obtaining stimulants for non-therapeutic use or distribution to others. Although the majority of stimulant medications for ADHD are used appropriately by individuals, survey studies have indicated that approximately 5% of college students have misused stimulants. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. Psychotic episodes can occur, especially with parenteral abuse.

**Nonstimulants**

Nonstimulant medications approved by the FDA for the treatment of ADHD include atomoxetine, clonidine extended release, and guanfacine extended release. Atomoxetine is a selective norepinephrine reuptake inhibitor used in the treatment of ADHD in children and adults. Atomoxetine increases the levels of norepinephrine in the prefrontal cortex by binding to the norepinephrine transporter and blocking reuptake. Despite atomoxetine’s proof of efficacy from multiple double-blind, randomized, placebo controlled trials, it has shown to be inferior when compared to stimulants such as long-acting methylphenidate OROS and mixed-amphetamine salts. Atomoxetine may be used as a first- or second-line treatment option for children and adults, but the efficacy rates are lower compared with stimulants. The primary advantage of atomoxetine is that it is not a controlled substance, and it can be used safely in patients with substance use disorders.

Two alpha2-adrenergic agonists have been approved by the FDA for the treatment of ADHD in children six to 17 years old: clonidine extended release and guanfacine extended release. As with atomoxetine, neither agent is a stimulant or a controlled substance. Both clonidine and guanfacine immediate-release have been used for many years as off-label treatments in ADHD. Although the exact mechanism of action for controlling ADHD symptoms is not well understood, it is most likely due to their binding to post-synaptic alpha2A receptors in the prefrontal cortex. Often, these agents are used in conjunction with stimulants for their sedating effects and help with sleep or rebound symptoms; however, they may be used first line in ADHD if there is a concern about substance abuse, drug diversion, or if contraindications to stimulant use exist. See Table 4 for detailed descriptions of currently available nonstimulants used for ADHD in the U.S.

**Table 4: Nonstimulant Medications Approved by FDA for ADHD**

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approval</th>
<th>Available Formulations</th>
<th>Dose</th>
<th>Onset of Action</th>
<th>Patient Counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine (Strattera®)</td>
<td>Age ≥ 6 years</td>
<td>10, 18, 25, 40, 60, 80, 100 mg capsules</td>
<td>0.5 mg/kg/day titrated up to 1.2 mg/kg/day (children &amp; adolescents &lt;70kg); 40 mg QD, max of 100 mg/day (adults)</td>
<td>2 – 4 weeks; 12 h duration</td>
<td>Reduce dose with strong CYP2D6 inhibitors (paroxetine, fluoxetine); may divide doses BID, but give 2nd dose in early evening; black-box warning for increased suicidal thinking in children and adolescents</td>
</tr>
<tr>
<td>Clonidine extended release (Kapvay®)</td>
<td>Age 6 – 17 years</td>
<td>0.1, 0.2 mg tablets</td>
<td>0.1 mg at bedtime, max 0.4 mg/day</td>
<td>2 – 4 weeks; 12 h duration</td>
<td>Must taper dose when discontinuing therapy; give BID if &gt;0.1 mg/day needed</td>
</tr>
<tr>
<td>Guanfacine extended release (Intuniv®)</td>
<td>Age 6 – 17 years</td>
<td>1, 2, 3, 4 mg tablets</td>
<td>1 mg QD, max 4 mg/day</td>
<td>2 – 4 week onset; 16 h</td>
<td>Less sedation compared to clonidine; must taper dose when discontinuing therapy; do NOT crush, chew or split;</td>
</tr>
</tbody>
</table>
Antidepressants such as bupropion, desipramine, clomipramine, imipramine, nortriptyline, and amitriptyline have also demonstrated efficacy in improvement of ADHD symptoms in both pediatric and adult populations.\textsuperscript{38,39} None are FDA-approved for the treatment of ADHD, and they are not recommended as first-line treatment options.\textsuperscript{39} However, patients with comorbidities, substance abuse, or patients who have failed stimulants or have contraindications to stimulants, may benefit from their use.\textsuperscript{40} It is important to note side effects, delayed response time (three to four weeks), contraindications, and black-box warnings associated with the antidepressants before recommending their use.\textsuperscript{40}

**Adverse Effects – Nonstimulants**

Adverse effects of atomoxetine include nausea, vomiting, and somnolence and usually occur upon initiation of therapy or dose increases which tend to resolve after several days of therapy.\textsuperscript{30,32} Decreased appetite can occur, but it is much less of a problem than with stimulants.\textsuperscript{32} Since atomoxetine undergoes hepatic metabolism via CYP2D6, caution is advised when given with strong CYP2D6 inhibitors such as fluoxetine and paroxetine and a reduction in dose may be necessary.\textsuperscript{18} Patients with a genetic polymorphism for the allele that codes for CYP2D6 that makes them poor metabolizers of the drug may also require a dose reduction, since the half-life of atomoxetine can be prolonged resulting in increased serum concentrations.\textsuperscript{18}

Adverse effects of the alpha\textsubscript{2}-adrenergic agonists include somnolence (especially with clonidine), bradycardia, and syncope.\textsuperscript{26,36} It is recommended that blood pressure and heart rate are monitored upon initiation and discontinuation of therapy.\textsuperscript{26} EKG monitoring is not necessary with either agent.\textsuperscript{11} It is important to note that the extended release tablets for both guanfacine ER and clonidine ER are not bioequivalent to their immediate release counterparts, therefore, one should not be substituted milligram-per-milligram for the other.\textsuperscript{18}

**Summary**

The past decade has seen several new pharmacotherapeutic interventions for ADHD treatment. ADHD diagnostic criteria have been updated with the official changes expected to be published in the fifth edition of the DSM in May 2013.\textsuperscript{6} The symptoms of ADHD can be debilitating and cause significant impairment in one’s daily life. Children, adolescents, and adults may be affected with this disorder.\textsuperscript{38} Emphasis of treatment should be placed on appropriate diagnosis and management of ADHD symptoms in order to improve patient outcomes. Pharmacists must stay up-to-date with current evidence and be familiar with the various agents available in order to provide accurate and consistent education, training, and counseling to patients, providers, and caregivers.
REFERENCES


LEARNING ASSESSMENT QUESTIONS:

1. Which of the following statements about ADHD are true?
   a. Diagnosis of ADHD requires at least 6 symptoms of hyperactivity, impulsivity, and/or inattentiveness to be present for at least 6 months.[ET1]
   b. Girls are diagnosed with ADHD more often than boys in the U.S.[ET2].
   c. Nonstimulants may be abruptly discontinued if no improvement of symptoms is seen.[ET3]
   d. All of the above

2. All of the following FDA-approved medications for ADHD are classified as Schedule II controlled substances except:
   a. atomoxetine[ET4]
   b. dextroamphetamine
   c. lisdexamfetamine
   d. methylphenidate[ET5]

3. Which of the following would be the best choice for initial treatment of a 4-year-old boy recently diagnosed with ADHD?
   a. atomoxetine
   b. behavioral parent training program[ET6]
   c. long-acting methylphenidate
   d. short-acting methylphenidate

4. Which of the following medications for ADHD should be tapered upon discontinuation?
   a. clonidine extended release[ET7]
   b. dextroamphetamine extended release
   c. methylphenidate extended release
   d. all of the above

5. Adverse effects of stimulants used for the treatment of ADHD include all of the following except:
   a. appetite suppression
   b. headache
   c. insomnia[ET8]
   d. weight gain[ET9]

6. Which stimulant medication is a prodrug that is activated in the gastrointestinal tract once the lysine residue is cleaved?
   a. Concerta®
   b. Focalin®
   c. Kapvay®
   d. Vyvanse®[ET10]
7. Antidepressants such as bupropion and desipramine may be used for the treatment of ADHD in which of the following instances?
   a. An instant response is needed
   b. Comorbid substance use disorder is present
   c. First-line FDA-approved treatment is required
   d. All of the above

8. Which agent used to treat ADHD is a selective inhibitor of norepinephrine reuptake?
   a. Adderall®
   b. Intuniv®
   c. Strattera®
   d. Vyvanse®