



## **Clinical Practice Guideline for Patients with Attention-Deficit/Hyperactivity Disorder**

## Magellan Healthcare Clinical Practice Guideline Taskforce

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## Purpose of This Document

Magellan Healthcare’s (Magellan’s) clinical practice guideline serves as an evidence-based framework for practitioners’ clinical decision-making for child, adolescent and adult patients with attention-deficit/hyperactivity disorder (ADHD). In June 2008, we revised the medications section of this document to include the American Heart Association’s (AHA) recommendations for screening children who may be vulnerable to sudden cardiac death. In September 2008, Magellan revised this section again to include a joint advisory statement of the American Academy of Pediatrics (AAP) and the AHA, issued as clarification to widespread misinterpretation of the earlier AHA recommendations. These new recommendations were endorsed by the American Academy of Child and Adolescent Psychiatry (AACAP), the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, the National Initiative for Children’s Healthcare Quality and the Society for Developmental and Behavioral Pediatrics. In 2015, we conducted another review of the published scientific literature and made numerous updates throughout the guideline.

In preparation of the 2020 revision, we conducted a review of the published scientific literature between March 2018 and May 2020. This guideline covers the main areas of psychiatric management of patients with ADHD, including topics from clinical features and epidemiology to various aspects of treatment approaches and planning. Nonetheless, it is not exhaustive as the behavioral health field is rapidly evolving with continuous changes in assessment and management techniques. While this guideline provides a brief overview, the reader is encouraged to review other sources that incorporate current and ongoing clinical developments, including the recently updated AAP Clinical Practice Guideline for the Diagnosis, Evaluation and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents (2019) with its companion Supplemental Information on systemic barriers to care and the . Comparative Effectiveness Review No. 203. AHRQ Publication No. 18-EHC005-EF. Agency for Healthcare Research and Quality, Rockville, MD, January 2018. and other referenced sources.

## Obtaining Copies of the Guideline

Magellan Healthcare’s Practice Guideline for the Treatment of Patients with Attention-Deficit Hyperactivity Disorder is available on the Magellan provider website at <https://www.MagellanHealth.com/provider>.

As with all guidelines, the Magellan Guideline augments, does not replace, sound clinical assessment and decision-making. As a matter of good practice, clinically sound exceptions to the treatment guidelines are noted in the medical record. Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal, approval, and uses of specific medications or devices. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

## Providing Feedback on the Guideline

Magellan welcomes feedback on adopted clinical practice guidelines. All suggestions and recommendations are considered in our review of the guideline.

Please submit your comments to:

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## Executive Summary

(A discussion of changes/new information under each topic in this CPG is based on a literature review through May 2020)

### Introduction

A recent prospective longitudinal study suggested that despite the prevailing assumption that adult ADHD is a childhood-onset neurodevelopmental disorder, not all adults presenting with ADHD symptoms have a childhood-onset neurodevelopmental disorder (Moffitt et al., 2015). In this study including both follow-back analyses and follow-forward analyses, participants belonging to a representative birth cohort of individuals (n=1037) were followed to age 38 and assessed for symptoms of ADHD, associated clinical features, neuropsychological deficits, comorbid disorders and genetic risk. Sources of data included participants, teachers, informants, neuropsychological test results and administrative records. Results of the study showed prevalence of childhood ADHD and of adult ADHD were 6 percent and 3 percent, respectively. Unexpected results showed virtually nonoverlapping sets of childhood and adult ADHD cases, with no history of childhood ADHD in 90 percent of all adult ADHD cases. Authors found little evidence that adult ADHD had a childhood onset and suggested that if these results are replicated, further studies must investigate the etiology of adult ADHD. In a review of the Moffitt study, Yager suggested, “Attentional problems associated with adult ADHD might instead be nonspecifically related to substance dependence and other comorbidities. Regardless, high impairment rates in adults with ADHD underscore the need for better understanding and treatment studies” (Yager, 2015). According to DSM-5™, “ADHD begins in childhood. The requirement that several symptoms be present before age 12 years conveys the importance of a substantial clinical presentation during childhood” (APA, 2013).

A prospective longitudinal study of a representative birth cohort (n=5249) in Brazil was conducted in order to replicate Moffitt et al’s (2015) findings (Caye et al., 2016). Participants were assessed for ADHD at 11 and 18 to 19 years of age. Results found only 17.2 percent of children with ADHD continued to have ADHD as young adults, and only 12.6 percent of young adults with ADHD had the disorder in childhood. This study suggests the existence of 2 syndromes with distinct developmental trajectories.

The persistence of childhood ADHD symptoms into adulthood has been related to several key factors (Hechtman et al., 2016). A recent study to determine what factors contribute to ADHD persistence used regression analyses to determine associations between childhood factors and adult ADHD symptom persistence (n= 453, mean age= 25 years) from the Multimodal Treatment Study of Children with ADHD (MTA). The study assessed participants on 8 factors and found initial ADHD symptom severity, parental mental health, and childhood comorbidity affected the persistence of ADHD symptoms in adulthood. Childhood IQ, socioeconomic status, parental education, and parent-child relationships showed no associations with adult ADHD symptom persistence. A separate longitudinal twin study (n=2040) conducted in England and Wales evaluated childhood ADHD factors to determine factors of young adult function of individuals with persistent, remitted, and late-onset young adult ADHD (Agnew-Blais et al., 2016). 247 participants met diagnostic criteria for childhood ADHD and 21.9 percent of those participants also met

diagnostic criteria for the disorder at age 18 years. Persistence was associated with more symptoms and lower IQ. This finding reiterates Hechtman et al.'s (2016) finding that ADHD symptom severity is associated with persistence, however it contradicts the finding that childhood IQ is not associated with persistence.

When diagnosing late onset ADHD, the evaluator needs to be particularly careful to obtain complete psychiatric histories and not just rely on ADHD screening instruments. According to one article, adolescents and young adults without childhood attention deficit hyperactivity disorder (ADHD) often present to clinics seeking stimulant medication for late-onset ADHD symptoms (Sibley MH, et al, 2018). The researchers found that approximately 95% of subjects who initially screened positive on symptom checklists were excluded from late-onset ADHD diagnosis. Among individuals with impairing late-onset ADHD symptoms, the most common reason for diagnostic exclusion was symptoms or impairment occurring exclusively in the context of heavy substance use. Most late-onset cases displayed onset in adolescence and an adolescence-limited presentation. There was no evidence for adult-onset ADHD independent of a complex psychiatric history.

### Epidemiology

In a recent report, the American Academy of Family Physicians noted that ADHD is the most common behavioral disorder in children and that the prevalence is increasing (Felt et al., 2014). Visser et al. reported trends in parent-reporting of health care provider-diagnosed and medicated ADHD in the United States from 2003-2011 (Visser et al., 2014). These trends were based on data obtained from the National Survey of Children's Health (NSCH), which reflected increasing prevalence and treatment by health care providers:

- In 2011, 11 percent of children/adolescents aged 4-17 had ever received an ADHD diagnosis; approximately one in five high school boys and one in 11 high school girls had been diagnosed with ADHD
- 83 percent of children/adolescents with a history of ADHD had current ADHD diagnosis
- 69 percent of children with current ADHD diagnosis were taking medications for ADHD
- Parent-reported history of ADHD increased from 2003 to 2011 by 42 percent, and
- Prevalence of medicated ADHD increased from 2007 to 2011 by 28 percent

A recent study investigated predictors of delays to ADHD treatment seeking by examining lifetime ADHD treatment seeking reported in the National Epidemiologic Survey on Alcohol and Related Conditions (Dakwar et al., 2014). Authors investigated predictors of ADHD treatment seeking separately for males and females, finding low cumulative probability of ADHD treatment seeking (55 percent), most not beginning until well after childhood, with gender not significantly affecting treatment seeking. Older age was associated with significantly longer delays in treatment seeking for both males and females. Lower education and an African-American background in males were associated with greater delays in ADHD treatment seeking compared with females with the same characteristics, while psychiatric comorbidity was associated with less delay in treatment seeking among males. Older age was the only predictor of delayed treatment seeking among females, while bipolar disorder was associated with faster treatment seeking among females. Authors noted the need for efforts at public outreach and greater treatment access,

especially to vulnerable male populations who may delay treatment seeking due to factors such as African-American background, paranoid personality disorder and low education (Dakwar et al., 2014).

A recent population-based study in Sweden investigated common etiological factors of ADHD and suicidal behavior to determine whether genetic and environmental risk factors were shared between the two disorders (Ljung et al., 2014). Researchers linked longitudinal population-based registers, e.g., The National Patient Register, The Swedish Prescribed Drug Register, The Multi-Generation Register, The Total Population Register and the Cause of Death Register to identify patients (51707) with ADHD. They analyzed the data from the registers to study both the occurrence of suicide in individuals with ADHD as well as the “familial risk across different levels of genetic relatedness” (Ljung et al., p. 959). After adjusting for comorbid psychiatric disorders, results showed increased risk of both attempted and completed suicide in individuals with ADHD compared with matched control participants. Observing high risk among first-degree relatives and lower risk of both completed and attempted suicide among more genetically distant relatives, researchers suggested that shared genetic factors, e.g., genetic variants associated with impulsivity (associated with both ADHD and suicidal behavior), contribute to the overlap between ADHD and suicidal behavior. They suggested the importance of targeting individuals as well as their family members for suicide prevention and treatment (Ljung et al., 2014).

In a recent study, researchers sought to determine whether polygenic risk previously found to be associated with ADHD, also predicts traits related to ADHD and autism spectrum disorder (ASD) in the general population (Martin et al., 2014). Polygenic risk scores for ADHD were calculated in the Avon Longitudinal Study of Parents and Children population sample (n=8229). An analysis found that “polygenic score, based on common genetic variants previously found to be associated with risk of a clinical diagnosis of ADHD, was also associated with ADHD traits measured at ages 7 and 10 years in the general population,” suggesting that “ADHD represents the extreme end of traits present in the general population” (Martin et al., p. 669). Children diagnosed with ADHD had more ASD-related social communication problems than children without an ADHD diagnosis, and children with ASD had more ADHD traits than those with neither diagnosis. Researchers noted the lack of clear-cut boundaries between different neurodevelopmental and psychiatric disorders. “The approach of testing genetic risks that contribute to dimensions that cut across diagnostic categories, rather than using DSM diagnoses, is in line with the Research Domain Criteria framework and is likely to be a valuable approach for future neurodevelopmental and psychiatric research” (Martin et al., 2014).

Rubia et al. noted, “ADHD is the most imaged child psychiatric disorder with over hundreds of published structural and functional imaging studies” (Rubia et al., 2014). In their recent review, authors discussed current findings on brain deficits in ADHD. Past meta-analytic findings have confirmed that patients with ADHD have cognitive domain dissociated deficits in fronto-striatal, fronto-parietal and fronto-cerebellar networks. Additionally, abnormalities in the functional connectivity between these regions may occur both during rest and during cognitive tasks. Authors noted that regions of the brain underactivated in ADHD increase in activation with age potentially reflecting a

developmental delay in brain functioning in ADHD. They also pointed out ADHD currently is diagnosed based on often unreliable subjective clinical and rating measures rather than objective neuroimaging biomarkers despite consistent evidence for brain structure and function deficits in ADHD. They suggested “multivariate pattern analyses for imaging data can make predictions, e.g. of class membership, for individual subjects as opposed to group-level inferences and have been successfully applied to other disorders” (Rubia et al., p. S10.) Authors concluded, “We have acquired substantial knowledge on the underlying neurobiological mechanisms of ADHD. However, more studies are needed that integrate different imaging modalities to understand the interplay between the changes in neurochemistry, brain function and brain structure and to assess longitudinal trajectories of the disorder. The next decade will need to focus on using neuroimaging techniques in a more clinically applied fashion, either to aid with individual diagnosis, prognosis of disease progression and treatment success of as a neurotherapy to normalize abnormally functioning brain regions” (Rubia et al., 2014).

Recent research has shown that symptoms of children with autism spectrum disorder (ASD) are often similar to the core features of ADHD: inattention, hyperactivity and impulsivity (Miodovnik et al., 2016). In a large surveillance study analyzing data from the 2011-2012 National Survey of Children’s Health, Miodovnik et al. examined a sample of children (n=1496), aged 2 – 17 with a diagnosis of ASD as reported by their parents, to investigate the relationship between the age at ADHD diagnosis and the age of ASD diagnosis. Some of the children (approximately 20 percent) received a diagnosis of ADHD prior to ASD diagnosis. In their analysis of the data, authors found that when compared with children with only ASD diagnosis, those who received ADHD diagnosis before ASD diagnosis were 16.7 times more likely to receive a diagnosis of ASD after six years of age (delayed diagnosis). Those with ADHD before ASD were more likely to have delayed diagnosis than those who received ADHD diagnosis after the ASD diagnosis. Authors noted support for their hypothesis that the diagnosis of ASD may be delayed when ADHD is diagnosis first, suggesting that ASD should be considered when evaluating children presenting with ADHD symptoms. Further, they emphasized the need for diagnostic criteria and screening measures that reflect the overlapping symptomatology between the two disorders (Miodovnik et al., 2016).

A recent meta-analysis assessed the relationship between ADHD and obesity, finding the pooled prevalence of obesity increased in adults with ADHD by about 70 percent compared with those without ADHD; an increase of about 40 percent was found in children with ADHD compared with children without ADHD (Cortese et al., 2016). Authors noted that both the impulsive and inattentive components of ADHD could increase the risk of obesity. They also suggested the sharing of common biological risk factors including genetic variants in ADHD and obesity. “A ‘reward deficiency syndrome,’ characterized by insufficient dopamine-related natural reinforcement that leads to ‘unnatural’ immediate rewards (such as inappropriate eating), has been reported in both ADHD and obesity” (Cortese et al., p. 41). Lastly, they suggested the possibility that factors associated with obesity lead to symptoms of ADHD, e.g., sleep- disordered breathing. Authors concluded that the risk for obesity should be part of the assessment and management of ADHD.

A recent prospective study of a nationwide population-based cohort in Denmark, with up to



32 year follow-up of individuals with ADHD (n=32,061), found that “children, adolescents, and adults with ADHD had decreased life expectancy and more than double the risk of death compared with people without ADHD” (Dalsgaard et al., 2015). The study reported that a diagnosis of ADHD in adulthood was associated with a greater risk of death than a diagnosis in childhood or adolescence. Conditions found to increase the risk of death in individuals with ADHD included comorbid oppositional defiant disorder, conduct disorder and substance use disorder. Authors further noted that the increased mortality rate ratios were mainly due to deaths related to unnatural causes, e.g., accidents. Authors suggested that Denmark is more restrictive in diagnosing ADHD than the United States, and that ADHD cases may have had more severe symptoms than those in countries that were less restrictive in diagnosing ADHD. However, they said that this is the first study noting ADHD’s association with increased mortality and the link to adult ADHD and emphasized the importance of early identification of ADHD. They also suggested more research on factors to improve life expectancy patients with ADHD (Dalsgaard et al., 2015).

## Evaluation

The evaluation of ADHD in children and adolescents include the following components (Felt, et al., 2014):

- History and physical examination (presence and duration of core ADHD symptoms; degree of functional impairment from perspective of patient, family and school; other possible conditions mimicking or coexisting with ADHD; risk factors including medical, environmental and genetic);
- Review of information across home and community settings;
- Application of the diagnostic criteria included in the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> ed., (DSM-5); and
- Use of validated behavioral rating scales that collect data from multiple observers across settings, such as the following (Felt et al., 2014; Dittmann et al., 2014):
  - National Institute for Children’s Health Quality (NICHQ) Vanderbilt Assessment Scale (NICHQ, 2015)
  - Brown Rating Scales (3-yr to adult - parent, teacher, or self-report)
  - ACTeRS Rating Scales (kindergarten to 8<sup>th</sup> grade - parent/teacher report; adolescents or adults - self-report)
  - Child Behavior Checklist (18 months to 18 years of age; parent/teacher or self-report)
  - Conners’ Parent Rating Scale-Revised 9CPRS-R)
  - ADHD rating Scale IV 9ADHD-RS-IV)
  - Swanson, Nolan and Pelham version IV (SNAP).
- Evaluate for other conditions mimicking or co-existing with ADHD, e.g., anxiety disorder, autism spectrum disorder, fetal alcohol syndrome, genetic disorders such as fragile X syndrome, hearing loss, intellectual disability, learning disorder, mood disorders, oppositional defiant disorder, seizure disorder, sleep disorder, speech and language disorder, and vision disorder (Felt et al., 2014).

A recent study tested an updated version of the Adult ADHD Self-Report Screening Scale (ASRS) to match DSM-5 criteria (Ustun et al., 2017). A machine-learning algorithm was used to build the scale from responses to 6 questions in the ASRS using optimal scoring rules. Of the total participants (n=637), 268 met DSM-5 criteria for adult ADHD in the

semistructured diagnostic interview. The 6-question screening scale was found to be successful in distinguishing cases from noncases both in the general population and in a specialty treatment setting. The short scale could be used as a practical screen for DSM-5 adult ADHD, and a full clinical assessment could be carried out in screened positives to confirm diagnosis.

### Treatment -General

A recent study focusing on improving the quality of community-based ADHD treatment included reviews of a random sample of 1,594 patient charts from 50 diverse pediatric practices, recruited from August 2010 through December 2012 (Epstein et al., 2014). The review of the extracted information for ADHD care found that “despite the publication of ADHD consensus guidelines more than a decade ago, adoption of evidence-based ADHD care in community-based pediatric settings remains poor” (Epstein et al., p. 1140). Deviations from recommended practices included those occurring at the pediatrician or practice level as well as those attributable primarily to patients. At the physician/practice level, results showed that pediatricians used DSM criteria for ADHD assessment in only two-thirds of patients, and used parent- and teacher-rating scales during assessment in only half of the patients. The study found other deviations from recommended practices, e.g., psychosocial treatment was recommended or used in only 13 percent of patients, while medications were prescribed in 93.4 percent of cases; only about half of children receiving medication had contact with pediatrician during first month of treatment; and in only 10 percent of cases, parent- and teacher-rating scales were used to monitor treatment. Researchers concluded that, based on these results, there is much room for improvement in current pediatrician-delivered ADHD care. They further suggested the use of electronic health records to “prompt/remind the physician to complete ADHD care behaviors or to use Web portals to aid in collecting rating scales” (Epstein et al., p. 1142).

A recent study analyzing data from the 2009-2010 National Survey of Children with Special Health Care Needs, a nationally representative, population-based telephone survey conducted by the Centers for Disease Control and Prevention, described parent- reported prevalence of treatments for current ADHD among children (n=9459) aged 4- 17 years with special health care needs (Visser et al., 2015). The most common treatment for ADHD was medication treatment, with almost 50 percent of children with current ADHD taking medication alone. Approximately 87 percent of children with ADHD were receiving either medication treatment or behavioral therapy. Less than one-third of children with ADHD were receiving both medication treatment and behavioral therapy. The most likely to receive combination treatment were those with severe ADHD and comorbidities. A little more than half of the children with ADHD had not received behavioral therapy in the past year. Authors noted that these data, collected in the years just before the release of the AAP’s 2011 diagnostic and treatment guidelines for ADHD, provide an important benchmark for clinical practice. They suggested the need for future research to “help improve our understanding of the barriers to the provision of behavioral therapy for childhood ADHD, particularly among the preschool population” (Visser et al., p. 7).

The American Academy of Pediatrics guideline for the diagnosis, evaluation and treatment

of ADHD presents varying recommendations for the treatment of children and youth with ADHD depending on age of the patient. For children aged 4 to 5, behavior therapy is the first line of treatment followed by methylphenidate. For school-aged children 6 to 11, treatment with FDA approved medications is first line of treatment, followed by behavior therapy or a combination of medication and behavior therapy. For adolescents aged 12 to 18, first line of treatment is FDA approved medication for ADHD, with the assent of the adolescent and followed by behavior therapy or a combination of medication and behavior therapy (AAP, 2011).

In a systematic review of 53 controlled studies including adolescent-specific treatments for ADHD, authors suggested that evidence “does not support current American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry professional guidelines, which state that stimulant medication is the preferred treatment for adolescents with ADHD” (Sibley et al., 2014, p. 218). The study found evidence demonstrating a similar range of effect sizes for medication and behavior therapy in the treatment of adolescents with ADHD, while noting that the majority of adolescents reported poor satisfaction with medication, decreasing potential for adherence. Authors suggested that oppositional teens obtain more benefit from behavior therapy than medication. Suggesting that a combined medication/behavior therapy may present the greatest therapeutic benefit, they indicated a need for studies of systematically delivered combined treatment for adolescents with ADHD.

A recent systematic review of pharmacological and psychosocial treatments for ADHD in adolescents (Chan et al, 2016, p.1997) included sixteen randomized clinical trials and 1 meta-analysis. It found that there was greatest evidence of efficacy for the extended-release methylphenidate and amphetamine class stimulant medications and atomoxetine than for the extended-release alpha2-adrenergic agonists guanfacine or clonidine. Psychosocial treatments incorporating behavior contingency management, motivational enhancement, and academic, organizational, and social skills training techniques were associated with inconsistent effects on ADHD symptoms and greater benefit for academic and organizational skills.

FDA approved drugs for the treatment of ADHD includes: stimulants (methylphenidate, dexamethylphenidate, mixed amphetamine salts, dextroamphetamine, lisdexamfetamine), nonstimulants (atomoxetine) and the extended release formulations of alpha-2 agonists (clonidine and guanfacine). For children under 6 years of age, the only approved drugs to treat ADHD are Adderall® and dextroamphetamine IR tablets.

### Treatment -Stimulants

A recent systematic literature review examined the efficacy of stimulants and nonstimulants as well as stimulant misuse with adolescents and adults, including college students with ADHD (Weyandt et al, 2014). Authors reported results reflecting that both stimulant and prostimulant medications are safe and effective in reducing ADHD symptoms in adolescents and adults with ADHD as well as improving psychosocial qualities. Other results showed a higher rate of prescription stimulant misuse among individuals with ADHD compared with those without ADHD. Short-acting agents were more misused than long-acting stimulants. For college students with

ADHD at risk of stimulant misuse, authors suggested that the prostimulant lisdexamfetamine dimesylate may be the ADHD medication of choice as it cannot be ground or dissolved into a short-acting stimulant. Authors emphasized the need for further studies concerning the misuse of prescription stimulants (Weyandt et al., 2014).

### Methylphenidates

Stimulant medication is often considered the first-line treatment for ADHD and includes immediate-release (IR) and extended-release (ER) formulations of methylphenidate (MPH). IR MPH is administered two to five times a day, imposing practical difficulties in treating children attending school in contrast to ER MPH, which is administered only once a day (Schawo et al., 2015). Authors noted that although existing clinical studies showed “no significant difference between the efficacy of short-acting and long-acting MPH under the assumption of full therapy compliance,” patients treated with IR MPH had more breaks in medication use, more medication switches and a shorter period on intended therapy. They noted that superior compliance of ER MPH may possibly lead to better effectiveness than IR MPH (Schawo et al., 2015).

Although the efficacy of immediate-release methylphenidate in the treatment of children has been extensively studied, fewer studies have evaluated its efficacy in the treatment of adults (aged 17 years and older) with ADHD in addition to a high rate of other psychiatric problems and functional difficulties (Epstein et al., 2014). The meta-analysis of 10 randomized controlled trials including adults with ADHD (n=466) found that immediate-release methylphenidate was effective versus placebo for improvements of symptoms including hyperactivity, impulsivity and inattentiveness. It was not determined whether the treatment was helpful for anxiety or depression, based on mixed results. Authors noted the high quality of the body of evidence showing that immediate-release methylphenidate improves ADHD symptoms in adults and suggested that the improvement was without serious side effects. Loss of appetite was the main adverse effect noted, but authors noted that a meta-analysis of adverse effects was not conducted. They suggested that this adverse effect with immediate-release methylphenidate might be advantageous among adults with both ADHD and obesity. Based on the evidence, they also suggested monitoring appetite and weight, especially during early phases of treatment (Epstein et al., 2013).

A recent FDA drug safety communication warned that chemical leukoderma, permanent loss of skin color due to repeated exposure to specific chemical compounds, may occur with use of methylphenidate transdermal system (Daytrana patch) for ADHD (FDA, 2015). The FDA cautioned patients (or their caregivers) with the skin color changes to discontinue using the patch, and report the changes to health care professionals. The condition, considered non-reversible, may cause emotional distress.

On April 17, 2015, the FDA approved methylphenidate extended-release (Aptensio XR™), available in capsule form (multilayer bead formulation) at varying dosing options (from 10 mg to 60 mg) for the treatment of ADHD (FDA, 2015). Administration in children with difficulty swallowing pills becomes easier when contents of an open capsule are sprinkled onto food. The starting dose is 10 mg once daily for patients aged six and older. Contraindications are similar to those of other central nervous system stimulants

(Magellan Health, 2015).

A randomized placebo-controlled double-blind study evaluated the efficacy (primary objective of study), safety and tolerability of a multilayer extended-release bead methylphenidate capsule (MPH-MLR) in children and adolescents aged 16 to 18 years with ADHD (Wigal et al., 2015). Researchers emphasized the unique release properties of MPH-MLR where 37 percent of the labeled dose is the immediate-release (IR) component. In this study, patients (n=230) were randomized to MPH-MLR at 10, 15, 20 or 40 mg or placebo once daily. The four stages of the study included: four week screening/baseline, one week double-blind treatment, 11 week open-label dose optimization period and 30 day follow-up. In the double-blind phase, patients received 10, 15, 20 or 40 mg of MPH-MLR or placebo. Continuing to the open-label dose optimization phase, patients received a once daily 10 mg dose, except where previous treatment experience indicated the necessity of beginning with a higher dose. During this 11 week phase, investigators titrated the dose up or down based on the ADHD Rating Scale, 4<sup>th</sup> Edition (ADHD-RS-IV) and the Clinical Global Impression (CGI)-Improvement Scale (CGI-I) scores to reach the optimal dose. The change from baseline to end of the double-blind period in the ADHD-RS-IV was the primary efficacy endpoint measure. Results showed decreases in the ADHD-RS-IV scores in the different groups as follows: placebo at -5.0; MPH-MLR at 10 mg, 15 mg, 20 mg and 40 mg; -9.1, -10.2, -12.0 and -12.6, respectively. Symptom improvement evidenced by these scores was greater in those receiving MPH-MLR, and the improvements were bigger with increased dosages. In the final open-label dose, the most common final open-label dose was 30 mg (Wigal et al., 2015).

Another recent study reviewed clinical trials for the use of methylphenidate in children, aged 6-18 and adults aged 18 or more, with a focus on OROS methylphenidate (Concerta®) (Katzman and Sternat, 2014). OROS methylphenidate (OROS MPH) has once-daily dosing utilizing an osmotic pump system. Based on the review of various clinical trials, authors concluded, “The greatest benefit of OROS MPH lies in its ability to offer symptomatic control not only during the traditional school (or in adults during the work day) but also in the evening” (Katzman and Sternat, p. 1006). When compared with IR MPH, OROS MPH was associated with better symptom control, especially in the evening. Studies showed OROS MPH treatment at doses ranging from 18 to 54 mg/day, compared with placebo, resulted in significant reductions in core ADHD symptoms as measured by teacher and parent IOWA Conners Scale. Treatment with OROS MPH in adolescents at doses ranging from 18 to 72 mg/day was associated with significant improvements in ADHD-RS scores while it also improved driving performance, reducing inattentive driving errors. In adults, studies found that OROS MPH at doses ranging from 36 to 108 mg/day, compared with placebo, was associated with significantly reduced symptoms of inattention and hyperactivity/impulsivity, as measured by tools, e.g., CGI-I. Authors concluded that their review of studies demonstrated benefits to children and adolescents with ADHD as well as adults with ADHD (Katzman and Sternat, 2014).

#### Dexmethylphenidate and Mixed Amphetamine Salts

On January 28, 2016 the FDA approved an amphetamine extended-release orally disintegrating tablet, Adzenys XR-ODT for treating ADHD in children aged 6 and older (FDA, 2016). When it becomes available, the orally disintegrating tablet will be offered in

six dosages: 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg and 18.8 mg, allowing the dose to be individualized. This tablet will disintegrate in the mouth, rather than being swallowed or sprinkled on food.

A small, eight week, double-blind, placebo-controlled, randomized, two period, crossover study examined the separate effects of three doses of extended-release (ER) dexamethylphenidate (d-MPH), ER mixed amphetamine salts (MAS), and placebo on objective measure of sleep in children (n=37), aged 10-17, with ADHD (Santisteban et al., 2014). Patients were randomized to treatment with d-MPH or MAS initially, with increasing dosages every week for four weeks (10, 20 and 25/30 mg). The randomized placebo period occurred at any week of treatment, except the week before the highest dose. After four weeks, patients were treated with the other medication for another four weeks. Results found that decreased sleep duration was associated with both medications, and it was shorter among patients receiving the highest dose of either medication compared with placebo. In sleep duration or schedule, there were no differences found between MAS and d-MPH leading the authors to conclude that at the group level, “there is no significant sleep benefit in using one medication over the other based upon objective measures” (Santisteban et al., p. 832). Noting that higher doses were associated with improved efficacy in terms of ADHD symptoms, they were also associated with negative effects on sleep. Authors advised clinicians to monitor sleep in patients receiving stimulant treatment, and to consider reducing the dose in patients to avoid the risk of shortened sleep duration. They also advised augmentation with behavior therapy which may result in lower stimulant dose (Santisteban et al., 2014).

#### Lisdexamfetamine dimesylate (LDX)

A recent study evaluated the long-term maintenance of the efficacy of the first long-acting stimulant prodrug lisdexamfetamine dimesylate (LDX) in children and adolescents with ADHD using a placebo-controlled, double-blind, randomized-withdrawal study design (Coghill et al., 2014). Patients, aged six to 17, with ADHD (n=157) who had completed a 26 week open label trial of LDX were randomized to their optimized dose (30, 50 or 70 mg per day) or switched to placebo for a six week randomized withdrawal period. The primary outcome measure was the proportion of patients with a 50 percent or greater increase in ADHD Rating Scale IV (ADHD-RS-IV) total score and a two point or greater increase in Clinical Global Impressions-Severity of Illness (CGI-S) score since the beginning of the six week randomized withdrawal period. This evaluation found that significantly fewer patients receiving LDX met treatment failure criteria at the end of the randomized-withdrawal study compared with those receiving placebo. The patients in the placebo condition experienced rapid return of symptoms on LDX withdrawal (at or before the week two visit after randomization). Based on increase in the ADHD-RS-IV total score, treatment failure at the end of the randomized-withdrawal period for the LDX group was 28.9 percent, compared with 79.2 percent for the placebo group. Based on a two point increase from baseline in CGI-S score at end of the randomized-withdrawal period, treatment failure was 17.1 percent and 69.8 percent of patients receiving LDX and placebo, respectively. Researchers summarized, “This placebo-controlled, double-blind, randomized-withdrawal study demonstrates the maintenance of efficacy of LDX after long-term treatment in children and adolescents with ADHD” (Coghill et al., p 655).

In another six week double-blind randomized-withdrawal study of long-term LDX

treatment in children and adolescents (n=153) with ADHD (moderate severity as indicated by ADHD-RS-IV), patients were randomized to continue LDX (fixed, optimized doses) or switched to placebo (Banaschewski et al., 2014). The primary outcome measure was the impact of continued long-term (at least 26 weeks) LDX treatment of children and adolescents with ADHD on improved health-related quality of life (HRQoL) and reduced functional impairment using the Child Health and Illness Profile-Child Edition: Parent Report Form (CHIP-CE: PRF) and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). Results showed, “Continued treatment with once-daily, optimized doses of LDX maintained the improvement in parentally perceived HRQoL and functional impairment acquired during at least 26 weeks of open-label treatment to a greater extent than placebo in this international, phase III, randomized-withdrawal study.” The domains where effectiveness was most pronounced were reducing risky behavior, improving relationships with family and peers, and improving academic achievement (Banaschewski et al., 2014).

A nine week, double-blind, randomized study assessed treatment response rates of LDX (dose-optimized at 30, 50 or 70 mg/day) and atomoxetine (ATX) in children and adolescents (n=200) with ADHD and an inadequate response to previous or current treatment with methylphenidates (Dittmann et al., 2014). Patients were randomized to dose-optimized LDX or ATX (patients at or less than 70 kg receiving 0.5-1.2 mg/kg/day and patients at or greater than 70 kg receiving 40, 80, or 100 mg/day). Response to treatment, indicated by improvements in ADHD-RS-IV, was significantly higher in patients treated with LDX than in the ATX group. The proportion of patients with 50 percent, 30 percent or 25 percent reduction from baseline in ADHD-RS-IV scores were 73 percent, 88.1 percent and 90.5 percent, respectively, in the LDX group compared with 50.4 percent, 73.7 percent and 76.7 percent in the ATX group, respectively. Additionally, after treatment during the nine week period, a larger percentage of patients receiving LDX had lower levels of ADHD severity than in the ATX group. Researchers noted, “The superior efficacy of LDX was maintained irrespective of the criteria used to determine a clinically relevant response to treatment” (Dittman et al, 2014), p.1067).

## Treatment - Non-Stimulants

### Atomoxetine (ATX)

A recent comprehensive review of studies examined the efficacy of atomoxetine treatment in 6-to 18-year-olds with ADHD (Savill et al., 2015). Authors reviewed 125 papers, which provided the basis of their conclusions. ATX, with a lack of abuse potential, was effective in improving core ADHD symptoms, functional outcomes, and quality of life in 10-12 weeks after beginning of treatment in various pediatric patient populations, e.g., both sexes, patients with various co-morbidities, patients both with and without prior ADHD medications. Compared with placebo, ATX was more effective in preventing relapse of ADHD after 10-52 weeks of ATX treatment. Authors noted the difficulty in comparing the efficacy of ATX in comparison with other medications due to deficiencies of studies. They emphasized the relatively gradual responses to ATX, and noted how responses in the first weeks of ATX treatment may predict responses over time. Authors cited a study showing that a “sizable proportion of patients who only have partial responses to atomoxetine at four weeks go on to have robust responses beyond this timepoint” (Savill et al., p. 146). They advised informing the patient/family of the likelihood of a gradual response to the

medication and that it often builds over time (Savill et al., 2015). In another study where data were pooled from seven ATX double-blind, placebo-controlled, randomized clinical trials conducted in pediatric patients aged 6-18 years, “baseline ADHD severity and symptom improvement during the first two weeks of treatment were highly predictive of robust response to treatment with atomoxetine” (Wietecha et al., 2015).

Another review of studies examining the use of atomoxetine in the management of ADHD cited several double-blind, randomized placebo controlled trial showing that ATX was significantly better in improving ADHD symptoms than placebo (Childress, 2016). Author also reported studies finding that ATX improves core ADHD symptoms as well as quality of life and emotional lability, with symptom improvement continuing to increase up to 52 weeks after the initiation of treatment. Studies found that, although ATX may be less effective than stimulant medication with a longer time to maximal response than stimulants, it is considered as a first-line treatment option and may be a preferred treatment for patients with a history of substance abuse (Childress, 2016).

### Alpha-2 Agonists - Clonidine and Guanfacine

A randomized, controlled study, assessing the efficacy and safety of extended release guanfacine hydrochloride (GXR) in the treatment of children and adolescents (aged 6-17) with ADHD of at least moderate severity, compared GXR with placebo, with an ATX arm included to provide reference data against placebo (Hervas et al., 2014). Patients (n=338), aged 6-17, with ADHD were randomized at baseline, to dose-optimized GXR, ATX or placebo for four or seven weeks (based on whether they were under or over the age of 13). Following this period was a six week double-blind maintenance period, a two week double-blind tapering period, and a follow-up after the last dose. GXR, in tablet form, was initiated at 1 mg/day in children and increased by 1 mg increments to a maximum of 4 mg/day, and in adolescents, it was increased to maximum dose of 4, 5, 6, or 7 mg/day based on weight. At baseline, mean ADHD-RS-IV scores were similar across the treatment groups. The changes in ADHD-RS-IV score from baseline to end of the study treatment duration were -23.9, -18.8, and -15 for GXR, ATX, and placebo, respectively. Percentages of patients showing “very much improved” or “much improved” in CGI-I scores were 67.9 percent, 56.3 percent and 44.1 percent for GXR, ATX and placebo, respectively. The proportions (percentage) of patients experiencing treatment-emergent adverse (TEA) events, mostly of mild or moderate intensity, were 77.2 percent, 67.9 percent and 65.8 percent in the GXR, ATX and placebo groups. Most common TEAs included the following: GXR: somnolence, headache and fatigue; ATX: decreases in appetite, nausea and fatigue; and placebo: headache, fatigue and abdominal pain. Improvement in efficacy was more rapid with GXR than ATX. Researchers concluded that this study demonstrated “a positive risk-benefit profile in the treatment of children and adolescents with ADHD with GXR doses of up to 7 mg (0.05-0.12mg/kg/day) and suggests that GXR will be a useful addition to the existing classes of medication effective in ADHD (Hervas et al., p. 1870).

A recent study meta-analyzed the efficacy and safety of alpha-2 agonists in the treatment of ADHD in youth aged 6-17 (Hirota et al., 2014). The 12 randomized trials consisted of randomized controlled trials comparing clonidine/guanfacine monotherapy with placebo as well as trials including patients with suboptimal response to stimulants who received clonidine/guanfacine or placebo added in. The studies compared the alpha-2 agonists with



placebo in youth (n=2276). The primary outcome measure was reduction in overall ADHD symptoms, based on rating scales, e.g., ADHD-RS-IV, and secondary outcome measures included symptoms, e.g., hyperactivity/impulsivity, inattentiveness, oppositional defiant disorder and adverse events. Based on the results of this study, researchers stated, “ $\alpha$ -2 agonists-both in monotherapy and as add-on treatment to stimulants were significantly more effective than placebo for total and specific attention-deficit/hyperactivity disorder (ADHD) symptoms as well as for oppositional defiant disorder symptoms. Pooled together,  $\alpha$ -2 agonist monotherapy and add-on treatment were associated with similar risks for discontinuation because of intolerability compared with placebo, reflecting their safety and acceptability by patients. However, given the significantly higher incidence of hypotension, bradycardia, fatigue, somnolence and sedation in participants randomized to  $\alpha$ -2 agonists compared with placebo, clinicians should monitor these side effects routinely” (Hirota et al., p. 171). In summarizing their results, researchers noted that  $\alpha$ -2 agonists are an alternative treatment for children and adolescents with ADHD who cannot tolerate psychostimulants or do not have a sufficient response to treatment with stimulants.

## Other Medications

### Risperidone

In a recent study, children (n=168), aged 6-12 years with ADHD and either oppositional defiant or conduct disorder, were randomized to nine weeks of basic treatment (parent training (PT), stimulant and placebo) or augmented treatment (PT, stimulant, and risperidone) (Aman et al., 2014). At the end of the first three weeks during which children received treatment with stimulant (titrated for optimal effect) and parents received PT, children who had continuing aggression and other disruptive behaviors received either placebo or risperidone as an add on treatment. Scores on the Nisonger Child Behavior Rating Form (NCBRF) Disruptive-Total Scale, the NCBRF Social Competence subscale, and the Antisocial Behavior Scale improved more with the augmented treatment than with basic treatment, while there was no significant advantage of augmented treatment evidenced by clinician ratings of the CGI-I. Researchers noted that “together, the findings indicate that risperidone, when added to optimized stimulant treatment and parent training, provides a moderate advantage in parental ratings of disruptive behavior for children with serious aggression and additional disruptive behaviors” (Aman et al., p.55). They also cautioned that results were based on a relatively short trial period of six weeks with possible emergence of problematic adverse events, e.g., weight gain, metabolic disturbance (Aman et al., 2014).

### Bupropion

A recent meta-analysis (including 28 double-blind, placebo-controlled studies comprising children and adolescents (n=4699) aged 4 to 15 with ADHD) compared the efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion (BUP) and methylphenidate in the treatment of ADHD in children and adolescents (Stuhec et al., 2015). Results showed levels of efficacy in reducing ADHD symptoms for these medications compared to placebo to be small for bupropion, modest for atomoxetine and methylphenidate and high for lisdexamfetamine. Discontinuation was statistically lower for methylphenidate compared to placebo treatment, and not significantly different for atomoxetine, lisdexamfetamine and bupropion. Researchers concluded, “LDX is the most efficacious treatment option. Despite the fact that the results of this meta-analysis show a low effect size in the case of BUP,

several new double-blind randomized studies, using the latest diagnostic ADHD criteria and appropriate methodology are needed to evaluate the comparative effectiveness of BUP in the treatment of ADHD in the treatment of children and adolescents with ADHD” (Stuhec et al., p. 155).

### Tricyclic Antidepressants

A recent Cochrane review of six randomized controlled trials including children and adolescents aged 6 to 18 with ADHD (n=216) assessed the efficacy of tricyclic antidepressants (TCAs) in the reduction of ADHD symptoms (Otasowie et al., 2014). The trial compared the following treatments: desipramine with placebo; nortriptyline with placebo; desipramine with clonidine and placebo; desipramine and clomipramine with methylphenidate and placebo. In comparison with placebo, desipramine outperformed placebo in the improvement of core ADHD symptom severity as assessed by parents, teachers and clinicians, and nortriptyline was efficacious in improving core symptoms by clinicians. On “all cause treatment discontinuation,” desipramine and placebo were similar. In comparison with clonidine, desipramine appeared more efficacious in reducing ADHD symptoms as rated by parents. Serious adverse effects were not identified in this review, although mild increases in diastolic blood pressure and pulse rates were noted, and patients receiving desipramine had significantly higher rates of appetite suppression compared to placebo and nortriptyline as associated with weight gain. Authors concluded, “Most evidence on TCAs relates to desipramine. Findings suggest that, in the short term, desipramine improves the core symptoms of ADHD, but its effect on the cardiovascular system remains an important clinical concern. Thus, evidence supporting the clinical use of desipramine for the treatment of children with ADHD is low” (Otasowie et al., 2014).

### Psychosocial Interventions

Although “a front-line intervention is stimulant medications, which are effective in approximately 80 percent of youth with ADHD,” psychosocial interventions play a prominent role in the management of youth with ADHD (Antshel, 2014, p. 80). Psychosocial interventions include behavioral interventions that have beneficial effects on aspects of child and parent functioning. Behavioral parent training (BPT) is nonspecific to ADHD, but is effective for children with disruptive behaviors. Past studies have shown that it is “a well-established evidence-based treatment for managing ADHD in children” (Antshel, p. 81).

Authors cited a previous meta-analysis of trials that found a lack of blinded evidence of ADHD core symptom decrease in children and adolescents with ADHD who received behavioral interventions (Daley et al., 2014). In this recent meta-analysis of randomized controlled trials across multiple outcome domains, authors found blinded evidence that behavioral interventions have positive effects on a range of other outcomes, i.e., improving parenting and decreasing childhood conduct problems. Outcomes measured included pre- to post-treatment changes in parenting quality, parenting self-concept, conduct problems, social skills and academic performance. Results found that “behavioral interventions improved parenting, decreasing negative and increasing positive parenting, and decreased children’s comorbid conduct problems” (Daley et al., p. 844). There were, however, no beneficial effects seen on parent mental health. Authors concluded, “The beneficial effects

on parenting and parents’ sense of empowerment and independently corroborated effects on conduct problems in children with ADHD” (Daley et al, p. 845).

### Dialectical Behavior Therapy Group Skills Training

A pilot randomized controlled trial evaluated dialectical behavior therapy (DBT) group skills training in the treatment of college students (n=33) between aged 18 and 24 (Fleming et al., 2015). Researchers cited studies finding that college students with ADHD have lower grade point averages and graduation rates; depressive symptoms, tobacco and alcohol use; overall psychological distress; and lower self-reported quality of life than their undergraduate peers. In this study, participants were randomly assigned to receive DBT group skills training or skills handouts during an eight week intervention phase. Participants were assessed at pre-treatment, post-treatment, and three month follow up, and the follow-up interviewer was blind to participant condition. Outcome measures included: Barkley Adult ADHD Rating Scale-IV (BAARS-IV) to measure ADHD symptoms; Brown ADD Rating Scales (BADDS) to measure executive functioning; ADHD Quality of Life Questionnaire (AAQoL) to measure life productivity, psychological health and life outlook (BDI-2); official transcripts including grade point average; Five Facet Mindfulness Questionnaire (FFMQ); and Conners’ Continuous Performance Test-2<sup>nd</sup> Edition (CPT-2). The DBT group skills training intervention included group sessions focused on the acquisition and strengthening of skills and individual coaching phone calls. The skills handouts group received a booklet including topics, e.g., psychoeducation about ADHD and executive functioning, organization, planning, time management, structuring environment and stress management. The DBT group skills training group had greater improvement in ADHD symptoms and executive functioning (greater treatment response rates and clinical recovery rates) and greater improvement in quality of life than the skills handouts group immediately after treatment as well as three months after treatment. Researchers suggested that the DBT group skills training intervention may also improve mindfulness and sustained attention. They suggested the need for “future studies to evaluate the relative efficacy and acceptability of psychopharmacological and psychosocial interventions, both independently and in conjunction, for the treatment of DHD among college students” (Fleming et al., p. 269). Researchers emphasized the need for further evaluation in a larger randomized trial.

### Cognitive Behavioral Therapy-Based Psychoeducational Groups for Adults With ADHD

A recent study evaluated a new manualized CBT-based psychoeducation (PEGASUS) for adults with ADHD and their significant others in an open clinical feasibility trial (Hirvikoski et al., 2015). PEGASUS was designed to constitute the first nonpharmacological treatment after diagnosis of ADHD in adults, with a main goal of providing knowledge about ADHD both to participants and their significant others and to empower them in sharing in their own treatment. This pilot study, evaluating both the feasibility and the efficacy of PEGASUS, included eight 2 ½ hour sessions in groups, including adults with ADHD (n=51) as well as their significant others (n=57). Focus of the sessions was on psychoeducation, with group lecturers “highlighting possibilities for change as well as pointing out common strengths in individuals with ADHD, thus applying techniques of acceptance” (Hirvikoski, p. 92). Results showed that this program was a feasible

intervention as 43 out of the 51 participants with ADHD completed the intervention and agreed that they would attend a similar course in the future; of the 57 significant others, 42 completed the intervention and were satisfied with the program. Efficacy was measured by improvement from baseline to post-intervention in results from various measures, including Questions about Family Members (QAFM), BECK Depression Inventory (BDI), Rosenberg’s Self-Esteem (RSE) Scale, and Adult Attention Deficit/Hyperactivity Disorder Quality-of-Life (AAQoL). Results for all participants indicated positive improvement in knowledge about ADHD, psychological well-being and subjective stress, and a trend toward improvement of self-esteem was observed in adults with ADHD. Researchers cautioned that these results are preliminary due to the open study design and additional information will be provided from a randomized controlled study of PEGUSUS that is currently in progress (Hirvikoski et al., 2015).

### Collaborative Care for Children with ADHD Symptom

A recent randomized effectiveness trial compared two care management systems, basic collaborative care and enhanced collaborative care, to treat urban children (n=156) aged 6 to 12 who were being evaluated for ADHD (Silverstein, et al., 2015). In both groups, care managers (lay providers without formal mental health backgrounds) served as liaison between primary care clinicians and a specialist, e.g., psychiatrist. In the enhanced collaborative care group only, enhanced care managers received training in motivational interviewing and were certified by a master trainer in Triple P’s Primary Care Module. This additional training helped the enhanced care managers address ambivalence toward engagement with behavioral health care, parental mental health and oppositional child behavior” (Silverstein, p. e860). Outcome measures, six and 12 months after randomization, were ADHD symptoms, measured by the Parent Swanson, Nolan and Pelson (SNAP-IV Questionnaire) and by oppositional symptoms and social skills. Results showed no differences in outcomes between the groups across the entire sample, but children who were ADHD diagnosable and in the enhanced care group showed greater decreases from baseline in inattention, hyperactivity/impulsivity, oppositionality and social skills than those in the basic care arm. Researchers noted that this study is novel in that it enrolled children based on presenting symptoms rather than ultimate diagnosis and instead of testing a care system against usual care, it studied “whether augmenting collaborative care with lay-delivered strategies to address common reasons for symptom persistence improves outcomes” (Silverstein et al., p. e863). They also noted how their emphasis on urban, low-income children makes their results relevant to primary care providers. Researchers stated, “Last, among children with ADHD-consistent presentations in the enhanced care group, there was a clinically meaningful increase in ADHD medication prescriptions. Given that the motivational interviewing script deliberately focused on medication use, it is possible that motivational interviewing started a cascade of events leading to increased receptivity to ADHD medication, and that this, in turn, could have led to improved outcomes” (Silverstein et al., p. e864).

## Combined Nonpharmacological and Pharmacological Treatment

### Combined Group Psychotherapy and Methylphenidate, and Combined Individual Clinical Management (Counseling) and Methylphenidate

A recent clinical trial, the Comparison of Methylphenidate and Psychotherapy in Adult ADHD study (COMPAS), examined the efficacy of nonpharmacological treatments in combination with methylphenidate or placebo (Philipsen et al., 2015). Researchers randomized adults (n=433) aged 18 to 55 with ADHD to one of the following treatment groups: highly structured group psychotherapy (GPT) and methylphenidate; GPT and placebo; less controlled individual clinical management (CM) and methylphenidate; and CM and placebo (Philipsen et al., 2015). Both GPT and CM sessions occurred weekly for the first 12 weeks and monthly for the following nine months, and patients received either methylphenidate or placebo for 12 months. Results showed improvements in ADHD symptoms in all four treatment groups indicated by changes from baseline to end of treatment in the ADHD index of the Conners Adult ADHD Rating Scale. Researchers noted that previous studies have shown superiority of GPT over general CM conditions; however, the results in this study showed that GPT was no more effective than CM in improving ADHD symptoms. This study found that combined treatment with GPT or CM with methylphenidate was superior to combinations with placebo. Researchers concluded, “To our knowledge, COMPAS is the first trial to demonstrate long-term maintenance effects of ADHD treatment under controlled conditions. We demonstrate that psychological interventions result in better outcomes when combined with methylphenidate as compared with placebo. Our data do not suggest that highly structured group intervention outperforms individual CM, which is much easier to implement in practical care than specifically tailored and highly structured GPT (Philipsen et al., 2015).

## Complementary/Alternative Treatments

### Neurofeedback

Researchers continue to investigate the efficacy of non pharmacological treatments for ADHD. Neurofeedback is one area of significant interest.

A recent study comparing the use of methylphenidate to neurofeedback treatment or physical activity concluded that “optimally titrated methylphenidate is superior to neurofeedback and physical activity in decreasing ADHD symptoms in children with ADHD” based on neurocognitive measures and parent reports (Gelade et al., 2016). The same researchers performed a six month follow up study (Gelade et al, 2017) and concluded that the initial superior findings dissipated over time. They found no significant difference on neurocognitive measures after controlling for medication use at follow-up and found that the initial superior results for methylphenidate became smaller or non-significant. Another recent study compared neurofeedback (EEG) with methylphenidate and physical activity in children with ADHD (Janssen et al 2016). The outcome measures were indices of response inhibition. This study was unique in that it simultaneously compared neurofeedback with stimulant treatment and a semiactive control group. The authors concluded the study showed specific and superior effects for medication treatment with MPH compared with theta/beta neurofeedback training on ERP indices of response inhibition.

A review of the current evidence for neurofeedback in the treatment of ADHD noted that recent meta-analytic evidence shows neurofeedback leads to significant decreases of ADHD core symptoms, but only in studies lacking well-blinded outcome measures (Holtmann et

al., 2014). Even in the best-blinded assessment, evidence did not demonstrate learning of self-regulation or significant effects. Although some studies have claimed that neurofeedback is efficacious and specific, authors conclude that “there is a strong need for more evidence from well-blinded, methodologically sound and sensitive trials before neurofeedback can be assigned this highest level of evidence as a front-line treatment of ADHD” (Holtmann et al., p. 789).

Magellan acknowledges that neurofeedback has provoked interest in behavioral health research due to the increased parental demand for nonpharmaceutical interventions and concerns over safety alerts related to stimulant drugs. Magellan will continue to monitor the research in this area. More large-site studies are needed to provide more evidence from well-blinded and methodologically sound trials. Magellan continues to consider neurofeedback as investigational for the treatment of ADHD in children and adolescents (Magellan Health, 2015).

### Diet

Many children do not experience reduction in the core symptoms of ADHD with pharmaceutical treatment (both stimulant and nonstimulant medication) while others experience short term side effects, e.g., appetite loss and sleep problems. Some studies have suggested that dietary interventions may be effective in treating ADHD in children (Rytter et al., 2014). These include elimination diets that remove elements, e.g., sugar, artificial sweeteners and food colorants, and food supplementation diets, which increase the intake of certain nutrients, e.g., essential fatty acids and amino acids. A systematic review of diet in the treatment of ADHD found that elimination diets and food supplementation diets seem to be the most promising dietary interventions for ADHD, but they suggested more studies are necessary before recommending them as treatment. Authors investigated 52 studies including diet interventions in children with ADHD to investigate whether the interventions resulted in improvement in core ADHD symptoms. They reviewed four meta-analyses, which found artificial food colorants had small adverse effects on the symptoms of ADHD in limited quality studies. In meta-analysis of a few randomized trials, authors found evidence of small to modest positive effect of fish oil supplementation. They concluded that, “for most dietary interventions there is not enough evidence to recommend their routine use in clinical practice” (Rytter et al., p. 14).

### Sleep-Focused Treatment

In a randomized trial, researchers evaluated whether a brief sleep intervention for children with both ADHD and sleep problems, i.e., sleep initiating and maintaining sleep, are effective in improving sleep problems as well as symptoms of ADHD. Children (n=244) aged 5 to 12 with ADHD, most of whom were also receiving treatment with stimulant medications, were randomized to an intervention group or a usual clinical care group. The intervention group received two face-to-face consultations (every two weeks) with a trained clinician who assessed the sleep problem, helped the parents obtain goals for sleep management, and provided parent training about sleep cycles and sleep hygiene strategies. The clinician then formulated a behavioral sleep management program based on the individual child’s particular sleep problems. The primary outcome, measured at baseline and at six months, included parent and teacher reported ADHD symptoms. Secondary outcomes included sleep problems reported by primary caregiver and as indicated on the

children’s sleep habits questionnaire. Researchers reported that the behavioral intervention group reported a greater decrease in ADHD symptoms as well as fewer moderate to severe sleep problems at both three and six months when compared with the usual care group. Researchers suggested the need for future trials that are more rigorous and that will test the long-term benefits of a brief behavioral sleep intervention as an adjunctive consideration (Hiscock et al., 2015).

### Trigeminal Nerve Stimulation

In an eight week, open, pilot investigation of trigeminal nerve stimulation (TNS) for the treatment of youth (n=24) aged 7-14 with ADHD, researchers’ sought to determine feasibility of conducting TNS research in this population. Other goals included determining potential effects of the treatment on ADHD symptoms (behavioral, cognitive and executive functioning, sleep, and side effects/adverse events (McGough et al., 2015). The treatment was administered nightly during sleep after participants and parents received instruction, and a parent-completed TNS compliance diary measured treatment adherence. The Investigator Completed Parent ADHD-RS and Conners Global Index were completed at baseline; week four and week eight were primary outcome measure for the effects of TNS on ADHD behavioral symptoms. Other rating scales assessed the effects of TNS on cognition and executive function, sleep, and side effects/adverse events. Nightly treatment compliance was reported for all 24 participants, and the ADHD-RS showed improvements in both inattentiveness and hyperactive/impulsive scales. Other rating scales showed improvement in parent- reported executive functioning and sleep problems. Researchers noted, “One of the most surprising and compelling findings from the current study was the dramatic improvement detected in several CSHQ subscales that suggests positive TNS benefits on sleep-related anxiety as well as total sleep and bedtime related problems” (McGough et al., p. 303). While suggesting a potential role for TNS as a treatment for ADHD, author also emphasized the need for larger controlled trial including a “sham” intervention.

### Physical Exercise

A systematic review and meta-analysis was conducted to determine the effectiveness of exercise interventions on ADHD-related symptoms such as inattention, hyperactivity/impulsivity, anxiety, and cognitive functions in children and adolescents (Cerrillo-Urbina et al;2015). Eight randomized controlled trials (n=249) satisfied the inclusion criteria and were grouped to the intervention program: aerobic and yoga exercise. The meta-analysis suggests short-term aerobic exercises ranging from 6-10 weeks reported a large effect on inattention, hyperactivity, impulsivity, anxiety, executive function and social disorders in children with ADHD. These results suggest promise in physical exercise as a supplementary intervention. However, due to the small number of studies, more studies should be done to produce clinically relevant conclusions.

## **Introduction**

A recent prospective longitudinal study suggested that despite the prevailing assumption that adult ADHD is a childhood-onset neurodevelopmental disorder, not all adults presenting with ADHD symptoms have a childhood-onset neurodevelopmental disorder

(Moffitt et al., 2015). In this study including both follow-back analyses and follow-forward analyses, participants belonging to a representative birth cohort of individuals (n=1037) were followed to age 38 and assessed for symptoms of ADHD, associated clinical features, neuropsychological deficits, comorbid disorders and genetic risk. Sources of data included participants, teachers, informants, neuropsychological test results and administrative records. Results of the study showed prevalence of childhood ADHD and of adult ADHD were 6 percent and 3 percent, respectively. Unexpected results showed virtually nonoverlapping sets of childhood and adult ADHD cases, with no history of childhood ADHD in 90 percent of all adult ADHD cases. Authors found little evidence that adult ADHD had a childhood onset and suggested that if these results are replicated, further studies must investigate the etiology of adult ADHD. In a review of the Moffitt study, Yager suggested, “Attentional problems associated with adult ADHD might instead be nonspecifically related to substance dependence and other comorbidities. Regardless, high impairment rates in adults with ADHD underscore the need for better understanding and treatment studies” (Yager, 2015). According to DSM-5™, “ADHD begins in childhood. The requirement that several symptoms be present before age 12 years conveys the importance of a substantial clinical presentation during childhood” (APA, 2013).

ADHD is a childhood-onset neurodevelopmental disorder characterized primarily by a persistent pattern of inattention, and/or hyperactivity-impulsivity that interferes with or reduces the quality of social, academic or occupational functioning (American Psychiatric Association, 2013). These dysfunctions can lead to behavioral problems in home, school, work, and social settings. Children with ADHD may have difficulty with learning in school, developing appropriate social skills, and managing frustration and aggression (Wilens et al., 2002). ADHD is also a developmental disorder whose presentation may change with maturation. There is often a decrease in overt hyperactivity and impulsivity with age, while attention problems are more likely to persist (Mick et al., 2004). In a later meta-analysis, authors reported studies suggesting that levels of hyperactivity-impulsivity symptoms decline significantly from early childhood through adolescence while inattentive symptoms decline minimally with age (Wilcutt, 2012). Their review of 86 studies of children and adolescents (n=163,688) and 11 studies of adults (n=14,112) also found no significant prevalence differences between regions of the world or countries; ADHD was observed across a large range of cultures.

The diagnostic criteria for ADHD are outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5™ (American Psychiatric Association, 2013). Diagnostic symptoms are divided into two major symptom domains: inattention and hyperactivity/impulsivity. Some researchers have stressed the need for criteria that are more appropriate for older adolescents and adults who often experience ADHD in a slightly different way than children and adolescents (Mick et al., 2004; McGough and Barkley, 2004; Spencer and Adler, 2004). The criterion items in DSM-5 include examples to facilitate application across the lifespan; the onset criterion has changed to “several inattentive or hyperactive-impulsive symptoms were present prior to aged 12,” replacing “symptoms that caused impairment were present before aged 7 years.” Six symptoms persisting for at least six months in one domain are required for an ADHD diagnosis in children and adolescents under the age of 17 while only five symptoms in either of the major domains are required



for older adolescents and adults. ADHD must be manifest in more than one setting, e.g., home, school, work (American Psychiatric Association, 2013).

## Epidemiology

In a recent report, the American Academy of Family Physicians noted that ADHD is the most common behavioral disorder in children and that the prevalence is increasing (Felt et al., 2014). Visser et al. reported trends in parent-reporting of health care provider-diagnosed and medicated ADHD in the United States from 2003-2011 (Visser et al., 2014). These trends were based on data obtained from the National Survey of Children’s Health (NSCH), which reflected increasing prevalence and treatment by health care providers:

- In 2011, 11 percent of children/adolescents aged 4-17 had ever received an ADHD diagnosis; approximately one in five high school boys and one in 11 high school girls had been diagnosed with ADHD
- 83 percent of children/adolescents with a history of ADHD had current ADHD diagnosis
- 69 percent of children with current ADHD diagnosis were taking medications for ADHD
- Parent-reported history of ADHD increased from 2003 to 2011 by 42 percent, and
- Prevalence of medicated ADHD increased from 2007 to 2011 by 28 percent.

A recent study investigated predictors of delays to ADHD treatment seeking by examining lifetime ADHD treatment seeking reported in the National Epidemiologic Survey on Alcohol and Related Conditions (Dakwar et al., 2014). Authors investigated predictors of ADHD treatment seeking separately for males and females, finding low cumulative probability of ADHD treatment seeking (55 percent), most not beginning until well after childhood, with gender not significantly affecting treatment seeking. Older age was associated with significantly longer delays in treatment seeking for both males and females. Lower education and an African-American background in males were associated with greater delays in ADHD treatment seeking compared with females with the same characteristics, while psychiatric comorbidity was associated with less delay in treatment seeking among males. Older age was the only predictor of delayed treatment seeking among females, while bipolar disorder was associated with faster treatment seeking among females. Authors noted the need for efforts at public outreach and greater treatment access, especially to vulnerable male populations who may delay treatment seeking due to factors such as African-American background, paranoid personality disorder and low education (Dakwar et al., 2014).

A recent population-based study in Sweden investigated common etiological factors of ADHD and suicidal behavior to determine whether genetic and environmental risk factors were shared between the two disorders (Ljung et al., 2014). Researchers linked longitudinal population-based registers, e.g., The National Patient Register, The Swedish Prescribed Drug Register, The Multi-Generation Register, The Total Population Register and the Cause of Death Register to identify patients (51707) with ADHD. They analyzed the data from the registers to study both the occurrence of suicide in individuals with ADHD as well as the “familial risk across different levels of genetic relatedness” (Ljung et al., p. 959).

After adjusting for comorbid psychiatric disorders, results showed increased risk of both attempted and completed suicide in individuals with ADHD compared with matched control participants. Observing high risk among first-degree relatives and lower risk of both completed and attempted suicide among more genetically distant relatives, researchers suggested that shared genetic factors, e.g., genetic variants associated with impulsivity (associated with both ADHD and suicidal behavior), contribute to the overlap between ADHD and suicidal behavior. They suggested the importance of targeting individuals as well as their family members for suicide prevention and treatment (Ljung et al., 2014).

In a recent study, researchers sought to determine whether polygenic risk previously found to be associated with ADHD, also predicts traits related to ADHD and autism spectrum disorder (ASD) in the general population (Martin et al., 2014). Polygenic risk scores for ADHD were calculated in the Avon Longitudinal Study of Parents and Children population sample (n=8229). An analysis found that “polygenic score, based on common genetic variants previously found to be associated with risk of a clinical diagnosis of ADHD, was also associated with ADHD traits measured at ages 7 and 10 years in the general population,” suggesting that “ADHD represents the extreme end of traits present in the general population” (Martin et al., p. 669). Children diagnosed with ADHD had more ASD-related social communication problems than children without an ADHD diagnosis, and children with ASD had more ADHD traits than those with neither diagnosis. Researchers noted the lack of clear-cut boundaries between different neurodevelopmental and psychiatric disorders. “The approach of testing genetic risks that contribute to dimensions that cut across diagnostic categories, rather than using DSM diagnoses, is in line with the Research Domain Criteria framework and is likely to be a valuable approach for future neurodevelopmental and psychiatric research” (Martin et al., 2014). Rubia et al. noted, “ADHD is the most imaged child psychiatric disorder with over hundreds of published structural and functional imaging studies” (Rubia et al., 2014). In their recent review, authors discussed current findings on brain deficits in ADHD. Past meta-analytic findings have confirmed that patients with ADHD have cognitive domain dissociated deficits in fronto-striatal, fronto-parietal and fronto-cerebellar networks. Additionally, abnormalities in the functional connectivity between these regions may occur both during rest and during cognitive tasks. Authors noted that regions of the brain underactivated in ADHD increase in activation with age potentially reflecting a developmental delay in brain functioning in ADHD. They also pointed out ADHD currently is diagnosed based on often unreliable subjective clinical and rating measures rather than objective neuroimaging biomarkers despite consistent evidence for brain structure and function deficits in ADHD. They suggested “multivariate pattern analyses for imaging data can make predictions, e.g. of class membership, for individual subjects as opposed to group-level inferences and have been successfully applied to other disorders” (Rubia et al., p. S10.) Authors concluded, “We have acquired substantial knowledge on the underlying neurobiological mechanisms of ADHD. However, more studies are needed that integrate different imaging modalities to understand the interplay between the changes in neurochemistry, brain function and brain structure and to assess longitudinal trajectories of the disorder. The next decade will need to focus on using neuroimaging techniques in a more clinically applied fashion, either to aid with individual diagnosis, prognosis of disease progression and treatment success of as a neurotherapy to normalize abnormally functioning brain regions” (Rubia et al., 2014).

Recent research has shown that symptoms of children with autism spectrum disorder (ASD) are often similar to the core features of ADHD: inattention, hyperactivity and impulsivity (Miodovnik et al., 2016). In a large surveillance study analyzing data from the 2011-2012 National Survey of Children’s Health, Miodovnik et al. examined a sample of children (n=1496), aged 2 – 17 with a diagnosis of ASD as reported by their parents, to investigate the relationship between the age at ADHD diagnosis and the age of ASD diagnosis. Some of the children (approximately 20 percent) received a diagnosis of ADHD prior to ASD diagnosis. In their analysis of the data, authors found that when compared with children with only ASD diagnosis, those who received ADHD diagnosis before ASD diagnosis were 16.7 times more likely to receive a diagnosis of ASD after six years of age (delayed diagnosis). Those with ADHD before ASD were 29.5 more likely to have delayed diagnosis than those who received ADHD diagnosis after the ASD diagnosis. Authors noted support for their hypothesis that the diagnosis of ASD may be delayed when ADHD is diagnosis first, suggesting that ASD should be considered when evaluating children presenting with ADHD symptoms. Further, they emphasized the need for diagnostic criteria and screening measures that reflect the overlapping symptomatology between the two disorders (Miodovnik et al., 2016).

A recent meta-analysis assessed the relationship between ADHD and obesity, finding the pooled prevalence of obesity increased in adults with ADHD by about 70 percent compared with those without ADHD; an increase of about 40 percent was found in children with ADHD compared with children without ADHD (Cortese et al., 2016). Authors noted that both the impulsive and inattentive components of ADHD could increase the risk of obesity. They also suggested the sharing of common biological risk factors including genetic variants in ADHD and obesity. “A ‘reward deficiency syndrome,’ characterized by insufficient dopamine-related natural reinforcement that leads to ‘unnatural’ immediate rewards (such as inappropriate eating), has been reported in both ADHD and obesity” (Cortese et al., p. 41). Lastly, they suggested the possibility that factors associated with obesity lead to symptoms of ADHD, e.g., sleep-disordered breathing. Authors concluded that the risk for obesity should be part of the assessment and management of ADHD.

A recent prospective study of a nationwide population-based cohort in Denmark, with up to 32 year follow-up of individuals with ADHD (n=32,061), found that “children, adolescents, and adults with ADHD had decreased life expectancy and more than double the risk of death compared with people without ADHD” (Dalsgaard et al., 2015). The study reported that a diagnosis of ADHD in adulthood was associated with a greater risk of death than a diagnosis in childhood or adolescence. Conditions found to increase the risk of death in individuals with ADHD included comorbid oppositional defiant disorder, conduct disorder and substance use disorder. Authors further noted that the increased mortality rate ratios were mainly due to deaths related to unnatural causes, e.g., accidents. Authors suggested that Denmark is more restrictive in diagnosing ADHD than the United States, and that ADHD cases may have had more severe symptoms than those in countries that were less restrictive in diagnosing ADHD. However, they said that this is the first study noting ADHD’s association with increased mortality and the link to adult ADHD and emphasized the importance of early identification of ADHD. They also suggested more research on factors to improve life expectancy patients with ADHD (Dalsgaard et al., 2015).

As stated by Goldman in 1998, “Attention-Deficit/Hyperactivity Disorder is one of the best-researched disorders in medicine, and the overall data on its validity is far more compelling than for most mental disorders and even for many medical conditions” (Goldman et al., 1998). There is a great cost to society from ADHD because of the resulting academic and occupational underachievement, conduct problems throughout the lifespan, higher levels of associated substance abuse, motor vehicle accidents, and interpersonal relationship problems (Wilens et al., 2002; Mick et al., 2004; Wilens 2004). Research has shown that ADHD costs the U.S. society between \$143 billion and \$266 billion in 2010 (approximately \$2,000 per household). Adults with ADHD accounted for 73 percent of those estimated costs. Costs resulted from lost productivity, expenditures related to health care, education and the criminal justice system. In addition to the cost in dollars, the “human cost is astounding” (American Psychiatric Association, 2014).

ADHD appears to be a neurologically heterogeneous disorder, with varying patterns of impairment in different individuals and with significant subtypes (American Academy of Pediatrics 2011; American Academy of Child and Adolescent Psychiatry, 2007; American Psychiatric Association, 2000; Nutt, 2007). A Canadian research team compared ADHD subtypes (n=371) on level of comorbidity, treatment response and etiology using data from subjects already enrolled in a randomized controlled trial of methylphenidate (Grizenko et al., 2010). Results showed significant differences in these parameters leading to speculation that ADHD subtypes may be separate and distinct disorders. Specifically, a higher frequency of ADHD children with combined/hyperactive subtype were good treatment responders, had a history of moderate stress during the mother’s pregnancy and were of L/L genotype for the 5-HTT-linked polymorphic region along with other notable differences in age, gender distribution, severity of symptoms and comorbidity between the subtypes (Grizenko et al., 2010). In DSM-5, subtypes have been replaced with specifiers, i.e., combined presentation (both inattention and hyperactivity-impulsivity); predominantly inattentive presentation; predominantly hyperactive/impulsive presentation; and partial remission (criteria met previously but not currently and symptoms continue to result in impairment in social, academic or occupational functioning) (American Psychiatric Association, 2013).

Childhood ADHD is reported to be much more prevalent in boys, though some experts argue that ADHD in girls is more often undetected. In contrast to earlier studies in which boys were reported as having poorer functioning, some reports suggest that non-referred boys and girls have similar impairment levels of cognitive, psychosocial, school and family functioning and that the previously described gender differences in functioning are due to referral biases rather than true gender differences (Biederman et al., 2005). In a later meta-analysis estimating the prevalence of ADHD, Wilcutt found males to be more likely than females in meeting criteria for an overall diagnosis of ADHD (Wilcutt, 2013). In the general population, ADHD is more frequent in males than in females, with a ratio of approximately 2:1 in children and 1.6:1 in adults. Males are less likely than females to present primarily with inattentive features (American Psychiatric Association, 2013).

The childhood prevalence of ADHD is similar in every culture studied, and depending on

the criteria used, has been reported as ranging from 3-15 percent, with at least 7 percent being a generally accepted average figure. These statistics indicate that it is the most common psychiatric disorder of childhood (American Academy of Child and Adolescent Psychiatry, 2007; Barbaresi et al., 2004). According to later analyses conducted with 2011-2012 data (parent-reported indicators of healthcare provider-diagnosed ADHD diagnosis and treatment) from the National Survey of Children's Health (NSCH), 11 percent of children/adolescents in the U.S. aged 4 to 17 had received an ADHD diagnosis at some time (Visser et al., 2013). The estimated national prevalence of current ADHD was 8.8 percent among children. Analyses of the 2011-2012 data found a significant increase from 2007 estimates in the prevalence of a history of ADHD, current ADHD, medicated ADHD, and moderate/severe ADHD. ADHD was higher among boys (15.1 percent) than among girls (6.7 percent) and increased with age. More than two-thirds of children with current ADHD were receiving medication treatment in 2011 (Visser et al., 2013). In most cultures, about 5 percent of children and about 2.5 percent of adults have ADHD according to population surveys (American Psychiatric Association, 2013). The majority of children with ADHD meet some or all of the criteria for this disorder as adults. For example, at aged 25 years, about 15 percent of people diagnosed with ADHD as children meet DSM-IV-TR criteria for the disorder, and about 65 percent meet DSM-IV-TR criteria for ADHD in partial remission (Nutt, 2007; Faraone, 2006).

Co-morbid psychiatric diagnoses are common in adolescents with ADHD. Findings from a study showed that when compared with controls, adolescent girls with ADHD at baseline followed five years later had higher rates of oppositional defiant disorder (28.6 percent vs. 1.9 percent) and major depressive disorder (22.1 percent vs. 1.9 percent) (Childress and Berry, 2012). Adolescent ADHD is also associated with conduct disorder, bipolar disorder, anxiety disorders, increased risk of substance use and substance use disorders (Childress and Berry, 2012).

Adult ADHD is both significantly under diagnosed and under treated (Faraone, 2004). The prevalence appears to be about 4-5 percent (Nutt, 2007; American Academy of Child and Adolescent Psychiatry, 2007). An unpublished study suggested adult women with ADHD are less likely to be diagnosed despite having more severe symptoms and emotional impairment than male patients (Robison et al., 2005). This finding is of particular concern since women respond at least as well to treatment as men. One study was unable to demonstrate any differences in comorbidity, social functioning and cognitive functioning between adults meeting full diagnostic criteria for ADHD and those having only residual (not full criteria) ADHD symptoms (Mick et al., 2004). A large community sample examining the stability and structure of ADHD symptoms from childhood to adulthood showed a greater persistence of inattentive than of hyperactive/impulsive childhood ADHD symptoms and found executive function problems as the most specific and consistent predictor of diagnosis. DSM-5 adds examples to the criterion items in the inattention domain for older adolescents and adults, e.g., returning calls, paying bills, keeping appointments; preparing reports, completing forms, reviewing lengthy papers; distraction from unrelated thoughts (American Psychiatric Association, 2013). Other research has shown that over 90 percent of adults with ADHD have inattentive symptoms requiring careful evaluation to determine or rule out comorbid conditions since inattention may be a component of several other disorders (Wilens et al., 2009).

The majority of adults with ADHD have at least one comorbid psychiatric disorder, which may be the clinician’s first clue of the diagnosis of ADHD (Wiles et al., 2002; Montano, 2004). A large clinical survey (n=447) conducted to determine the prevalence of current and lifetime Axis I and II disorders in adult men and women with ADHD revealed the following: (1) Men with ADHD were more likely to have antisocial personality disorder and higher rates of current drug use than women with ADHD; (2) women with ADHD had higher rates of past and current panic disorder and past anorexia and bulimia; and (3) women with ADHD were more likely to have bipolar disorder than men with ADHD (Cumyn et al., 2009). Anxiety disorders, major depressive disorder and substance use disorders occur more often in individuals with ADHD than in the general population, but substance use disorders occur in only a minority of adults with ADHD. Other disorders that may co-occur with ADHD include antisocial and other personality disorders as well as obsessive-compulsive disorder, autism spectrum disorder and tic disorders (American Psychiatric Association, 2013). A study reporting on a large sample of pediatric patients (n=158) diagnosed with a chronic tic disorder (TD) compared clinical features based on whether the patients had TD comorbid with obsessive compulsive disorder (OCD), TD comorbid with ADHD, or TD with the absence of either diagnosis (Lebowitz et al., 2012). Compared with chronic TD without OCD or ADHD, chronic TD with comorbid ADHD resulted in higher levels of stress and poorer functioning whereas chronic TD with comorbid OCD resulted in greater severity on measures of psychopathology including depression and anxiety. Authors suggested research is needed to further examine the links between TD, OCD and ADHD (Lebowitz et al., 2012).

Adults with ADHD are less likely to have graduated from high school or to have attended college. They have lower occupational achievement, change jobs more frequently, are more likely to be fired or quit and perform more poorly on the job. They have more psychological maladjustment, more occurrences of multiple marriages and much more substance abuse. A study of adult violent offenders found that after controlling for age, gender and substance use disorders, ADHD was associated with reactive but not proactive violence (Retz et al., 2010). In a study of older adolescents and young adults with ADHD, it was shown that the subjects exhibited “no driving knowledge deficits, but compared with controls, they had elevated rates of speeding citations, suspended licenses, crashes, and accidents causing bodily injury.” It was also found that “They were more likely to be rated by themselves and others as having poorer driving habits” (Mick et al., 2004). The American Academy of Pediatrics’ guideline suggests special concern should be taken to provide medication coverage to control symptoms while driving, while also advising the use of longer-acting or late-afternoon short-acting medication (American Academy of Pediatrics, 2011).

Despite the multiple issues arising from untreated or partially treated ADHD, it needs to be stressed that there is a broad range of social and occupational outcomes, with many individuals having success in the social and occupational realms despite ongoing symptoms.

The causes of ADHD have not been determined conclusively and continue to be studied. ADHD appears to be the result of a complex interaction of genetic, environmental and biological factors (American Academy of Child and Adolescent Psychiatry, 2007; Nutt DJ 2007; Pliszka 2006). Evidence for the genetic factors includes a pool of 17 twin studies

reporting heritability (genetic factors) influence of about 76 percent (Faraone, 2004). However, more recent review of these earlier studies has warned that heritability estimates were strongly influenced by rater effects and assessment instruments used in these studies (Freitag et al., 2010). In addition, parents of children with ADHD had been reported as being much more likely to have ADHD than are parents of children without ADHD (Faraone, 2004). Since then, a study of 323 trios (mother, father and identified ADHD patient) found that ADHD severity was higher for children whose parents had ADHD versus those whose parents did not; that both parents may confer risks for both subtypes with fathers conferring greater risk for severity of hyperactivity-impulsivity; and that biparental ADHD may not have an additive or synergistic effect on the probands ADHD severity (Takeda et al., 2010). Results of one study suggest that large, rare duplications in the genome, e.g., CHRNA7 duplications, are associated with ADHD. CHRNA7 has also been implicated in other psychiatric conditions, e.g., autism spectrum disorder, and has been associated with conduct disorder (Ross, 2011). Although specific genes have been correlated with ADHD, they are not sufficient causal factors. Possible influences on ADHD symptoms include visual and hearing impairments, sleep disorders, nutritional deficiencies, metabolic abnormalities and epilepsy (American Psychiatric Association, 2013).

Suspected environmental factors include brain injury in utero, perinatal stress, fetal exposure to nicotine and alcohol, low birth weight/prematurity and traumatic brain injury (Nair 2006; Grizenko et al., 2008). More recent data from the 2001-2004 National Health and Nutritional Health Examination Survey (NHANES) have shown that both prenatal tobacco exposure (maternal cigarette use during pregnancy) and childhood lead exposure were associated with ADHD in children (Froehlich et al., 2009). A prospective longitudinal study conducted in the Canadian Arctic found that prenatal exposure to methyl mercury was associated with greater attention problems (reported by classroom teachers) consistent with ADHD. The study also found that postnatal lead exposure was associated with greater hyperactivity-impulsivity symptoms consistent with ADHD (Boucher et al., 2012). In a study assessing the relationship between the prevalence of ADHD and solar intensity, researchers found a lower prevalence of ADHD in areas with high solar intensity (SI). They suggested that the preventative effect of high SI might be related to an improvement of circadian clock disturbances associated with ADHD. Researchers pointed out that these findings were specific to ADHD, not for the prevalence of autism spectrum disorders or major depressive disorders (Arns et al., 2012).

Biological factors have been identified through studies that have employed brain-imaging techniques and neuropsychological testing. Such studies have revealed evidence of structural and functional brain abnormalities in ADHD. Of particular importance are functional abnormalities in the frontal, temporal, sub-cortical, left occipital and cerebellar neural circuits, decreases in white matter volume, and widespread brain pathophysiologic abnormalities. Such biological findings suggest that any causality theory must provide a model for understanding broad-based brain dysfunction (Faraone, 2004; Monastera 2005a; Valera et al., 2010). In a meta-analysis of task-based functional MRI studies of ADHD, researchers found evidence of ADHD-related dysfunction in multiple neuronal systems involved in higher-level cognitive functions as well as sensorimotor processes. Researchers suggested that ADHD is a disorder characterized by possible compensatory mechanisms, e.g., hyperactivation in visual areas, in addition to functional deficiencies (Cortese et al.,

2012).

A recent review of literature acknowledged an emerging association between addictive gaming and ADHD as indicated by the occurrence of gaming addiction as a co-morbid disorder of ADHD. The DSM-5 includes internet gaming disorder under “Conditions for Further Study,” noting that the proposed criteria set and disorder is not officially recognized and should not be used for clinical purposes. Authors suggest future studies are important to understand the common psychological and neurotransmitter mechanisms underlying ADHD and computer game and video game addiction, and to explore new trends and developments in the diagnose and treatment of both conditions (Weinstein and Weizman, 2012).

In a recent study examining the association between advancing paternal age at childbearing and increased risk of psychiatric and academic problems in offspring, researchers performed a population-based cohort study of everyone born in Sweden from 1973 until 2001 (n=2,615,081). They documented the associations between paternal age at childhood and psychiatric disorders (autism spectrum disorder, ADHD, schizophrenia, suicide attempts, bipolar disorder, substance use disorders) in offspring, finding that a child born to a 45-year-old father is 13 times more likely to have ADHD than a child born to a 24-year-old father and is 2.5 times more likely to have suicidal behavior or a substance use problem. Children born to a 45-year-old father were 3.5 times more likely to have autism, and almost 25 times more likely to have bipolar disorder than offspring of a 24-year-old father. Researchers indicated that the findings are consistent with the hypothesis that offspring morbidity may result from new genetic mutations occurring during spermatogenesis (Nauert 2014).

## Evaluation

The evaluation of ADHD in children and adolescents include the following components (Felt, et al., 2014):

- History and physical examination (presence and duration of core ADHD symptoms; degree of functional impairment from perspective of patient, family and school; other possible conditions mimicking or coexisting with ADHD; risk factors including medical, environmental and genetic);
- Review of information across home and community settings;
- Application of the diagnostic criteria included in the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> ed., (DSM-5); and
- Use of validated behavioral rating scales that collect data from multiple observers across settings, such as the following (Felt et al., 2014; Dittmann et al., 2014):
  - National Institute for Children’s Health Quality (NICHQ) Vanderbilt Assessment Scale (NICHQ, 2015)
  - Brown Rating Scales (3-yr to adult - parent, teacher, or self-report)
  - ACTeRS Rating Scales (kindergarten to 8<sup>th</sup> grade - parent/teacher report; adolescents or adults - self-report)
  - Child Behavior Checklist (aged 18 months to 18; parent/teacher or self-report)
  - Conners’ Parent Rating Scale-Revised 9CPRS-R)



- ADHD rating Scale IV (ADHD-RS-IV)
- Swanson, Nolan and Pelham version IV (SNAP).
- Evaluate for other conditions mimicking or co-existing with ADHD, e.g., anxiety disorder, autism spectrum disorder, fetal alcohol syndrome, genetic disorders such as fragile X syndrome, hearing loss, intellectual disability, learning disorder, mood disorders, oppositional defiant disorder, seizure disorder, sleep disorder, speech and language disorder, and vision disorder (Felt et al., 2014).

The diagnosis of ADHD is determined using DSM-5 criteria. The trained healthcare clinician should analyze data from a variety of sources, since no single test, rating scale or observational finding determines the diagnosis (Cincinnati Children’s Hospital Medical Center, 2004). However, the use of structured rating scales that have been found valid and reliable with large populations is recommended (Nutt, 2007). Any parental concern about inattention, impulsivity or hyperactivity in a child aged 4 through 18 should be taken seriously by the clinician and lead to further investigation. An evaluation for ADHD should be initiated by the primary care clinician for any child presenting with academic or behavioral problems and symptoms of inattention, hyperactivity or impulsivity (American Academy of Pediatrics, 2011). A family history of ADHD lends support to suspecting the diagnosis (Faraone, 2004; AAP Subcommittee on ADHD, 2011).

At a minimum, data obtained for diagnosing ADHD in children and adolescents should include the following (American Academy of Child and Adolescent Psychiatry, 2007; Nutt 2007, AAP Subcommittee on ADHD, 2011; American Academy of Pediatrics, 2011):

- Determination by primary care clinician that DSM-5 criteria for ADHD have been met and the ruling out of alternative cause of symptoms
- Obtaining psychiatric, developmental, social, educational, family and medical history from parents, guardians, teachers and other school and mental health clinicians involved in the child’s care. Family history should include questions about parental ADHD and cardiac history
- Assessment by primary care clinician for other conditions co-existing with ADHD (such as emotional or behavioral, developmental and physical conditions); review of medical evaluation, including physical exam and lab tests, to rule out medical causes of the signs and symptoms
- Assessment by primary care clinician for urgent conditions, such as suicidal thoughts or behaviors with potential to injure child/adolescent or others, e.g., temper outbursts
- Recognition by the primary care clinician that ADHD is a chronic condition and consideration of children and adolescents with ADHD as having special health care needs
- Rating scales from the patient and parents, e.g., Brown ADD Scales for Children, Adolescents, and Adults (Brown, 2001); Conners Parent Rating Scale-Revised (Conners, 1997)
- Reports and rating scales from teachers, e.g., Brown ADD Scales for Children, Adolescents, and Adults (Brown, 2001); Conners Teacher Rating Scale-Revised (Conners, 1997)
- Comprehensive assessment for comorbid psychiatric disorders
- Careful substance abuse evaluation for adolescents with newly diagnosed ADHD

- Clinical observation.

The criteria for diagnosing children with ADHD are included in the DSM-5. For the diagnosis, children and adolescents through aged 16 must present with at least six symptoms from one or both of the two major domains: inattention or hyperactivity/impulsivity. A persistent pattern of inattention and/or hyperactivity-impulsivity must be present in two or more settings (such as home or school), and must interfere with or reduce the quality of social, academic or occupational functioning. ADHD must have begun in childhood; several of the symptoms must have been present before 12 years of age, compared with aged 7 in the DSM-IV. Accurate confirmation of substantial symptoms should be confirmed by observations of the child in the setting(s) by multiple informants, e.g., teachers, parent or third party (American Psychiatric Association, 2013).

Although ADHD begins in childhood, it can continue through adulthood. Adults with ADHD often present for evaluation after diagnosis of one of their children. Reasons for the delayed diagnosis until adulthood can include: 1) the diagnosis being obscured in childhood by associated problems such as oppositional defiant disorder (ODD), conduct disorder and mood disorder, 2) child erroneously labeled as a “troublemaker” or a “daydreamer” and 3) past perception that the disorder was mainly a disorder in children (Mick et al., 2004; McGough and Barkley, 2004; Biederman and Faraone, 2004, Wilens et al., 2004; Wilens et al., 2004; Nutt, 2007; Dalsgaard, 2013). DSM-5 adds new examples to the criterion items facilitating application to adults as well as children and adolescents. Adults must meet five symptoms in either of the two domains: inattention and hyperactivity/impulsivity (American Psychiatric Association, 2013).

Adults commonly have more cognitive, e.g., inattentive, than hyperactive symptoms. When hyperactivity is present, it tends to become more of a subjective sensation rather than an observable sign. Inattentive symptoms affect executive functions and can manifest in problems with organized planning, multitasking and time management. A variety of self-report and clinician-administered rating scales is available to aid in the assessment for these symptoms in adulthood. Examples of such screening scales are the Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist developed by the World Health Organization (available at <http://www.hcp.med.harvard.edu/ncs/asrs.php>) (Kessler et al., in press; Nutt 2007) and the Wender Utah Rating Scale (Ward, 1993). The Brown ADD Scales (Brown, 2001), Wender-Reimherr Adult ADHD Scale (Ward et al., 1993) and others can be used to determine symptom severity. Clinicians make the diagnosis after considering the patients’ reported ADHD symptoms from childhood, data from collateral sources, and current symptoms and functioning (Spencer and Adler, 2004; Wilens et al., 2004). As in children, there must be “clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning” (American Psychiatric Association, 2013).

### ***Differential Diagnosis***

<p><b>Determine that symptoms of ADHD do not occur only during the course of a psychotic</b></p>
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**disorder, e.g., schizophrenia, and are not better explained by another mental disorder, e.g., mood disorder, anxiety disorder, dissociative disorder or a personality disorder.** Symptoms of the following disorders should be distinguished from those of ADHD: intermittent explosive disorder; stereotypic movement disorder; Tourette’s disorder; specific learning disorders; intellectual developmental disorder; autism spectrum disorder; reactive attachment disorder; anxiety disorders; depressive disorders; bipolar disorder; disruptive mood dysregulation disorder; substance use disorders; personality disorders; psychotic disorders; and neurocognitive disorders (American Psychiatric Association, 2013). Neurobehavioral adverse effects of medication and sexual, physical and emotional abuse can also cause ADHD-like symptoms (DSM- IV-TR, 2000; Spencer et al., 2004; Cincinnati Children’s Hospital Medical Center, 2004).

When evaluating a patient who presents with symptoms consistent with ADHD, it is recommended that clinicians evaluate for behavioral health comorbidity. Significant overlap among symptoms of ADHD and other psychiatric disorders often complicates the diagnosis of comorbidities and the treatment process. According to DSM-5, approximately 50 percent of children with the combined presentation (inattention and hyperactivity/ impulsivity) and about 25 percent of those with the predominantly inattentive presentation also have symptoms meeting criteria for oppositional defiant disorder. Specific learning disorder co-occurs often with ADHD and conduct disorder co-occurs in about 25 percent of children or adolescents with the combined presentation. A majority of children and adolescents with disruptive mood dysregulation disorder have symptoms meeting criteria for ADHD. Substance use disorders are present in a minority of adults with ADHD, but co-occur in this group more frequently than among adults in the general population (American Psychiatric Association, 2013). Also, gender and age suggest differing likelihoods of the presence and type of behavioral health co- morbidities. While previous studies reported boys having a greater degree of comorbidity, more recent reports suggest that psychiatric comorbidities are similar for both boys and girls in non- referred cases of ADHD (Biederman et al., 2005). One study **suggested** that ADHD is a stronger risk factor for comorbid substance use disorders in girls. Regarding age, comorbid depression in younger children may seem less frequent but could be easy to miss, given the difficulty of accurate diagnosis in this age group.

The presence of certain comorbidities may suggest the likelihood of different presentation specifiers of ADHD. Patients with co- morbid anxiety as a group tend to have a greater degree of inattention rather than impulsivity. Conversely, those with co-morbid oppositional defiant disorder or conduct disorder tend to be more impulsive rather than inattentive. Emotional lability (EL) in children and adolescents with the combined presentation may be associated with increased severity of ADHD core symptoms and more symptoms of comorbid psychopathology, i.e., ODD, affective symptoms and substance abuse (Sobanski et al., 2010; Barkley et al., 2010).

Sleep disorders are highly comorbid with ADHD. Different sleep disorders seem to address different subtypes and correlate with severity of symptoms, i.e., sleep related movement disorders in hyperactive and combined ADHD subtypes (Silvestri et al., 2009).

In evaluating comorbidity in children, a narrow-band scale, such as the Vanderbilt ADHD Diagnostic Parent and Teacher Scales (Wolraich et al., 2003) is recommended by the American Academy of Child and Adolescent Psychiatry (American Academy of Child and Adolescent Psychiatry, 2007) and the American Academy of Pediatrics (American Academy of Pediatrics, 2000a; 2000b; Leslie et al., 2004).

It is sufficient for detecting comorbidity as well as core ADHD symptoms and impairment (Cincinnati Children’s Hospital Medical Center, 2004; Pliszka, 2003; Frazier et al., 2004; Waxmonsky, 2003).

Adults with ADHD have higher rates of comorbid anxiety disorders, mood disorders, substance use disorders and cigarette smoking than those without ADHD. Additionally, approximately 15- 20 percent of adults with anxiety, bipolar, depressive and substance use disorders also have ADHD (Pliszka, 2003; Wilens, 2004). Studies from community samples continue to demonstrate significant association between the number of self-reported childhood ADHD symptoms and risk for overweight and obesity in adulthood (Fuemmeler et al., 2010).

**Determine that a medical evaluation has occurred during the diagnostic process to rule out medical causes of the symptoms and any contraindications for stimulant medication treatment (Pliszka, 2006).** Potential medical causes of inattention include seizures, sequelae of head trauma, acute or chronic medical illnesses, such as lead poisoning, other encephalopathies, poor nutrition, insufficient sleep, and hearing and vision problems. The following tests are not supported by the evidence for a routine use in the evaluation of ADHD, but may prove helpful in selected cases:

- Lead or thyroid testing
- Brain imaging
- Genetic or chromosomal testing
- Electroencephalogram (EEG)
- Computerized performance tests (CPT).

The latter two lack sufficient specificity and sensitivity for clinical use. In general, complete psychological or neuropsychological testing is not necessary in the absence of indications of low cognitive function or performance significantly below IQ that should be explored further (Cincinnati Children’s Hospital Medical Center, 2004).

Psychological testing can assist in the differential diagnosis, identify possible co-morbidity, help evaluate the extent of ADHD deficits, or to guide treatment modifications. Such testing is appropriate only after initial face-to-face diagnostic evaluation demonstrates one of these needs (Cincinnati Children’s Hospital Medical Center, 2004; Frazier et al., 2004).

When a child or adolescent is evaluated using psychological testing for educational purposes, e.g., to establish presence of learning disability, the school is usually the most appropriate agent to conduct the testing. Educational testing and accommodations for learning disabilities are federally mandated by the Individuals with Disabilities Education Act (IDEA) (Frazier et al., 2004; Waxmonsky, 2003).

## Treatment

A recent study focusing on improving the quality of community-based ADHD treatment included reviews of a random sample of 1,594 patient charts from 50 diverse pediatric practices, recruited from August 2010 through December 2012 (Epstein et al., 2014). The

review of the extracted information for ADHD care found that “despite the publication of ADHD consensus guidelines more than a decade ago, adoption of evidence-based ADHD care in community-based pediatric settings remains poor” (Epstein et al., p. 1140). Deviations from recommended practices included those occurring at the pediatrician or practice level as well as those attributable primarily to patients. At the physician/practice level, results showed that pediatricians used DSM criteria for ADHD assessment in only two-thirds of patients, and used parent- and teacher-rating scales during assessment in only half of the patients. The study found other deviations from recommended practices, e.g., psychosocial treatment was recommended or used in only 13 percent of patients, while medications were prescribed in 93.4 percent of cases; only about half of children receiving medication had contact with pediatrician during first month of treatment; and in only 10 percent of cases, parent- and teacher-rating scales were used to monitor treatment. Researchers concluded that, based on these results, there is much room for improvement in current pediatrician-delivered ADHD care. They further suggested the use of electronic health records to “prompt/remind the physician to complete ADHD care behaviors or to use Web portals to aid in collecting rating scales” (Epstein et al., p. 1142).

A recent study analyzing data from the 2009-2010 National Survey of Children with Special Health Care Needs, a nationally representative, population-based telephone survey conducted by the Centers for Disease Control and Prevention, described parent-reported prevalence of treatments for current ADHD among children (n=9459) aged 4-17 years with special health care needs (Visser et al., 2015). The most common treatment for ADHD was medication treatment, with almost 50 percent of children with current ADHD taking medication alone. Approximately 87 percent of children with ADHD were receiving either medication treatment or behavioral therapy. Less than one-third of children with ADHD were receiving both medication treatment and behavioral therapy. The most likely to receive combination treatment were those with severe ADHD and comorbidities. A little more than half of the children with ADHD had not received behavioral therapy in the past year. Authors noted that these data, collected in the years just before the release of the AAP’s 2011 diagnostic and treatment guidelines for ADHD, provide an important benchmark for clinical practice. They suggested the need for future research to “help improve our understanding of the barriers to the provision of behavioral therapy for childhood ADHD, particularly among the preschool population” (Visser et al., p. 7).

The American Academy of Pediatrics guideline for the diagnosis, evaluation and treatment of ADHD presents varying recommendations for the treatment of children and youth with ADHD depending on age of the patient. For children aged 4 to 5, behavior therapy is the first line of treatment followed by methylphenidate. For school-aged children 6 to 11, treatment with FDA approved medications is first line of treatment, followed by behavior therapy or a combination of medication and behavior therapy. For adolescents aged 12 to 18, first line of treatment is FDA approved medication for ADHD, with the assent of the adolescent and followed by behavior therapy or a combination of medication and behavior therapy (AAP, 2011).

In a recent updated systematic review of 53 controlled studies including adolescent-specific treatments for ADHD, authors suggested that evidence “does not support current American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry

professional guidelines, which state that stimulant medication is the preferred treatment for adolescents with ADHD” (Sibley et al., 2014, p. 218). The study found evidence demonstrating a similar range of effect sizes for medication and behavior therapy in the treatment of adolescents with ADHD, while noting that the majority of adolescents reported poor satisfaction with medication, decreasing potential for adherence. Authors suggested that oppositional teens obtain more benefit from behavior therapy than medication. Suggesting that a combined medication/behavior therapy may present the greatest therapeutic benefit, they indicated a need for studies of systematically delivered combined treatment for adolescents with ADHD.

FDA approved drugs for the treatment of ADHD includes: stimulants (methylphenidate, dexamethylphenidate, mixed amphetamine salts, dextroamphetamine, lisdexamfetamine), nonstimulants (atomoxetine) and the extended release formulations of alpha-2 agonists (clonidine and guanfacine). For children under 6 years of age, the only approved drugs to treat ADHD are Adderall® and dextroamphetamine IR tablets.

Treatment should address neurological dysfunction, and any concomitant behavioral manifestations, learning disabilities, comorbid disorders and psychosocial issues. The American Academy of Pediatric’s most current clinical practice guideline for ADHD recommends that for children aged 4-5, evidence-based parent-and/or teacher-administered behavior therapy should be prescribed by the primary care clinician as the first line of treatment. Methylphenidate should be prescribed if behavior interventions do not provide significant improvement and there is moderate-to severe continuing disturbance in functioning. For children aged 6-11, the guideline recommends that the preferred treatment is a combination of FDA-approved medications and evidence-based parent-and/or teacher-administered behavior therapy. Guideline reports that evidence is strong for stimulant medications and less strong for atomoxetine, extended-release guanfacine and extended clonidine (in that order). The guideline recommends that for adolescents (aged 12-18), FDA-approved medication for ADHD (with the adolescent’s approval) and behavior therapy are the preferred treatment (American Academy of Pediatrics, 2011).

In the decade ended in 2009, the largest increase in any category of outpatient prescriptions was for ADHD medications to children (Levine et al., 2013). Medications are supported by the preponderance of clinical literature as first-line treatments for core ADHD dysfunction and resulting symptoms, but are best administered in the context of a comprehensive treatment plan that considers evidence-based psychosocial interventions (American Academy of Child and Adolescent Psychiatry, 2007). Treatment progress can be assessed by clinical observations and interviews, as well as rating scales completed by parents and teachers. The hallmark of treatment planning in children is a firm alliance with the parents, patient and teachers to make sure that consistent, coordinated efforts are applied across settings (Pliszka, 2003; Wilens and Dodson, 2004; Waxmonsky, 2003).

## Medication Treatment

Several FDA approved medications are available for ADHD preventing the need for off-label use of other medications. These include stimulants, i.e., methylphenidate or

amphetamine compounds, selective norepinephrine-reuptake inhibitors, i.e., atomoxetine, and  $\alpha$ 2-adrenergic agents, i.e., extended-release guanfacine and extended-release clonidine. Choice of medication should be affected by factors including the age of the patient, efficacy of an agent for a particular patient, the preferred length of coverage time, the ability to swallow pills or capsules and cost of the medicine. Norepinephrine-reuptake inhibitors and  $\alpha$ 2-adrenergic agents are not approved for preschool-aged children. For most children, stimulant medications are highly effective in reducing the symptoms of ADHD (American Academy of Pediatrics, 2011).

Medication strategies should improve targeted ADHD symptoms with minimal adverse effects; address comorbidity, if any; be appropriate relative to the patient's abuse potential; provide smooth day-long coverage; target dopaminergic and/or noradrenergic systems; be administered in a form that maximizes compliance (e.g., extended release or transdermal patch) and preserve patient safety (Wilens and Dodson, 2004; Pliszka, 2006). Significant treatment preferences of patients and parents of children with ADHD should be matched with the appropriate medication to optimize patient adherence to ADHD treatment (Hodgkins et al, 2012). Combining medications may be required, but unnecessary polypharmacy should be avoided. On February 11, 2011, FDA approved the use of extended-release guanfacine and in 2010 approved extended-release clonidine as adjunctive therapy with stimulant medications for the treatment of ADHD (Osterweil, 2010; Waknine, 2011). Long-term treatment with medications is necessary for many patients with ADHD. One meta-analysis of 13 studies found that improvements in symptoms from atomoxetine treatment persisted over 24 months with no dosage escalation and no evidence of tolerance or safety concerns (Wilens, 2006; Kratochvil et al., 2006a). Periodic medication-free trials may be useful to determine the need for continuing medication. However, the guideline group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) argued that clinical evidence is not conclusive on the risk-benefits of drug holidays since there are inherent risks attached to the intermittent cessation of treatment - i.e., higher incidence of burn accidents and emergency room visits in children not receiving their normal medications (Graham et al., 2011).

Most children and adolescents with ADHD who do not have significant co-morbidity will respond satisfactorily to pharmacological agents (i.e., amphetamine and methylphenidate preparations and atomoxetine) after an adequate length of time at appropriate doses (American Academy of Child and Adolescent Psychiatry, 2007). If a patient does not respond, the physician should carefully review the patient's diagnosis of ADHD and consider any undetected comorbid conditions or developmental disorders and determine whether these may be primary problems in impairing the patient's attention and/or impulse control. A referral to a child and adolescent psychiatrist may be considered at this point (American Academy of Child and Adolescent Psychiatry, 2007).

In general, when treating a patient with ADHD and suspected or confirmed comorbidities, it is appropriate to address the ADHD first if the co-morbidity is less severe, e.g., mild to moderate anxiety, mild to moderate depression; or to address the comorbidity first if it is severe and puts the patient at risk, e.g., severe depression, acute mania. Acute mania, if present, must be stabilized prior to initiation of a stimulant for ADHD symptoms (Pliszka, 2003; Waxmonsky, 2003).

## Stimulants

A recent systematic literature review examined the efficacy of stimulants and nonstimulants as well as stimulant misuse with adolescents and adults, including college students with ADHD (Weyandt et al, 2014). Authors reported results reflecting that both stimulant and prostimulant medications are safe and effective in reducing ADHD symptoms in adolescents and adults with ADHD as well as improving psychosocial qualities. Other results showed a higher rate of prescription stimulant misuse among individuals with ADHD compared with those without ADHD. Short-acting agents were more misused than long-acting stimulants. For college students with ADHD at risk of stimulant misuse, authors suggested that the prostimulant lisdexamfetamine dimesylate may be the ADHD medication of choice as it cannot be ground or dissolved into a short-acting stimulant. Authors emphasized the need for further studies concerning the misuse of prescription stimulants (Weyandt et al., 2014).

### Methylphenidates

Stimulant medication is often considered the first-line treatment for ADHD and includes immediate-release (IR) and extended-release (ER) formulations of methylphenidate (MPH). IR MPH is administered two to five times a day, imposing practical difficulties in treating children attending school in contrast to ER MPH, which is administered only once a day (Schawo et al., 2015). Authors noted that although existing clinical studies showed “no significant difference between the efficacy of short-acting and long-acting MPH under the assumption of full therapy compliance,” patients treated with IR MPH had more breaks in medication use, more medication switches and a shorter period on intended therapy. They noted that superior compliance of ER MPH may possibly lead to better effectiveness than IR MPH (Schawo et al., 2015).

Although the efficacy of immediate-release methylphenidate in the treatment of children has been extensively studied, fewer studies have evaluated its efficacy in the treatment of adults (aged 17 years and older) with ADHD in addition to a high rate of other psychiatric problems and functional difficulties (Epstein et al., 2014). The meta-analysis of 10 randomized controlled trials including adults with ADHD (n=466) found that immediate-release methylphenidate was effective versus placebo for improvements of symptoms including hyperactivity, impulsivity and inattentiveness. It was not determined whether the treatment was helpful for anxiety or depression, based on mixed results. Authors noted the high quality of the body of evidence showing that immediate-release methylphenidate improves ADHD symptoms in adults and suggested that the improvement was without serious side effects. Loss of appetite was the main adverse effect noted, but authors noted that a meta-analysis of adverse effects was not conducted. They suggested that this adverse effect with immediate-release methylphenidate might be advantageous among adults with both ADHD and obesity. Based on the evidence, they also suggested monitoring appetite and weight, especially during early phases of treatment (Epstein et al., 2013).

A recent FDA drug safety communication warned that chemical leukoderma, permanent loss of skin color due to repeated exposure to specific chemical compounds, may occur with



use of methylphenidate transdermal system (Daytrana patch) for ADHD (FDA, 2015). The FDA cautioned patients (or their caregivers) with the skin color changes to discontinue using the patch, and report the changes to health care professionals. The condition, considered non-reversible, may cause emotional distress.

Due to concerns about potential risks to pregnant women, there is a growing body of research evaluating the impact of methylphenidate on pregnant women. One study examined over four million pregnancies in the United States and five Nordic countries (Huybrechts et al, 2018.) All of the women had been dispensed methylphenidate or amphetamines during the first trimester of the pregnancy. The results suggested that there is a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate but not to amphetamines. The researchers concluded “this information becomes important when weighing the risks and benefits of alternative treatment strategies for attention-deficit/hyperactivity disorder in women of reproductive age and during early pregnancy”. This risk/benefit analysis is particularly important in light of the significant increase in the use of ADHD medications by women between the ages of 15 and 44. The proportion of reproductive-aged women treated with an ADHD medication increased by 344% between 2003 and 2015 (Andersen KN, 2018.). On April 17, 2015, the FDA approved methylphenidate extended-release (Aptensio XR™), available in capsule form (multilayer bead formulation) at varying dosing options (from 10 mg to 60 mg) for the treatment of ADHD (FDA, 2015). Administration in children with difficulty swallowing pills becomes easier when contents of an open capsule are sprinkled onto food. The starting dose is 10 mg once daily for patients aged six and older. Contraindications are similar to those of other central nervous system stimulants (Magellan Health, 2015).

A randomized placebo-controlled double-blind study evaluated the efficacy (primary objective of study), safety and tolerability of a multilayer extended-release bead methylphenidate capsule (MPH-MLR) in children and adolescents aged 16 to 18 years with ADHD (Wigal et al., 2015). Researchers emphasized the unique release properties of MPH-MLR where 37 percent of the labeled dose is the immediate-release (IR) component. In this study, patients (n=230) were randomized to MPH-MLR at 10, 15, 20 or 40 mg or placebo once daily. The four stages of the study included: four week screening/baseline, one week double-blind treatment, 11 week open-label dose optimization period and 30 day follow-up. In the double-blind phase, patients received 10, 15, 20 or 40 mg of MPH-MLR or placebo. Continuing to the open-label dose optimization phase, patients received a once daily 10 mg dose, except where previous treatment experience indicated the necessity of beginning with a higher dose. During this 11 week phase, investigators titrated the dose up or down based on the ADHD Rating Scale, 4<sup>th</sup> Edition (ADHD-RS-IV) and the Clinical Global Impression (CGI)-Improvement Scale (CGI-I) scores to reach the optimal dose. The change from baseline to end of the double-blind period in the ADHD-RS-IV was the primary efficacy endpoint measure. Results showed decreases in the ADHD-RS-IV scores in the different groups as follows: placebo at -5.0; MPH-MLR at 10 mg, 15 mg, 20 mg and 40 mg; -9.1, -10.2, -12.0 and -12.6, respectively. Symptom improvement evidenced by these scores was greater in those receiving MPH-MLR, and the improvements were bigger with increased dosages. In the final open-label dose, the most common final open-label dose was 30 mg (Wigal et al., 2015).

Another recent study reviewed clinical trials for the use of methylphenidate in children, aged 6-18 and adults aged 18 or more, with a focus on OROS methylphenidate (Concerta®) (Katzman and Sternat, 2014). OROS methylphenidate (OROS MPH) has once-daily dosing utilizing an osmotic pump system. Based on the review of various clinical trials, authors concluded, “The greatest benefit of OROS MPH lies in its ability to offer symptomatic control not only during the traditional school (or in adults during the work day) but also in the evening” (Katzman and Sternat, p. 1006). When compared with IR MPH, OROS MPH was associated with better symptom control, especially in the evening. Studies showed OROS MPH treatment at doses ranging from 18 to 54 mg/day, compared with placebo, resulted in significant reductions in core ADHD symptoms as measured by teacher and parent IOWA Conners Scale. Treatment with OROS MPH in adolescents at doses ranging from 18 to 72 mg/day was associated with significant improvements in ADHD-RS scores while it also improved driving performance, reducing inattentive driving errors. In adults, studies found that OROS MPH at doses ranging from 36 to 108 mg/day, compared with placebo, was associated with significantly reduced symptoms of inattention and hyperactivity/impulsivity, as measured by tools, e.g., CGI-I. Authors concluded that their review of studies demonstrated benefits to children and adolescents with ADHD as well as adults with ADHD (Katzman and Sternat, 2014).

### Dexmethylphenidate and Mixed Amphetamine Salts

On January 28, 2016 the FDA approved an amphetamine extended-release orally disintegrating tablet, Adzenys XR-ODT for treating ADHD in children aged 6 and older (FDA, 2016). When it becomes available, the orally disintegrating tablet will be offered in six dosages: 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg and 18.8 mg, allowing the dose to be individualized. This tablet will disintegrate in the mouth, rather than being swallowed or sprinkled on food.

A small, eight week, double-blind, placebo-controlled, randomized, two period, crossover study examined the separate effects of three doses of extended-release (ER) dexmethylphenidate (d-MPH), ER mixed amphetamine salts (MAS), and placebo on objective measure of sleep in children (n=37), aged 10-17, with ADHD (Santisteban et al., 2014). Patients were randomized to treatment with d-MPH or MAS initially, with increasing dosages every week for four weeks (10, 20 and 25/30 mg). The randomized placebo period occurred at any week of treatment, except the week before the highest dose. After four weeks, patients were treated with the other medication for another four weeks. Results found that decreased sleep duration was associated with both medications, and it was shorter among patients receiving the highest dose of either medication compared with placebo. In sleep duration or schedule, there were no differences found between MAS and d-MPH leading the authors to conclude that at the group level, “there is no significant sleep benefit in using one medication over the other based upon objective measures” (Santisteban et al., p. 832). Noting that higher doses were associated with improved efficacy in terms of ADHD symptoms, they were also associated with negative effects on sleep. Authors advised clinicians to monitor sleep in patients receiving stimulant treatment, and to consider reducing the dose in patients to avoid the risk of shortened sleep duration. They also advised augmentation with behavior therapy which may result in lower stimulant dose (Santisteban et al., 2014).

Lisdexamfetamine dimesylate (LDX)

A recent study evaluated the long-term maintenance of the efficacy of the first long-acting stimulant prodrug lisdexamfetamine dimesylate (LDX) in children and adolescents with ADHD using a placebo-controlled, double-blind, randomized-withdrawal study design (Coghill et al., 2014). Patients, aged six to 17, with ADHD (n=157) who had completed a 26 week open label trial of LDX were randomized to their optimized dose (30, 50 or 70 mg per day) or switched to placebo for a six week randomized withdrawal period. The primary outcome measure was the proportion of patients with a 50 percent or greater increase in ADHD Rating Scale IV (ADHD-RS-IV) total score and a two point or greater increase in Clinical Global Impressions-Severity of Illness (CGI-S) score since the beginning of the six week randomized withdrawal period. This evaluation found that significantly fewer patients receiving LDX met treatment failure criteria at the end of the randomized-withdrawal study compared with those receiving placebo. The patients in the placebo condition experienced rapid return of symptoms on LDX withdrawal (at or before the week two visit after randomization). Based on increase in the ADHD-RS-IV total score, treatment failure at the end of the randomized-withdrawal period for the LDX group was 28.9 percent, compared with 79.2 percent for the placebo group. Based on a two point increase from baseline in CGI-S score at end of the randomized-withdrawal period, treatment failure was 17.1 percent and 69.8 percent of patients receiving LDX and placebo, respectively. Researchers summarized, “This placebo-controlled, double-blind, randomized-withdrawal study demonstrates the maintenance of efficacy of LDX after long-term treatment in children and adolescents with ADHD” (Coghill et al., p 655).

In another six week double-blind randomized-withdrawal study of long-term LDX treatment in children and adolescents (n=153) with ADHD (moderate severity as indicated by ADHD-RS-IV), patients were randomized to continue LDX (fixed, optimized doses) or switched to placebo (Banaschewski et al., 2014). The primary outcome measure was the impact of continued long-term (at least 26 weeks) LDX treatment of children and adolescents with ADHD on improved health-related quality of life (HRQoL) and reduced functional impairment using the Child Health and Illness Profile-Child Edition: Parent Report Form (CHIP-CE: PRF) and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). Results showed, “Continued treatment with once-daily, optimized doses of LDX maintained the improvement in parentally perceived HRQoL and functional impairment acquired during at least 26 weeks of open-label treatment to a greater extent than placebo in this international, phase III, randomized-withdrawal study.” The domains where effectiveness was most pronounced were reducing risky behavior, improving relationships with family and peers, and improving academic achievement (Banaschewski et al., 2014).

A nine week, double-blind, randomized study assessed treatment response rates of LDX (dose-optimized at 30, 50 or 70 mg/day) and atomoxetine (ATX) in children and adolescents (n=200) with ADHD and an inadequate response to previous or current treatment with methylphenidates (Dittmann et al., 2014). Patients were randomized to dose-optimized LDX or ATX (patients at or less than 70 kg receiving 0.5-1.2 mg/kg/day and patients at or greater than 70 kg receiving 40, 80, or 100 mg/day). Response to treatment, indicated by

improvements in ADHD-RS-IV, was significantly higher in patients treated with LDX than in the ATX group. The proportion of patients with 50 percent, 30 percent or 25 percent reduction from baseline in ADHD-RS-IV scores were 73 percent, 88.1 percent and 90.5 percent, respectively, in the LDX group compared with 50.4 percent, 73.7 percent and 76.7 percent in the ATX group, respectively. Additionally, after treatment during the nine week period, a larger percentage of patients receiving LDX had lower levels of ADHD severity than in the ATX group.

Researchers noted, “The superior efficacy of LDX was maintained irrespective of the criteria used to determine a clinically relevant response to treatment” (Dittman et al, 2014), p.1067).

The most commonly used psychotropic medications in children are stimulants, e.g., methylphenidate and amphetamines, widely prescribed for the treatment of ADHD. The utilization of these medications for ADHD treatment in children aged 18 and younger was examined in an analysis of a nationally representative annual survey of U.S. households, Medical Expenditure Panel Survey, to determine trends by age, sex, race/ethnicity, family income and geographic region (Zuvekas, 2012). The study found that overall, pediatric use of stimulants has been steadily increasing from 1996 to 2008, especially by adolescents. Greater use occurred in non-Hispanic white children than in African American or Hispanic children. Across all income groups, there were similar patterns of increase. Across regions of the United States, there were significant differences in use with the West showing a lower rate of utilization than the Northeast. A threefold higher utilization rate was evident in boys, consistent with the higher prevalence of ADHD in boys. When the researchers compared the estimated rates of utilization of stimulant medication with the estimated prevalence of ADHD in the community, it appeared that the majority of children diagnosed with ADHD were not receiving treatment with stimulants. The annual increase in the number treated with stimulants rose from 2.9 percent of all U.S. children and adolescents in 1996 to 3.5 percent in 2008 (Zuvekas, 2012).

The amphetamines and methylphenidate remain first line treatments and are available in short-acting and slow-release formulations, as well as a transdermal patch for methylphenidate (American Academy of Child and Adolescent Psychiatry, 2006; Nutt 2007; Pliszka et al., 2006; Brown, 2005; King 2006; Gibson, 2006; Banaschewski, 2006). More recent research and development has focused on other modes of improved drug delivery in order to extend the duration of action, i.e., capsules, sprinkleable capsules, tablets, chewable tables, oral solution (Correll et al., 2011). A refined form of methylphenidate, dexamethylphenidate hydrochloride, is long acting and reported to be twice as potent (Weiss, 2004; Wigal et al., 2004; Arnold et al., 2004) with similar or less severe side effects than methylphenidate hydrochloride. Triple-bead mixed amphetamine salts (MAS) is an enhanced extended-release amphetamine formulation designed for duration of action up to 16 hours. It has been shown to be effective in the treatment of adults with ADHD resulting in significant improvements in executive function and quality of life (Spencer et al., 2008).

Lisdexamfetamine dimesylate, a long-acting amphetamine, is the first pro-drug stimulant used in the treatment of ADHD. It is a therapeutically inactive molecule that is converted to the essential amino acid, l-lysine and active d-amphetamine after oral ingestion. This

drug was developed for its long duration of effect and reduced potential for risk of abuse. At doses of 30, 50 and 70 mg. per day, it demonstrated significant improvements in ADHD symptoms in adults (Adler, Goodman et al., 2008). Lisdexamfetamine dimesylate was approved in 2008 to treat adults with ADHD and in November, 2010 it was approved to treat adolescents (aged 13-17). In January 2012, it was approved as a maintenance treatment in adults and in May 2013, it received approval as maintenance treatment in children and adolescents, aged 6-17, making it the only stimulant approved for maintenance in individuals with ADHD older than 6 years (Brauser, 2013). In a review of literature examining the efficacy of lisdexamfetamine, one study showed statistically significant improvement in executive functioning in adults with ADHD treated with lisdexamfetamine using the Brown Attention-Deficit Scale, while another study showed improvement in Permanent Product Measure of Performance scores in adults treated with lisdexamfetamine when compared with placebo (Madaan et al., 2013).

Higher stimulant doses are generally associated with better reduction in symptoms (Pliszka, 2006). At least 70 percent of school-aged children with ADHD respond favorably to stimulant medications. Preschool age children also benefit from these medications, although their response may be less robust than that seen in older children and a short-acting form may be needed to achieve appropriate dosing. Teens with comorbid conduct problems are usually insufficiently treated by stimulants alone, and need psychosocial treatments in combination (Chronis et al., 2006). Many adults, including those never treated in childhood, can benefit from the use of stimulant medications (Adler, Zimmerman et al., 2009).

An algorithm of the Texas Children's Medication Algorithm Project (TCMAP) recommends, for ADHD without comorbidity, an initial trial of either methylphenidate or amphetamine, and if response is not sufficient, switching to the stimulant not tried initially; if the second stimulant does not produce an acceptable outcome, an alternative medication, such as atomoxetine, can be tried (Pliszka et al., 2006; Newcorn et al., 2008; AAP Subcommittee on ADHD, 2011; Correll et al., 2011). In terms of treatment of adults with ADHD, meta-analytic findings support use of both stimulant and non-stimulant medications but with stimulants showing the greater treatment efficacy and no differences between short- and long-acting compounds (Faraone et al., 2010).

The stimulants primarily affect the core symptoms of hyperactivity, impulsivity, inattentiveness and associated aggressiveness. The onset is rapid, the dose easily adjusted and adverse effects are generally mild and easily managed. The optimal dose cannot be predetermined by age, weight, height, gender or severity of the ADHD and weight-adjusted milligram-per-kilogram-per-day dosing is not supported by evidence and consensus (Pliszka et al., 2006). Rather, a careful milligram-based dose titration is thought to yield the most appropriate dose for a given patient (Pliszka et al., 2006). When medication is used, the prescribing physician, parents and teacher should clearly define the target symptoms. Rating scales may be useful in helping gauge the effectiveness of the medication on the target symptoms (Cincinnati Children's Hospital Medical Center, 2004; Pliszka, 2003; Steinhoff, 2004; Reeves and Schweitzer, 2004; Biederman and Spencer, 2004).

Selection of short vs. longer-acting preparations of methylphenidate and amphetamines should be based on the individual's symptom profile, history of response to an agent in the patient's family, ease of administration, likelihood of non-compliance if a school-day dose is required (Pliszka, 2006), abuse potential and adverse effects. Also, varying the wear time of the methylphenidate transdermal system or reducing an oral dose of one-daily methylphenidate in children can regulate the duration of the medication effect. This may be done in order to accommodate to the schedules of the patient. This reduction in exposure to methylphenidate results in shorter coverage of ADHD symptoms but fewer late afternoon or early evening drug side effects and insomnia (Wilens et al., 2008; Faraone et al., 2009). Stimulants should be used cautiously or withheld when there is suspicion of untreated mania, psychosis, substance abuse, tic disorder or concern about growth retardation (Pliszka et al., 2006; Steinhoff, 2004; Reeves and Schweitzer, 2004; Biederman and Spencer, 2004).

Stimulants are not effective in relieving core ADHD symptoms for 10 percent to 30 percent of patients, and negative side effects, including headache, insomnia, abdominal pain, blood pressure changes, appetite reduction, tics, weight loss, sleep disturbances, and reductions in growth rate for children are common (Lindsay 2006; Kratochvil et al., 2005; Sadeh et al., 2006; Cortese et al., 2006; American Academy of Pediatrics). One study showed that when children were on higher doses of stimulants, there was a more persistent effect on decreasing growth velocity. By the third year of treatment, effects diminished. Hallucinations and other psychotic symptoms are an uncommon additional significant adverse effect of stimulants (American Academy of Pediatrics, 2011). There is also some preliminary evidence that long-acting amphetamines or methylphenidate medications may produce rebound effects that may hinder late evening or early morning driving safety in adolescent male drivers (Cox et al., 2008). However, typical parental concerns, e.g., beliefs that there is haphazard diagnosing and over-prescribing, that school alternative programs are being neglected and that the causes of symptoms are only social and cultural, are not supported by research (Safer, 2000).

In a very small number of children (0.16 per million prescriptions and 0.53 per million prescriptions for methylphenidate and amphetamine, respectively) stimulant use has been associated with sudden death, usually from adverse cardiovascular events (Gephart, 2006). In May 2008, a joint advisory statement of the American Academy of Pediatrics (AAP) and the American Hospital Association (AHA), with endorsement by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, the National Initiative for Children's Healthcare Quality and the Society for Developmental and Behavioral Pediatrics, was issued to address controversies in cardiac assessment prior to stimulant treatment for ADHD:

- An AHA Scientific Statement issued in April 2008 included a review of data that show children with heart conditions have a higher incidence of ADHD.
- Because certain heart conditions in children may be difficult (even, in some cases, impossible) to detect, the AAP and AHA feel that it is prudent to carefully assess children for heart conditions, if they need to receive treatment with drugs for ADHD.
- Obtaining a patient and family health history\* and doing a physical exam focused on

cardiovascular disease risk factors (Class I recommendations in the statement) are recommended by the AAP and AHA for assessing the patient before treating with drugs for ADHD.

- Acquiring an ECG is a Class IIa recommendation. This means it is reasonable for a physician to consider obtaining an ECG as part of the evaluation of children being considered for stimulant drug therapy, but this should be at the physician’s judgment, and it is not mandatory to obtain one.
- Treatment of a patient with ADHD should not be withheld because an ECG is not done. The child’s physician is the best person to make the assessment about whether there is a need for an ECG.
- Medications that treat ADHD have not been shown to cause heart conditions nor have they been demonstrated to cause sudden cardiac death. However, some of these medications can increase or decrease heart rate and blood pressure. While these side effects are not usually considered dangerous, they should be monitored in children with heart conditions as the physician feels necessary. (AHA Newsroom, 2008)

\* Specifically, the AAP ADHD guideline notes “It is important to expand the history to include the specific cardiac symptoms, Wolf-Parkinson-White syndrome, sudden death in the family, hypertrophic cardiomyopathy, and long QT syndrome” (AAP Subcommittee, 2011, p.10).

The most recent update of the American Academy of Pediatrics’ guideline indicates that more evidence is required to identify whether stimulant drug therapy is an increased risk for adverse cardiovascular events (American Academy of Pediatrics, 2011). The guidelines states, “it is important to obtain a careful history of cardiac symptoms; a cardiac family history, particularly of arrhythmias, sudden death and death at a young age from cardiac conditions; and vital signs, cardiac physical examination and further evaluation on the basis of clinical judgment.” In one study<sup>5</sup>, researchers assessed whether treatment with stimulant medication in participants of the Multimodal Treatment Study of Children with ADHD (MTS) over a 10-year period was associated with increased heart rate or increased blood pressure (Vitiello et al., 2012). Children (n=579) who were 7-9 years of age were randomly assigned to 14 months of behavioral therapy, pharmacotherapy, e.g. methylphenidate, combination of behavioral and pharmacotherapy, or usual community treatment followed by several years of naturalistic treatment. At the end of 14 months of treatment, children who received stimulant medication alone or medication plus behavioral therapy had higher heart rates than those treated with behavioral therapy alone. Over the 10 years of the study, stimulant treatment did not increase the risk for pre-hypertension or hypertension although stimulants had a persistent adrenergic effect on heart rate during the treatment period (Vitiello et al., 2012).

FDA updated its communication on the cardiovascular safety review of medications used for treating ADHD in adults, stating that FDA recommendations have not changed (FDA, 2011). The drug safety announcement referred to studies evaluating heart attacks, sudden deaths and strokes in adults that found no increased risk of serious adverse cardiovascular events in adults receiving treatment with ADHD medications. It advised healthcare professionals to take special note that stimulants and atomoxetine should not be used to

treat patients with serious heart problems or those for whom an increased blood pressure or heart rate would be problematic. It further advised that changes in heart rate or blood pressure should be monitored periodically in patients treated with stimulants or atomoxetine. The FDA also updated its communication on the cardiovascular safety review of medications used for treating

ADHD in children and young adults, reporting the results of a study that did not find an association between use of ADHD medications and cardiovascular events (FDA 2011). The safety announcement advised healthcare professionals that stimulants and atomoxetine should not be used in children and young adults with serious heart problems or in patients for whom increased blood pressure or heart rate would be problematic and all patients treated with ADHD medications should be monitored for changes in blood pressure and/or heart rate.

Another previously reported safety concern for treatment with methylphenidate and mixed amphetamine salts was whether these drugs induce chromosomal damage in peripheral blood lymphocytes of children with ADHD posing an increased risk for cancer. A more recent study found that treatment with these drugs for three months did not induce cryogenetic damage (i.e., structural aberration, micronuclei and sister chromatid exchanges) in children, but that longer-term effects of these drugs on chromosomal changes still need to be investigated (Witt et al., 2008).

On December 17, 2013, FDA issued a safety announcement warning of rare risk of prolonged and sometimes painful erections known as priapism in males taking methylphenidate ADHD medications (FDA, 2013). The updated drug labels and patient Medication Guides advise patients to seek immediate medical treatment if they develop erections lasting longer than four hours to prevent permanent damage to the penis. The safety communication advised health care professionals that atomoxetine has also been associated with priapism in young children, adolescents and adults, and caution is warranted when considering changing patients from methylphenidate to atomoxetine (FDA, 2013).

Concern about the potential for abuse of stimulant medications is legitimate, and there have been reports of children/adolescents giving or selling their medication to others. Abuse potential can be decreased by using long-acting stimulant preparations or drugs from other classes with established efficacy in treating ADHD with no abuse potential (i.e., atomoxetine or extended-release preparations of guanfacine or clonidine discussed in the following sections). Stimulants appear to have a protective effect against the development of a substance use disorder in children and adolescents, with a significant reduction of risk (Wilens et al., 2003). The AAP ADHD guideline specifies the following stimulant medications having less abuse potential: (1) lisdexamfetamine; (2) dermal methylphenidate; or (3) OROS (sustained release) methylphenidate due either to their chemical composition or preparation, making extraction of the stimulant more difficult (AAP Subcommittee on ADHD, 2011).

Although ADHD research in the adult population has increased, less research has been conducted with college students. In a recent review systematically reviewing studies



concerning misuse of prescription stimulants among college students with and without ADHD, authors included studies (n=22) that related to stimulant misuse within this sample. The review found that a substantial percentage of college students are using stimulants for non-medical purposes (from 5.3 percent to 34 percent). The National Survey on Drug Use and Health (NSDUH) found approximately one third of the national sample reported misusing ADHD medication during their lifetimes (80 percent of these between 12 and 25 years of age). Authors conclude that, based on their study, prescription stimulant misuse is continuing to rise among college students to enhance their cognitive performance, and the students usually obtain the stimulants from their peers. Authors suggest additional research is needed to understand the effects of prescription stimulants, e.g., physiological, morphological and cognitive, to address the misuse of prescription stimulants among the college student population to help develop appropriate intervention and prevention programs (Weyandt et al., 2013).

## Non-Stimulants

### Atomoxetine (ATX)

A recent comprehensive review of studies examined the efficacy of atomoxetine treatment in 6-18-year-olds with ADHD (Savill et al., 2015). Authors reviewed 125 papers, which provided the basis of their conclusions. ATX, with a lack of abuse potential, was effective in improving core ADHD symptoms, functional outcomes, and quality of life in 10-12 weeks after beginning of treatment in various pediatric patient populations, e.g., both sexes, patients with various co-morbidities, patients both with and without prior ADHD medications. Compared with placebo, ATX was more effective in preventing relapse of ADHD after 10-52 weeks of ATX treatment. Authors noted the difficulty in comparing the efficacy of ATX in comparison with other medications due to deficiencies of studies. They emphasized the relatively gradual responses to ATX, and noted how responses in the first weeks of ATX treatment may predict responses over time. Authors cited a study showing that a “sizable proportion of patients who only have partial responses to atomoxetine at four weeks go on to have robust responses beyond this timepoint” (Savill et al., p. 146). They advised informing the patient/family of the likelihood of a gradual response to the medication and that it often builds over time (Savill et al., 2015). In another study where data were pooled from seven ATX double-blind, placebo-controlled, randomized clinical trials conducted in pediatric patients aged 6-18 years, “baseline ADHD severity and symptom improvement during the first two weeks of treatment were highly predictive of robust response to treatment with atomoxetine” (Wietecha et al., 2015).

Another review of studies examining the use of atomoxetine in the management of ADHD cited several double-blind, randomized placebo controlled trial showing that ATX was significantly better in improving ADHD symptoms than placebo (Childress, 2016). Author also reported studies finding that ATX improves core ADHD symptoms as well as quality of life and emotional lability, with symptom improvement continuing to increase up to 52 weeks after the initiation of treatment. Studies found that, although ATX may be less effective than stimulant medication with a longer time to maximal response than stimulants, it is considered as a first-line treatment option and may be a preferred

treatment for patients with a history of substance abuse (Childress, 2016).

Atomoxetine was introduced in 2002 as an effective first line medication for both childhood and adult ADHD. It is not a controlled substance, making prescribing more convenient for patients and physicians, as well as eliminating abuse potential. Another advantage is that it is relatively long-acting, with once daily dosing in most patients. Clinical research continues to demonstrate the efficacy and tolerability of atomoxetine in treating children and adults with ADHD (Adler, Spencer et al., 2008). Meta-analytic findings from six controlled trials show that atomoxetine is an effective and generally well-tolerated treatment of ADHD in both younger (aged 6-7) and older children (aged 8-12) (Kratochvil et al., 2008).

Atomoxetine shares some adverse effects with stimulants, but appears to have much less potential for aggravation of tics and insomnia. It is purported to be a good choice when anxiety, depression, tics, substance abuse and Oppositional Defiant Disorder (ODD) symptoms complicate ADHD in children or adults (Cheung et al., 2007; Bangs, Hazel et al., 2008; Wilens et al., 2008). There have been reports of sexual adverse effects. Clinicians have reported using atomoxetine in combination with stimulants when a patient has not responded adequately to a trial of either alone (Pliszka et al., 2006). For example, if atomoxetine did not remit symptoms during the day and stimulants did not remit symptoms in the evening, the two types of medications might productively be combined. The TCMAP panel included a stimulant-atomoxetine combination as a third line treatment in the absence of controlled data but warned that it should be used only after full monotherapy trials of two stimulants sequentially, and atomoxetine alone, have not provided full remission (Pliszka et al., 2006).

Although a recent drug safety announcement from FDA found no association between the use of ADHD medications and cardiovascular events, it did recommend that stimulant products and atomoxetine should generally not be used in patients with serious heart problems or in those for whom an increase in heart rate or blood pressure would be problematic. It further advised that patients treated with ADHD medications should be monitored for changes in heart rate and/or blood pressure periodically (FDA, 2011).

Atomoxetine has been associated with six reported cases of hepatotoxicity but none of these cases resulted in a liver transplant. A Postmarket Review of the FDA cautions both patients and caregivers to be alert to the signs and symptoms of liver injury throughout atomoxetine treatment and directs prescribers to discontinue the drug if a patient presents with jaundice or laboratory evidence of hepatotoxicity (FDA, 2009; Pliszka et al., 2006; Steinhoff, 2004; Reeves and Schweitzer, 2004; Biederman and Spencer, 2004). In addition, atomoxetine has a black box warning from the FDA regarding possible increased suicidality (Lindsay, 2006). More recent meta-analytic findings also showed that although uncommon, suicidal ideation was significantly more frequent in pediatric ADHD patients treated with atomoxetine compared to those treated with placebo. However, no patients in atomoxetine ADHD clinical trials committed suicide (Bangs, Tauscher-Wisniewski et al., 2008). The American Academy of Pediatrics' clinical practice guideline for ADHD refers only to atomoxetine in relation to increased suicidal thoughts with no mention of suicidal ideation in relation to stimulants (American Academy of Pediatrics, 2011). A later meta-analysis of atomoxetine and methylphenidate comparator trials analyzed suicide related events

identified in five randomized controlled double-blind pediatric ADHD clinical studies involving atomoxetine and methylphenidate. Results showed no difference in risk between atomoxetine and methylphenidate. Authors caution that clinicians should not underestimate the risk of suicide associated with ADHD, even as they have no reason to choose treatments solely based on any presumption of differential risk of suicide-related events (Bushe and Savill, 2013).

Atomoxetine has not been found as effective at treating primary ADHD symptoms as the stimulants and has more recently come to be considered a second-line treatment (American Academy of Child and Adolescent Psychiatry, 2006; Pliszka et al., 2006; King, 2006; Gibson, 2006; Soreff, 2009; Newcorn et al., 2008; Newcorn et al., 2009). New clinical trial data have shown that while both treatment with atomoxetine or osmotically-released methylphenidate (OROS-MPH) produced robust improvements in ADHD symptoms, response to OROS-MPH was superior to that for atomoxetine. Also, approximately one-third of the patients in this large (n=516), placebo-controlled, double-blind, cross-over study responded better to one or the other suggesting that there may be preferential responders. Researchers argued that this supports the practice of changing to a different class of medication if there is a poor response to or tolerance of the first agent (Newcorn et al., 2008). Similarly, The Integrated Data Exploratory Analysis Study showed that the clinical response to atomoxetine was bimodal in that most subjects were either responders (47 percent) or non-responders (40 percent) or showing a minimal response (13 percent). No demographic or clinical factors were associated with these divergent profiles of response, but patients who ultimately achieve a good response show at least a partial response by the fourth week of treatment (Newcorn, 2009).

### Alpha-2 Agonists - Clonidine and Guanfacine

A randomized, controlled study, assessing the efficacy and safety of extended release guanfacine hydrochloride (GXR) in the treatment of children and adolescents (aged 6-with ADHD of at least moderate severity, compared GXR with placebo, with an TX arm included to provide reference data against placebo (Hervas et al., 2014). Patients (n=338), aged 6-17, with ADHD were randomized at baseline, to dose-optimized GXR, ATX or placebo for four or seven weeks (based on whether they were under or over the age of 13). Following this period was a six week double-blind maintenance period, a two week double-blind tapering period, and a follow-up after the last dose. GXR, in tablet form, was initiated at 1 mg/day in children and increased by 1 mg increments to a maximum of 4 mg/day, and in adolescents, it was increased to maximum dose of 4, 5, 6, or 7 mg/day based on weight. At baseline, mean ADHD-RS-IV scores were similar across the treatment groups. The changes in ADHD-RS-IV score from baseline to end of the study treatment duration were -23.9, -18.8, and -15 for GXR, ATX, and placebo, respectively. Percentages of patients showing “very much improved” or “much improved” in CGI-I scores were 67.9 percent, 56.3 percent and 44.1 percent for GXR, ATX and placebo, respectively. The proportions (percentage) of patients experiencing treatment-emergent adverse (TEA) events, mostly of mild or moderate intensity, were 77.2 percent, 67.9 percent and 65.8 percent in the GXR, ATX and placebo groups. Most common TEAs included the following: GXR: somnolence, headache and fatigue; ATX: decreases in appetite, nausea and fatigue; and placebo: headache, fatigue and abdominal pain. Improvement in efficacy was more rapid with GXR than ATX. Researchers concluded that this study demonstrated “a positive risk-benefit profile in the

treatment of children and adolescents with ADHD with GXR doses of up to 7 mg (0.05-0.12mg/kg/day) and suggests that GXR will be a useful addition to the existing classes of medication effective in ADHD (Hervas et al., p. 1870).

A recent study meta-analyzed the efficacy and safety of alpha-2 agonists in the treatment of ADHD in youth aged 6-17 (Hirota et al., 2014). The 12 randomized trials consisted of randomized controlled trials comparing clonidine/guanfacine monotherapy with placebo as well as trials including patients with suboptimal response to stimulants who received clonidine/guanfacine or placebo added in. The studies compared the alpha-2 agonists with placebo in youth (n=2276). The primary outcome measure was reduction in overall ADHD symptoms, based on rating scales, e.g., ADHD-RS-IV, and secondary outcome measures included symptoms, e.g., hyperactivity/impulsivity, inattentiveness, oppositional defiant disorder and adverse events. Based on the results of this study, researchers stated, “alpha-2 agonists—both in monotherapy and as add-on treatment to stimulants were significantly more effective than placebo for total and specific attention-deficit/hyperactivity disorder (ADHD) symptoms as well as for oppositional defiant disorder symptoms. Pooled together, alpha-2 agonist monotherapy and add-on treatment were associated with similar risks for discontinuation because of intolerability compared with placebo, reflecting their safety and acceptability by patients. However, given the significantly higher incidence of hypotension, bradycardia, fatigue, somnolence and sedation in participants randomized to alpha-2 agonists compared with placebo, clinicians should monitor these side effects routinely” (Hirota et al., p. 171). In summarizing their results, researchers noted that alpha-2 agonists are an alternative treatment for children and adolescents with ADHD who cannot tolerate psychostimulants or do not have a sufficient response to treatment with stimulants.

Alpha-adrenergic agonists, e.g., extended release clonidine and extended release guanfacine, affect ADHD symptoms by affecting the noradrenergic system and generally have greater benefit for hyperactivity/impulsivity symptoms than for inattention. In 2009, the FDA approved guanfacine extended release tablets for the once-daily treatment of ADHD in children and adolescents aged six to 17 years. The approval was based on data from two similarly designed phase three double-blind parallel group trials of 669 children and adolescents. Significant clinical improvement was demonstrated for patients who were randomized to receive guanfacine once daily and uptitrated by 1 mg/week to a maintenance dose of 1 to 4 mg/day (Waknine, 2009; Biederman et al., 2008). Sedative side effects may limit their usefulness in daytime, but may make them useful at bedtime for assistance with sleep. Abrupt discontinuation of these agents can be associated with rebound hypertension. In 2010, the FDA also approved clonidine extended release tablets for the treatment of ADHD based on two double-blind parallel group trials of 433 children and adolescents (FDA.gov, 2011). There are reports of serious cardiac adverse effects with clonidine, especially when used in combination with stimulants. However, a more recent examination of the safety and tolerability of clonidine when used alone or with methylphenidate in children with ADHD reported that it appeared safe and well-tolerated in children with ADHD who do not have a baseline or family history of cardiovascular problems. Nonetheless, these researchers reported that 17 percent of their sample who were treated with clonidine experienced asymptomatic bradycardia (HR < 60 bpm) and underscored the need to regularly monitor changes in blood pressure and heart rate when prescribing clonidine. The AAP ADHD guideline also indicated that both guanfacine and clonidine have

evidence to support their usage as adjunctive therapy with stimulants (Waxmonsky, 2003; Steinhoff, 2004; Biederman and Spencer, 2004; Spencer et al., 2002; Pliszka et al., 2006; Daviss et al., 2008, AAP Subcommittee on ADHD, 2011). Additionally, a randomized control trial (n=198) demonstrated the safety and clinical efficacy of using extended-release clonidine in combination with stimulant medication for children and adolescents with ADHD experiencing a partial response to stimulants (Kollins et al., 2011).

### Antidepressants

A recent meta-analysis (including 28 double-blind, placebo-controlled studies comprising children and adolescents (n=4699) between aged 4 and 15 with ADHD) with a focus on bupropion compared the efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion (BUP) and methylphenidate in the treatment of ADHD in children and adolescents (Stuhec et al., 2015). Results showed levels of efficacy in reducing ADHD symptoms for these medications compared to placebo to be small for bupropion, modest for atomoxetine and methylphenidate and high for lisdexamfetamine. Discontinuation was statistically lower for methylphenidate compared to placebo treatment, and not significantly different for atomoxetine, lisdexamfetamine and bupropion. Researchers concluded, “LDX is the most efficacious treatment option. Despite the fact that the results of this meta-analysis show a low effect size in the case of BUP, several new double-blind randomized studies, using the latest diagnostic ADHD criteria and appropriate methodology are needed to evaluate the comparative effectiveness of BUP in the treatment of ADHD in the treatment of children and adolescents with ADHD” (Stuhec et al., p. 155).

A recent Cochrane review of six randomized controlled trials including children and adolescents aged 6 to 18 with ADHD (n=216) assessed the efficacy of tricyclic antidepressants (TCAs) in the reduction of ADHD symptoms (Otasowie et al., 2014). The trial compared the following treatments: desipramine with placebo, nortriptyline with placebo, desipramine with clonidine and placebo, desipramine and clomipramine with methylphenidate and placebo. In comparison with placebo, desipramine outperformed placebo in the improvement of core ADHD symptom severity as assessed by parents, teachers and clinicians, and nortriptyline was efficacious in improving core symptoms by clinicians. On “all cause treatment discontinuation,” desipramine and placebo were similar. In comparison with clonidine, desipramine appeared more efficacious in reducing ADHD symptoms as rated by parents. Serious adverse effects were not identified in this review, although mild increases in diastolic blood pressure and pulse rates were noted, and patients receiving desipramine had significantly higher rates of appetite suppression compared to placebo and nortriptyline as associated with weight gain. Authors concluded, “Most evidence on TCAs relates to desipramine. Findings suggest that, in the short term, desipramine improves the core symptoms of ADHD, but its effect on the cardiovascular system remains an important clinical concern. Thus, evidence supporting the clinical use of desipramine for the treatment of children with ADHD is low” (Otasowie et al., 2014).

Third-line medications used to treat ADHD include bupropion and tricyclic antidepressants (TCAs). Bupropion is a weakly dopaminergic and adrenergic agent and is available in slow-release forms. Meta-analytic findings of bupropion clinical trials indicated a beneficial effect compared with placebo for improvement of ADHD symptoms in adult patients (Verbeeck et

al., 2009). Additionally, in at least one study, it has shown efficacy comparable to methylphenidate. It may be a useful agent in patients with comorbid unipolar and bipolar depression, anxiety disorders and/or substance abuse including the diversion of psychostimulant prescriptions (Verbeek, et al., 2009). Bupropion carries a higher risk of seizures than most other antidepressant medications, especially at higher doses, and should not be used in patients with a history of seizures. It should be used with caution in children with a history of eating disorder (Kratochvil et al., 2006b; Pliszka et al., 2006).

Before the advent of atomoxetine, tricyclic antidepressants (e.g., imipramine and nortriptyline) were the primary alternative to stimulant treatment of ADHD having shown efficacy in symptom reduction in ADHD. Desipramine use in children and adolescents should be avoided due to reports of sudden death (Amitai and Frischer, 2006; Pliszka et al., 2006). TCAs can be lethal in overdose. Children being treated with TCAs should be monitored with electrocardiogram at baseline and on stable dosing. For these reasons, there has been a decline in the use of TCAs for the treatment of ADHD (Schatzberg et al., 2010).

Many patients with both ADHD and depression or anxiety disorders need treatment with both stimulants and antidepressants or benzodiazepines. A recent study evaluated whether response to osmotic release oral system methylphenidate (OROS-MPH) in adults with ADHD was moderated by the concomitant use of antidepressants (non-MAOI antidepressants), benzodiazepines, or a history of depression. Patients (n=227) were randomized to OROS-MPH or placebo. The study found that concomitant use of antidepressants does not affect the safety or efficacy of OROS-MPH although a history of mood or anxiety disorders was a moderator of ADHD symptoms (Biederman et al., 2012).

Antidepressants have been the subject of concerns regarding possible increased suicidal behavior in children, adolescents and young adults (Hammad et al., 2006), especially at initiation and around changes in dosing. The FDA identified specific antidepressants in a 2004 analysis and eventually directed manufacturers of all antidepressants to include a boxed warning and expanded warning statements alerting clinicians to an increased risk of suicidal thinking and behavior in children and adolescents being treated with these agents (Food and Drug Administration, 2004a, 2004b, 2004c, 2005a). Clinical evidence, however, has not been conclusive in guiding clinicians toward or away from use of these agents in children and young adults (Bridge et al., 2007; Hughes et al., 2007).

In the absence of definitive evidence from clinical literature, FDA advisories or other credible sources determining that the risk of increased suicidality for patients treated with antidepressants makes their use inadvisable, Magellan's position remains that clinical evidence strongly supports the use and effectiveness of antidepressant medications in all age groups, and that careful, frequent and proactive monitoring for changes in status that could indicate suicidality is crucial to preserving the safety of these patients (U.S. Food and Drug Administration, 2004a, 2004b, 2004c, 2005a; Hughes et al., 2007; American Academy of Child and Adolescent Psychiatry 2007; Cheung et al., 2007; Williams et al., 2009; Marshall et al., 2010). When a current or past history of suicidality is present, such monitoring should occur at every session. In addition, Magellan recommends that the clinician contact patients who miss appointments, especially when there are reasonable

grounds for concern about safety. Further, prescribing physicians and other clinicians involved in the care of patients taking antidepressants, as well as patients and their families, should stay alert and watchful for warning signs of possible increased suicidality and take prompt action if any adverse effects are observed (Hughes et al., 2007).

## Other Medications

### Risperidone

In a recent study, children (n=168), aged 6-12 with ADHD and either oppositional defiant or conduct disorder, were randomized to nine weeks of basic treatment (parent training (PT), stimulant and placebo) or augmented treatment (PT, stimulant and risperidone) (Aman et al., 2014). At the end of the first three weeks during which children received treatment with stimulant (titrated for optimal effect) and parents received PT, children who had continuing aggression and other disruptive behaviors received either placebo or risperidone as an add on treatment. Scores on the Nisonger Child Behavior Rating Form (NCBRF) Disruptive-Total Scale, the NCBRF Social Competence subscale, and the Antisocial Behavior Scale improved more with the augmented treatment than with basic treatment, while there was no significant advantage of augmented treatment evidenced by clinician ratings of the CGI-I. Researchers noted that “together, the findings indicate that risperidone, when added to optimized stimulant treatment and parent training, provides a moderate advantage in parental ratings of disruptive behavior for children with serious aggression and additional disruptive behaviors” (Aman et al., p.55). They also cautioned that results were based on a relatively short trial period of six weeks with possible emergence of problematic adverse events, e.g., weight gain, metabolic disturbance (Aman et al., 2014).

Modafinil does not have FDA approval for the treatment of ADHD, but there are reports of its usefulness in children, adolescents and adults (Pliszka, 2003; Waxmonsky, 2003; Steinhoff, 2004; Biederman and Spencer, 2004; Spencer et al., 2002; Lindsay, 2006; Ballon, 2006; Kahbazi et al., 2009). However, more research is needed to establish the safety and efficacy of this agent for ADHD treatment (Pliszka et al., 2006). A later study compared the efficacy and safety of modafinil, compared with methylphenidate, on continuous attention task in children with ADHD. Children (n=28) completed a baseline test followed by a single dose of either methylphenidate or modafinil after which the test was repeated. A dose of the medication not previously administered followed, after which a third test was performed. Results showed no difference between improvements observed with either medication and adverse events were mild for both medications. They included abdominal pain, diarrhea and hyposomnia. Researchers suggested that modafinil is as effective as methylphenidate and stressed the need for a larger scale long-term study to confirm the results (Goez, et al, 2012).

Off-label use of the second generation antipsychotic (SGA) drug, risperidone, has shown promise in reported study results of children with aggressive behavior associated with conduct disorder, disruptive behavior disorders, ADHD, and/or mental retardation/subaverage IQ (Correll et al., 2011; Agency for Healthcare Research and Quality 2011). These findings need to be corroborated with supporting evidence from future

clinical studies comparing antipsychotics with behavioral intervention, combination treatments and placebo (Correll et al., 2011).

A systematic review and pooled analysis of data on antipsychotic use in children with ADHD, conducted recently due to concerns raised about antipsychotic prescribing to youth with ADHD, focused on the frequency of ADHD in youth receiving antipsychotic treatment; frequency of antipsychotic use in youth with ADHD; and frequency of antipsychotic treated ADHD youth among those in the general population. Data was obtained from studies (n=21) including youth through aged 19 (n=20 million). Based on this review, authors reported persistent growth in antipsychotic use among children and adolescents over the decade beginning in the early 1990s, with ADHD associated with a substantial proportion of these prescriptions. With the exception of disruptive behavior disorder, ADHD was the most common diagnosis associated with antipsychotic use in the antipsychotic treated youth cohort. Authors expressed concern that antipsychotics, not approved by the FDA for the treatment of ADHD, should be the last resort for treatment of impulsivity, oppositionality and aggression. Further, they suggested that clinicians should follow guidelines, combining approved ADHD medications with psychosocial interventions before the addition of antipsychotics (Birnbaum et al., 2013). Clinical trials using SGAs with children and adolescents found that these medications increase the risk of developing hyperglycemia, hyperlipidemia, hyperprolactinemia and diabetes. Additionally, they can cause weight gain and drowsiness (Harrison et al., 2012). Ongoing medical monitoring of safety issues/concerns associated with the side effects of SGAs is recommended by Magellan in its guidelines, *Appropriate Use of Psychotropic Drugs in Children and Adolescents: A Clinical Monograph*. Magellan cautions that a type of clinical, cultural and “social iatrogenesis” resulting in an increased use of dangerous and unnecessary treatment can result in both injury and increased cost of health care (Magellan, 2013).

The central nervous system stimulant, pemoline, has fallen from use due to a risk of liver failure that is 10-25 times greater than the risk in the general population (Marotta and Roberts, 1998). In 2005, the FDA concluded that the risks associated with this drug outweigh any potential benefits and the manufacturer stopped sales and marketing of the drug in the United States (FDA, 2005).

## Non-Pharmacological Treatments

### Psychosocial Interventions

Although “a front-line intervention is stimulant medications, which are effective in approximately 80 percent of youth with ADHD,” psychosocial interventions play a prominent role in the management of youth with ADHD (Antshel, 2014, p. 80). Psychosocial interventions include behavioral interventions that have beneficial effects on aspects of child and parent functioning. Behavioral parent training (BPT) is nonspecific to ADHD, but is effective for children with disruptive behaviors. Past studies have shown that it is “a well-established evidence-based treatment for managing ADHD in children” (Antshel, p. 81).



Authors cited a previous meta-analysis of trials that found a lack of blinded evidence of ADHD core symptom decrease in children and adolescents with ADHD who received behavioral interventions (Daley et al., 2014). In this recent meta-analysis of randomized controlled trials across multiple outcome domains, authors found blinded evidence that behavioral interventions have positive effects on a range of other outcomes, i.e., improving parenting and decreasing childhood conduct problems. Outcomes measured included pre- to post-treatment changes in parenting quality, parenting self-concept, conduct problems, social skills and academic performance. Results found that “behavioral interventions improved parenting, decreasing negative and increasing positive parenting, and decreased children’s comorbid conduct problems” (Daley et al., p. 844). There were, however, no beneficial effects seen on parent mental health. Authors concluded, “the beneficial effects on parenting and parents’ sense of empowerment and independently corroborated effects on conduct problems in children with ADHD” (Daley et al, p. 845).

### Dialectical Behavior Therapy Group Skills Training

A pilot randomized controlled trial evaluated dialectical behavior therapy (DBT) group skills training in the treatment of college students (n=33) between aged 18 and 24 (Fleming et al., 2015). Researchers cited studies finding that college students with ADHD have lower grade point averages and graduation rates; depressive symptoms, tobacco and alcohol use; overall psychological distress; and lower self-reported quality of life than their undergraduate peers. In this study, participants were randomly assigned to receive DBT group skills training or skills handouts during an eight week intervention phase. Participants were assessed at pre-treatment, post-treatment, and three month follow up, and the follow-up interviewer was blind to participant condition. Outcome measures included: Barkley Adult ADHD Rating Scale-IV (BAARS-IV) to measure ADHD symptoms; Brown ADD Rating Scales (BADDS) to measure executive functioning; ADHD Quality of Life Questionnaire (AAQoL) to measure life productivity, psychological health and life outlook (BDI-2); official transcripts including grade point average; Five Facet Mindfulness Questionnaire (FFMQ); and Conners’ Continuous Performance Test-2<sup>nd</sup> Edition (CPT-2). The DBT group skills training intervention included group sessions focused on the acquisition and strengthening of skills and individual coaching phone calls. The skills handouts group received a booklet including topics, e.g., psychoeducation about ADHD and executive functioning, organization, planning, time management, structuring environment and stress management. The DBT group skills training group had greater improvement in ADHD symptoms and executive functioning (greater treatment response rates and clinical recovery rates) and greater improvement in quality of life than the skills handouts group immediately after treatment as well as three months after treatment. Researchers suggested that the DBT group skills training intervention may also improve mindfulness and sustained attention. They suggested the need for “future studies to evaluate the relative efficacy and acceptability of psychopharmacological and psychosocial interventions, both independently and in conjunction, for the treatment of DHD among college students” (Fleming et al., p. 269). Researchers emphasized the need for further evaluation in a larger randomized trial.

### Cognitive Behavioral Therapy-Based Psychoeducational Groups for Adults With ADHD

A recent study evaluated a new manualized CBT-based psychoeducation (PEGASUS) for adults with ADHD and their significant others in an open clinical feasibility trial (Hirvikoski et al., 2015). PEGASUS was designed to constitute the first nonpharmacological treatment after diagnosis of ADHD in adults, with a main goal of providing knowledge about ADHD both to participants and their significant others and to empower them in sharing in their own treatment. This pilot study, evaluating both the feasibility and the efficacy of PEGASUS, included eight 2 ½ hour sessions in groups, including adults with ADHD (n=51) as well as their significant others (n=57). Focus of the sessions was on psychoeducation, with group lecturers “highlighting possibilities for change as well as pointing out common strengths in individuals with ADHD, thus applying techniques of acceptance” (Hirvikoski, p. 92). Results showed that this program was a feasible intervention as 43 out of the 51 participants with ADHD completed the intervention and agreed that they would attend a similar course in the future; of the 57 significant others, 42 completed the intervention and were satisfied with the program. Efficacy was measured by improvement from baseline to post-intervention in results from various measures, including Questions about Family Members (QAFM), BECK Depression Inventory (BDI), Rosenberg’s Self-Esteem (RSE) Scale, and Adult Attention Deficit/Hyperactivity Disorder Quality-of-Life (AAQoL). Results for all participants indicated positive improvement in knowledge about ADHD, psychological well-being and subjective stress, and a trend toward improvement of self-esteem was observed in adults with ADHD. Researchers cautioned that these results are preliminary due to the open study design and additional information will be provided from a randomized controlled study of PEGASUS that is currently in progress (Hirvikoski et al., 2015).

### Collaborative Care for Children with ADHD Symptom

A recent randomized effectiveness trial compared two care management systems, basic collaborative care and enhanced collaborative care, to treat urban children (n=156) aged 6 to 12 who were being evaluated for ADHD (Silverstein, et al., 2015). In both groups, care managers (lay providers without formal mental health backgrounds) served as liaison between primary care clinicians and a specialist, e.g., psychiatrist. In the enhanced collaborative care group only, enhanced care managers received training in motivational interviewing and were certified by a master trainer in Triple P’s Primary Care Module. This additional training helped the enhanced care managers address ambivalence toward engagement with behavioral health care, parental mental health and oppositional child behavior” (Silverstein, p. e860). Outcome measures, six and 12 months after randomization, were ADHD symptoms, measured by the Parent Swanson, Nolan and Pelson (SNAP-IV Questionnaire) and by oppositional symptoms and social skills. Results showed no differences in outcomes between the groups across the entire sample, but children who were ADHD diagnosable and in the enhanced care group showed greater decreases from baseline in inattention, hyperactivity/impulsivity, oppositionality and social skills than those in the basic care arm. Researchers noted that this study is novel in that it enrolled children based on presenting symptoms rather than ultimate diagnosis and instead of testing a care system against usual care, it studied “whether augmenting collaborative care with lay-delivered strategies to address common reasons for symptom persistence improves outcomes” (Silverstein et al., p. e863). They also noted how their emphasis on urban, low-income children makes their results relevant to primary care providers. Researchers stated, “Last, among children with ADHD-consistent presentations in the enhanced care group,

there was a clinically meaningful increase in ADHD medication prescriptions. Given that the motivational interviewing script deliberately focused on medication use, it is possible that motivational interviewing started a cascade of events leading to increased receptivity to ADHD medication, and that this, in turn, could have led to improved outcomes” (Silverstein et al., p. e864).

Psychosocial treatments, such as behavior therapy, include evidence-based parent training and classroom behavior interventions that reinforce adaptive and positive behaviors and decrease or eliminate inappropriate behaviors, altering the motivation of the child or adolescent to control attention, activity, and impulsivity (American Academy of Pediatrics, 2011). The American Academy of Pediatrics guideline differentiates behavior therapy from psychological interventions that are designed to change the child or adolescent’s emotional status or thought patterns, noting that gains achieved in the psychological treatment setting do not usually transfer to home or school and have not demonstrated efficacy for the ADHD core symptoms (American Academy of Pediatrics, 2011). Researchers cautioned that better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training and dietary interventions. This suggests that effects based on unblinded assessments may be significantly inflated. Further, they suggest that this bias may be present especially in behavioral interventions as parents are often involved in delivery of the treatment (Sonuga-Barke et al., 2013).

### Behavior Therapy

The goal of behavior therapy is to modify the physical and social environment to change or alter behavior (American Academy of Pediatrics, 2011). It includes training parents to improve their abilities to modify their child’s behavior, and to improve the child’s ability for self-regulation of behavior. School programs and supports include interventions in which teachers are primary intervenors and where the intervention takes place in the school setting. In a recent paper, researchers studied the data from their earlier clinical trial that compared a comprehensive behavioral parenting training (BPT) approach, Strategies to Enhance Positive Parenting (STEPP) program, to a traditional group-based BPT program (Chacko et al., 2012). Both programs included a collaborative, large group format to discuss and learn about effective parenting strategies. The STEPP program, however, also included enhancements, e.g., intake procedure addressing possible practical barriers to treatment participation; maternal expectation regarding their parenting behavior and child’s behavior; and enhanced maternal expectations for treatment. By analysis, researchers extended the findings of the earlier study, highlighting the variability in rates of participant attendance and homework completion at each session regardless of treatment group. Significantly, they found that treatment group predicted the average variability in session attendance and completion of homework, thus providing stronger evidence in support of the STEPP program to encourage attendance and homework completion when compared to traditional BPT (Chacko et al., 2012).

### Other Psychosocial Therapy

Psychoeducation, which should be delivered to all patients with ADHD and in the case of minors, to the parents or other caregivers as well, should include information about:

- ADHD, its presentation in the patient, the plan of treatment and rationale, available treatments, including medications and their benefits, risks, side effects and psychotherapeutic interventions
- Co-morbid disorders, if any, and how treatment of these is integrated with ADHD treatment
- Social and peer support available locally for children and adults with ADHD and their families, such as CHADD (Children and Adults with Attention-Deficit/Hyperactivity Disorder) activities and resources
- Rights to educational needs assessments through the school system, if appropriate, under the Individuals with Disabilities in Education Act (IDEA) and Section 504 of the Civil Rights Act
- Increased risk for suicidal behavior and early warning signs of possible increases in such behavior, if antidepressants or atomoxetine are prescribed.

Although carefully titrated pharmacotherapy with stimulants has been found superior to psychosocial treatments and combination treatments in reducing ADHD core symptoms, most patients experience social, familial, occupational and/or educational effects of the disorder that are responsive to psychotherapeutic intervention (MTA Cooperative Group, 1999a, 1999b; Correll et al., 2011). Psychotherapeutic interventions can be administered in combination with medications or, in rare cases, as the sole intervention, such as after the failure of adequate trials of first, second, third and fourth line medications and/or in response to parental refusal to allow medication or inordinate health and safety risks associated with medication treatment (American Academy of Child and Adolescent Psychiatry, 2007; Pliszka et al., 2006). In child/adolescent patients treated with medication who have co-morbid mental health disorders and/or unsupportive, chaotic or conflict-ridden family environments, the use of family interventions (American Academy of Child and Adolescent Psychiatry, 2007; Chronis 2006) is recommended. In addition, the AAP ADHD guideline (2011) recommends the initiation of ADHD treatment in preschool-aged children (ages 4-5 years) with evidence-based parent and/or teacher administered behavior therapy alone as the first line of treatment. The primary care clinician may prescribe methylphenidate if there is moderate-to-severe continuing disturbance in the child's function after the behavior interventions, American Academy of Pediatrics, 2011).

Family interventions that coach parents on contingency management methods have been shown to be useful in decreasing punitive and ineffective parenting styles that may perpetuate behavioral problems in children and adolescents with ADHD. Behavioral models that focused on parent training specifically for fathers also have resulted in symptom improvement in children along with increased satisfaction and engagement in the treatment process by the fathers (Chronis, 2006; Fabiano et al., 2009). Manual-based parent training has been evaluated in two dozen studies noting that it is associated with less severe parental ratings of problem behavior in their children, and fewer rater-observed, negative child-parent interactions, with an average effect size of .87 (Chronis, 2006).

Classroom behavior-management techniques have been found to be effective, particularly the daily report card intervention that addresses child-specific targeted improvements with measurable goals (Chronis 2006; Evans and Youngstrom, 2006). Teachers are taught to use

points and token reward systems, time outs, planned ignoring and response costs, as well as to provide a highly structured environment by setting schedules for the child’s use throughout the day. Limiting distraction during class and study, both in school and at home, may be helpful. Academic interventions and special education placement may be necessary.

Particularly in children or adolescents for whom aggressive behavior is a problem or who have a co-morbid conduct disorder, behavioral modification techniques that address social skills should be a component of treatment (Chronis, 2006). The short-term effectiveness of behavioral therapy has been demonstrated, but there is little evidence to show that the gains made during therapy are maintained after treatment is stopped and behavioral modification may be best delivered in combination with medication treatment (Pliszka et al., 2006; MTA Cooperative Group, 1999a, 1999b; 2004a, 2004b).

After-school programs are in early stages of development using manual-based treatment focused on targeted educational, social, and recreational skills, home-work completion, and school and home behavior. In one clinical trial, individual counselors provided support to students in achieving goals and implemented a behavioral-point system to reward both individual and group behaviors. Parents also participated to review program content and to learn skills for managing home behaviors. Preliminary findings for these public middle school students showed modest beneficial effects on behavioral and academic outcomes. Continued research on these types of after-school interventions is necessary (Molina et al., 2008).

Psychotherapeutic treatment of ADHD has been studied far less in adults than in children, and consensus guidelines specific to adults are not available. Cognitive behavioral therapy, life-skills coaching and training in organizational skills appear useful, although evidence to support their long-term benefit in reducing core symptoms of ADHD is lacking. Accepted psychotherapies are used to treat co-morbid disorders in adults, as well as children, with ADHD (Wilens et al., 2004). In a recent review of literature, authors reported the results of recent, randomized controlled trials using CBT for treating ADHD in adults. In one study, adults on medication for ADHD (n=86) were randomly assigned to CBT or relaxation with educational training (Mongia and Hechtman, 2012). The CBT modules included psychoeducation, organization and planning, distractibility, and cognitive restructuring while the relaxation modules included psychoeducation in progressive muscular relaxation and ADHD-specific relaxation. Results of this study showed a greater reduction in post-treatment scores. Based on a rating of the change in ADHD symptoms using ADHD Rating Scale, Clinical Global Impression Scale, and self-report, the CBT group achieved a greater reduction than the relaxation group in post-treatment scores in addition to maintaining these gains over 12 months. Researchers suggested that CBT for continued symptoms for ADHD in adults on medication is more effective compared with relaxation treatment with education support. In another study, adults on medication for ADHD (n=88) were randomized to meta-cognitive (including CBT skills:

organization, planning and time management) or supportive psychotherapy. Results from this study found improvement in the severity of ADHD for meta-cognitive over supportive

psychotherapy group based on the use of self-ratings, observers and blinded evaluators. In another study, adults with ADHD who were receiving CBT and medication (n=23) were compared in terms of outcomes (ADHD-RS and Conners' Adult Rating Scales) to those who received CBT and placebo. In terms of core symptoms and functioning, patients in both groups improved in terms of core symptoms and functioning while maintain treatment gains at 20 weeks. Researchers proposed that CBT may be effective for adults not on medication, suggesting that medication is not essential for increasing receptivity to CBT (Mongia and Hechtman, 2012).

A randomized controlled pilot study assessed the efficacy of psychoeducation as compared with cognitive behavioral group therapy in adults with ADHD. Individuals (n=32) were randomized to either a psychoeducation group or a cognitive behavioral group therapy group. The psychoeducation program provided education and information about ADHD to the group while the CBT program focused on coping skills training. Results of this study found significant improvements on inattention, hyperactivity, impulsivity and self-esteem in both groups. In addition, members of both groups showed a decrease in anxiety symptoms and lower scores in depression. Researchers concluded that psychoeducation was demonstrated to be an effective treatment of the core symptoms of ADHD (Estrada et al., 2013).

#### Combined Group Psychotherapy and Methylphenidate, and Combined Individual Clinical Management (Counseling) and Methylphenidate

A recent clinical trial, the Comparison of Methylphenidate and Psychotherapy in Adult ADHD study (COMPAS), examined the efficacy of nonpharmacological treatments in combination with methylphenidate or placebo. Researchers randomized adults (n=433) aged 18 to 55 with ADHD to one of the following treatment groups: highly structured group psychotherapy (GPT) and methylphenidate, GPT and placebo, less controlled individual clinical management (CM) and methylphenidate, and CM and placebo (Philipsen et al., 2015). Both GPT and CM sessions occurred weekly for the first 12 weeks and monthly for the following nine months, and patients received either methylphenidate or placebo for 12 months. Results showed improvements in ADHD symptoms in all four treatment groups indicated by changes from baseline to end of treatment in the ADHD index of the Conners Adult ADHD Rating Scale. Researchers noted that previous studies have shown superiority of GPT over general CM conditions; however, the results in this study showed that GPT was no more effective than CM in improving ADHD symptoms. This study found that combined treatment with GPT or CM with methylphenidate was superior to combinations with placebo. Researchers concluded, "To our knowledge, COMPAS is the first trial to demonstrate long-term maintenance effects of ADHD treatment under controlled conditions. We demonstrate that psychological interventions result in better outcomes when combined with methylphenidate as compared with placebo. Our data do not suggest that highly structured group intervention outperforms individual CM, which is much easier to implement in practical care than specifically tailored and highly structured GPT (Philipsen et al., 2015).

### Alternative/Complementary Treatments

### EEG-Neurofeedback

A recent review of the current evidence for neurofeedback in the treatment of ADHD noted that recent meta-analytic evidence shows neurofeedback leads to significant decreases of ADHD core symptoms, but only in studies lacking well-blinded outcome measures (Holtmann et al., 2014). Even in the best-blinded assessment, evidence did not demonstrate learning of self-regulation or significant effects. Although some studies have claimed that neurofeedback is efficacious and specific, authors conclude that “there is a strong need for more evidence from well-blinded, methodologically sound and sensitive trials before neurofeedback can be assigned this highest level of evidence as a front-line treatment of ADHD” (Holtmann et al., p. 789). Magellan acknowledges that neurofeedback has provoked interest in behavioral health research due to the increased parental demand for nonpharmaceutical interventions and concerns over safety alerts related to stimulant drugs. However, Magellan has determined that more large-site studies are needed to provide more evidence from well-blinded and methodologically sound trials, and considers neurofeedback as investigational for the treatment of ADHD in children and adolescents (Magellan Health, 2015).

Numerous case and controlled-group studies have been published regarding use of EEG biofeedback (aka neurofeedback) in the treatment of ADHD (Gevensleben, 2010/2009 et al., 2009; Strehl et al., 2006; Monastra 2005a, 2005b; Carmody 2001; Fuchs 2003; Linden 1996; Monastra 2002; Rossiter 1995). EEG biofeedback uses analysis of brain wave patterns, i.e., beta and theta activity, sensorimotor rhythms, and/or slow cortical potentials (negative or positive EEG polarizations) along with a reward system to help patients with ADHD change patterns of wave activity in their brains. Several published case studies have suggested that EEG biofeedback is an effective treatment for the primary symptoms of ADHD, especially attention, hyperactivity and impulsivity, with no adverse effects and persistence of treatment effects over time (Gevensleben, et al., 2010/2009; Strehl et al., 2006; Monastra 2005a, 2005b; Carmody 2001; Fuchs 2003; Linden 1996; Monastra 2002; Rossiter 1995). However, the limitations of both study size and design create significant questions about the efficacy of this treatment modality (Monastra, 2005a, 2005b) and further research is needed if benefits from this and other alternative treatments are to be established.

A recent randomized controlled trial with six-month follow-up compared the efficacy of neurofeedback (40 theta/beta training sessions) and methylphenidate (1 mg/kg/day) in the treatment of children with ADHD (n=23) based on teacher and parent reports. Results of this study showed that neurofeedback reduced the primary symptoms of ADHD and improved functional impairment similar to the results of treatment with methylphenidate. Improvements in academic performance were detected only in the neurofeedback group. Researchers cautioned that this study relies on a small sample and randomized controlled studies with larger number of participants are needed (Meisel et al., 2013). In another randomized and controlled study, children and adolescents with ADHD (n=91) were randomized to one of three treatments: neurofeedback, methylphenidate, or combined neurofeedback and methylphenidate.

Results of this study showed that neurofeedback improved attention and hyperactivity symptoms in children and adolescents as assessed by parental reports and that the combination of neurofeedback and methylphenidate produced the same effects. Researchers suggested that the effects of neurofeedback may result from the extraordinary amount of time spent with the therapist during neurofeedback and cognitive-behavioral training introduced under neurofeedback (Duric et al., 2012).

### Transcranial Magnetic Stimulation

In a randomized, sham-controlled crossover study, researchers tested the safety and efficacy of transcranial magnetic stimulation (TMS) in the treatment of young adults and adolescents aged 14-21 (n=9) with ADHD (Weaver et al., 2012). During the study, individuals were randomized in the first treatment phase to receive active TMS or sham and were crossed over to the other treatment modality in the second phase. Results showed significant improvement in Clinical Global Impression-Improvement Scale (CGI-I) in those randomized to active TMS first as well as to those randomized first to Sham TMS. Although both groups improved during the first phase of treatment, only those assigned to active TMS improved during the second phase, suggesting that placebo-type effects were washed out with completion of the first phase. No serious adverse effects, including seizures and EEG changes, resulted from the treatment (the study excluded individuals with increased risk of seizure). Researchers concluded that this exploratory study shows encouraging results of the potential efficacy of TMS for ADHD (Weaver et al., 2012). Although the sham-controlled crossover study design was well conceived, the number of study subjects was far too small to allow for any conclusions regarding efficacy of TMS for ADHD treatment, and TMS remains an experimental treatment for children and adolescents with ADHD. Please see Magellan’s Technology Assessment, “Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment for Treatment Resistant Major Depression” for further information (Magellan, 2013).

### Dietary Therapy

Many children do not experience reduction in the core symptoms of ADHD with pharmaceutical treatment (both stimulant and nonstimulant medication) while others experience short term side effects, e.g., appetite loss and sleep problems. Some studies have suggested that dietary interventions may be effective in treating ADHD in children (Rytter et al., 2014). These include elimination diets that remove elements, e.g., sugar, artificial sweeteners and food colorants, and food supplementation diets, which increase the intake of certain nutrients, e.g., essential fatty acids and amino acids. A systematic review of diet in the treatment of ADHD found that elimination diets and food supplementation diets seem to be the most promising dietary interventions for ADHD, but they suggested more studies are necessary before recommending them as treatment. Authors investigated 52 studies including diet interventions in children with ADHD to investigate whether the interventions resulted in improvement in core ADHD symptoms. They reviewed four meta-analyses, which found artificial food colorants had small adverse effects on the symptoms of ADHD in limited quality studies. In meta-analysis of a few randomized trials, authors found evidence of small to modest positive effect of fish oil supplementation. They concluded that, “for most dietary interventions there is not enough evidence to recommend their routine use in



clinical practice” (Rytter et al., p. 14).

Additional alternative treatments including the use of St. John’s Wort (Weber et al., 2008), homeopathy (Heirs et al., 2007), dietary sugar reduction and dietary supplementation with herbs and vitamins, have been unsupported by research (American Academy of Child and Adolescent Psychiatry, 2006). Also, there are very limited data supporting the premise that food dyes, preservatives or other additives adversely influence behavior in children (Cruz et al., 2006).

Conversely, there have been other more recent studies of alternative treatments that have shown positive results. Findings from a randomized clinical trial conducted in Italy showed that compared to placebo, the nutritional supplement L-acetylcarnitine (LAC) was effective for ADHD symptoms in Fragile X Syndrome Boys. LAC is the acetyl ester of L-carnitine, a fundamental compound that plays an essential role in the metabolism of fatty acids in mitochondria. These results were promising because it is estimated that over 70 percent of FXS boys meet diagnostic criteria for ADHD. Researchers reported previous observations that have shown while FXS boys respond to stimulants, their mood becomes unstable at higher doses necessitating a need for alternative pharmacological treatment (Torrioli et al., 2008).

Another scientific study reported promising results for iron supplementation (80 mg/day) in iron-deficient (30ng/mL) non-anemic children with ADHD where clinical improvements in symptoms were significant. Here authors suggested that careful dietary history and necessary lab work be done and then re-evaluated prior to instituting treatment. (Konofal et al., 2008) Another clinical trial revealed that supplementation with omega-3/omega-6 fatty acids did not result in symptom improvement for the majority of ADHD subjects. There was, however, a distinct subgroup of patients in this study characterized by inattention and associated neurodevelopmental disorders (i.e., Developmental Coordination Disorder, Reading Disorder and Disorder of Written Expression) who responded with meaningful reduction of ADHD symptoms after six months of treatment (Johnson et al., 2009). Other studies have reported promising findings on the impact of polyunsaturated fatty acids (PUFA) in the treatment of ADHD symptoms and attendant emotional and sleep problems. One systematic review supported daily supplementation of both combination long-chain n-3 and n-6 fatty acids and another large observational study (n=810) reported beneficial effects of combination omega-3 and omega-6 fatty acids along with supplemental zinc and magnesium in treating children with the disorder (Transler et al., 2010; Huss et al., 2010). In a recent meta-analysis of randomized controlled trials of dietary treatments for ADHD, the effects of treatment with omega-3 supplements, omega-6 supplements and combination of both omega-3 and omega-6 supplements were significant, although the beneficial effects of ADHD symptoms was small (Sonuga-Barke et al., 2013).

### Sleep-Focused Treatment

In a randomized trial, researchers evaluated whether a brief sleep intervention for children with both ADHD and sleep problems, i.e., sleep initiating and maintaining sleep, are effective in improving sleep problems as well as symptoms of ADHD. Children (n=244) aged 5 to 12 with ADHD, most of whom were also receiving treatment with

stimulant medications, were randomized to an intervention group or a usual clinical care group. The intervention group received two face-to-face consultations (every two weeks) with a trained clinician who assessed the sleep problem, helped the parents obtain goals for sleep management and provided parent training about sleep cycles and sleep hygiene strategies. The clinician then formulated a behavioral sleep management program based on the individual child's particular sleep problems. The primary outcome, measured at baseline and at six months, included parent and teacher reported ADHD symptoms. Secondary outcomes included sleep problems reported by primary caregiver and as indicated on the children's sleep habits questionnaire. Researchers reported that the behavioral intervention group reported a greater decrease in ADHD symptoms as well as fewer moderate to severe sleep problems at both three and six months when compared with the usual care group. Researchers suggested the need for future trials that are more rigorous and that will test the long-term benefits of a brief behavioural sleep intervention as an adjunctive consideration (Hiscock et al., 2015).

### Trigeminal Nerve Stimulation

In an eight week, open, pilot investigation of trigeminal nerve stimulation (TNS) for the treatment of youth (n=24) aged 7-14 with ADHD, researchers' sought to determine feasibility of conducting TNS research in this population. Other goals included determining potential effects of the treatment on ADHD symptoms (behavioral, cognitive and executive functioning, sleep and side effects/adverse events (McGough et al., 2015). The treatment was administered nightly during sleep after participants and parents received instruction, and a parent-completed TNS compliance diary measured treatment adherence. The Investigator Completed Parent ADHD-RS and Conners Global Index were completed at baseline; week four and week eight were primary outcome measure for the effects of TNS on ADHD behavioral symptoms. Other rating scales assessed the effects of TNS on cognition and executive function, sleep and side effects/adverse events. Nightly treatment compliance was reported for all 24 participants, and the ADHD-RS showed improvements in both inattentiveness and hyperactive/impulsive scales. Other rating scales showed improvement in parent- reported executive functioning and sleep problems. Researchers noted, "One of the most surprising and compelling findings from the current study was the dramatic improvement detected in several CSHQ subscales that suggests positive TNS benefits on sleep-related anxiety as well as total sleep and bedtime related problems" (McGough et al., p. 303). While suggesting a potential role for TNS as a treatment for ADHD, author also emphasized the need for larger controlled trial including a "sham" intervention.

## **Level of Care**

It is rare that a patient with a sole diagnosis of ADHD would require a hospital level of care. Usually, the need for an intensive level of care is based on the presence of symptoms associated with a comorbid condition. Such symptoms would likely be of the hostile or violent type associated with bipolar disorder, conduct disorder, oppositional defiant disorder, psychotic disorder, or adjustment disorder with disturbance of conduct. Alternatively, symptoms requiring a more intensive level of care could be associated with risk of self-harm<sup>4\*</sup> or hospitalization for actual injury from being the victim of

interpersonal violence, since children and adolescents with ADHD are at higher risk for suicidal behavior and interpersonal violence (Lam 2005). Of these, conduct disorder would present most often with a pattern of violent behavior toward people and/or animals that potentially at times could require the safety of a hospital level of care, although for this population there have been effective multi-focused treatment approaches that include both medication and psychosocial treatments (Connor et al., 2006).

Most often, treatment for ADHD and co-morbidities occurs in an outpatient setting. When aggressive behavior is not responding to outpatient care, in-home treatment may be an adjunctive or alternative course. In-home treatment can be an effective way to deliver family interventions, including modeling ways for parents to deal with their child's aggressive and hostile behaviors and providing problem-solving and social skills training.

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\* Magellan has adopted a clinical practice guideline that addresses suicidal behavior: the Magellan Clinical Practice Guideline for Assessing and Managing the Suicidal Patient (Magellan Health, 2018). Clinicians are referred to that document for additional information on managing suicidal behavior in patients with ADHD.

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