Clinical Practice Guideline for Patients with Attention Deficit/Hyperactivity Disorder

Magellan Health
Clinical Practice Guideline Task Force

Thomas G. Carlton, M.D.
Nancy D. Donachie, M.D.
Kathleen K. Frampton, R.N., B.S.N., M.P.H.
Gary Henschen, M.D.
Pamela E. Kumar, R.N., B.S.N.
Kathryn Kvederis, M.D., D.F.A.P.A.
Louis A. Parrot, M.D., Ph.D.
Clifton A. Smith, D.O., M.S.
Fatimah A. Tamil, M.D., M.P.H.
Antoinette Valenti, M.D.
Fred Waxenberg, Ph.D.
Effective August 31, 2007, Magellan Health Services (Magellan) re-adopted the Clinical Practice Guideline for the Treatment of Patients With Attention-Deficit Hyperactivity Disorder, Second Edition, written by Magellan to serve as an evidence-based framework for practitioners’ clinical decision-making with child, adolescent, and adult patients who have a diagnosis of attention-deficit hyperactivity disorder. 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 preparation of the 2014 revision, we conducted another review of the published scientific literature through September 2013, along with available practitioner input. This guideline covers the main areas of psychiatric management of patients with this disorder, covering topics from clinical features and epidemiology to various aspects of treatment approach and planning. Nonetheless, it is not intended to be 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 may incorporate ongoing clinical developments, including the AACAP Practice Parameters for ADHD; the AAP Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents; and other sources (citations).

Obtaining Copies of the Guideline
This Magellan 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 is intended to augment, not replace, sound clinical assessment and decision-making. As a matter of good practice, clinically sound exceptions to the treatment guidelines should be 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 Guidelines**
Magellan welcomes feedback on adopted clinical practice guidelines. All suggestions and recommendations are taken into consideration in our review. Comments may be submitted to:

Clinical Operations Coordinator  
Re: CPG  
Magellan Health  
6950 Columbia Gateway Drive  
Columbia, Maryland 21046  
CPG@MagellanHealth.com

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INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (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/impulsively. 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

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 cost 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
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). A recent unpublished study suggests 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 a 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 of 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; Monastra 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 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 years of age 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

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- 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 16 years of age 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, Wilen et al., 2004; Wilen 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; Wilen et al., 2004).
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

Determine that symptoms of ADHD do not occur only during the course of a psychotic 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 comorbidity, 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**

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 4-5 years of age, 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 6-11 years of age, 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 (12-18 years of age), 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).

**Medications**

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 α₂-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 α₂-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; Waxmonskey, 2003).

**Stimulants**
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 tablets, oral solution (Correll et al., 2011). A refined form of methylphenidate, dexmethylphenidate 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 years, 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...
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, 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).

**Atomoxetine**

Atomoxetine, a non-stimulant, selective norepinephrine reuptake inhibitor, 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 (6-7 years) and older children (8-12 years) (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).

**Extended release guanfacine and extended release clonidine**

Alpha-adrenergic agonists, e.g., extended release clonidine and extended release guanfacine, effect 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 (Waxmons, 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**

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 (Verbeeck, 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 of 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 (U.S. 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
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 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, suggesting that effects based on most proximal assessments (mostly 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 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).

**EEG-Neurofeedback**

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 14-21 years of age (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**
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).

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** 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.

* 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 Services, 2012). Clinicians are referred to that document for additional
information on managing suicidal behavior in patients with ADHD.
Healthcare Effectiveness Data and Information Set (HEDIS) Measures
The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of performance measures developed and maintained by the National Committee for Quality Assurance (NCQA). Two HEDIS measures that include ADHD diagnosis are: Follow-Up for Children Prescribed ADHD Medication (ADD) and Follow-Up after Hospitalization for Mental Illness (FUH).

The HEDIS measure **Follow Up for Children Prescribed ADHD Medication (ADD)**, like almost all HEDIS measures, focuses on processes, rather than on outcome measures. Children aged 6 – 12 years who have been prescribed medications used for ADHD treatment must be seen by a prescriber within 30 days of the ADHD drug prescription fill date and two more times during the following 270 days. The measure **Follow-Up after Hospitalization for Mental Illness (FUH)** also focuses on processes. Children 6 years and older who have been treated in an acute inpatient setting should receive a follow-up visit within 30 days of discharge, preferably within the first seven days after the discharge.
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