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Introduction to Magellan's Adopted Clinical Practice Guidelines
for the Assessment and Treatment of Children
With Autism Spectrum Disorders

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Purpose of This Document

This document is an introduction to the Magellan Healthcare (Magellan) adopted clinical practice guideline (CPG) for the treatment of children with autistic spectrum disorder (ASD). As with all CPGs, the adopted guideline and this introduction are intended to augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to this practice guideline should be noted in the member's treatment record, documenting the clinical reasoning used in making the exception. Magellan periodically requests clinical files from providers in order to monitor compliance with adopted guidelines. Clear documentation of the rationale for exceptions to the guideline's recommendations should be present in the member's treatment record whenever there is evidence of deviation from the guideline.

Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval of specific medications or devices, and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings that are issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

Executive Summary
(A discussion of additions/changes in this updated guideline.)

Epidemiology and Etiology
A recent report from the Centers for Disease Control Prevention (CDC) examined survey-based estimates of the lifetime prevalence of ASD and compared them with estimates from previous years (Zablotsky et al, 2015). The CDC's 2014 National Health Interview Survey (NHIS) reported an estimated parent-reported prevalence of ASD (based on 2014 data) of 2.24 percent, compared with a prevalence of 1.25 percent based on 2011-2013 data. However, authors acknowledged that revised question ordering and a new approach to inquiring about developmental disabilities in this survey may have affected the prevalence estimates. The overall prevalence of children with ASD, other developmental disability, or intellectual disability was not significantly changed from 2011-2014. Authors suggested that the change may not be completely related to changes in the wording of the survey, but that the new survey was "more sensitive in capturing the full population of children with ASD than estimates based on the 2011-2013 data" (Zablotsky et al, P.5). In the 2014 survey, the ASD questions included Asperger's disorder and pervasive developmental disorder (PDD). In a recent review, Yu et al. discussed the steady increase in prevalence of ASD from 2006 through 2010 while noting variability from state to state (Yu et al., 2016). They suggested that the increase may be related to increased awareness and availability of services for ASD, as well as to potential environmental factors.

In a recent study, authors compared ASD prevalence and diagnosis age across racial/ethnic groups in a population-based sample from the 2009-2010 National Survey of Children with Special Health Care Needs (NS-CSHCN). They cited recent studies suggesting an increase in ASD prevalence along with a decrease in ASD diagnosis age in children in the United States (Jo et al, 2015). From the NS-CSHCN sample, authors identified non-Hispanic white, non-Hispanic black, Hispanic-English

language and Hispanic-other language children aged 3-17 (n=2729) with ASD (reported by parents). Findings showed that for children aged 3-4, the mean diagnosis age was comparable across racial/ethnic/language groups, whereas aged 5-17 non-Hispanic white children with mild or moderate ASD had a higher proportion of later diagnoses than the same aged non-Hispanic black or Hispanic-other language children. Authors suggested that this disparity may be due to possible under-identification of mild/moderate ASD of older children in the two minority groups (Jo et al., 2015).

CDC's Study to Explore Early Development (SEED) examined the phenotypic profiles of children aged 30-68 months (Wiggins et al., 2015). The large sample in this study provided an opportunity to investigate a range of ASD phenotypes and to help identify risk factors for the development of ASD. The children in the SEED sample (n = 2600) were classified as ASD or non-ASD as follows: ASD – 707 children, Development Delay (DD) with ASD symptoms – 305 children, DD without ASD symptoms – 690 and population comparison (POP) – 898 children. Children in SEED differed in degrees of ASD impairment and associated deficits (cognitive, adaptive, behavioral and social functioning). Language delay, sensory integration disorder and motor delay were the most common condition reported by parents of children with ASD. More parent-reported ADHD was reported in the DD with ASD symptoms children while more parent-reported Down syndrome was reported in children with DD without ASD symptoms than in other groups. Similar frequencies of parent-reported obsessive compulsive disorder, self-injurious behaviors and language delays occurred in children with ASD as well as in children classified as DD with ASD; frequencies were higher than those reported among the other two groups of children. Deficits across cognitive, behavioral and social functioning were greater in children with ASD, followed in order by children with DD with ASD symptoms, DD without ASD symptoms and POP. Authors suggested that data showing phenotypically similar symptoms of children classified as ASD and those classified as DD with ASD provides preliminary clues to pivotal symptoms, potentially helping to delineate ASD etiologies (Wiggins et al., 2015).

Genetics is also important in the etiology of ASD. In a recent study, researchers "demonstrated differences related to morphological stratification of ASD probands based on clinical examination" (Tammimies et al., 2015, p. 901). Researchers performed chromosomal microarray analysis (CMA) and whole-exome sequencing (WES) in a group of children with ASD (n = 258 probands). They found comparable molecular diagnostic yields of CMA and WES among the heterogeneous sample of children with ASD, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes. Researchers noted that "the broad phenotype spectrum of ASD is also reflected in the underlying genetic etiology" and suggested that "medical evaluation of ASD children may help identify populations more likely to achieve a molecular diagnosis with genetic testing" (Tammimies et al., p. 901). They concluded that more study is required on the use of genome-wide tests to provide molecular diagnosis for children with ASD.

A recent study evaluated the association between ASD prevalence, at the census tract level, and proximity to sources of pollution, i.e., industrial facilities releasing arsenic, lead or mercury (Dickerson et al., 2015). To estimate prevalence of ASD among eight-year old children, researchers used 2000 to 2008 surveillance data from five sites of the Autism and Developmental Disabilities Monitoring (ADDM) network and 2000

census data. Reported on-site air releases of arsenic, lead, and/or mercury were obtained from the U.S. Environmental Protection Agency Toxics Release Inventory (TRI). Results showed greater ASD prevalence with closer proximity to TRI sites in existence during birth years, consistent with results of prior studies. Additionally the results suggested that exposure to arsenic, lead or mercury released from the industrial facilities may have had an impact from a further distance than in past studies. Researchers concluded that the results are suggestive of the association between urban residential proximity to industrial facilities emitting arsenic, lead and mercury and higher ASD prevalence (Dickerson et al., 2015).

Comorbid Disorders
In a recent clinical synthesis, authors reported common psychiatric disorders and medical disorders for individuals with ASD as follows (Yu et al., 2016):

Comorbid Psychiatric disorders:
- *Intellectual disability* (ID) – 20 percent to 53 percent of individuals with ASD
- *Psychiatric disorders*, e.g., attention-deficit hyperactivity disorder (ADHD), anxiety disorders, obsessive-compulsive disorder (OCD), depression, and schizophrenia – approximately 70 percent of individuals with ASD
- *Two or more psychiatric disorders* – Nearly 40 percent of individuals with ASD
- *Anxiety spectrum disorders* – most common psychiatric condition comorbid with ASD (may be byproduct of core symptoms instead of comorbid condition)
- *Obsessive Compulsive Disorder* – 44 percent of individuals with ASD
- *Catatonia* – highest risk in adolescence.
- Amr et al. (2012) found that 63 % of children with ASD were diagnosed with at least one comorbid disorder, with the most prevalent being anxiety disorders at 58.3 % (55% of this was due to OCD). This was followed by AD/HD at 31.6 %, conduct disorders at 23.3 %, and major depressive disorder at 13.3 %.
- Gjevik et al. (2011) found that 72 % of children and adolescents with ASD were diagnosed with at least one comorbid disorder. Anxiety disorders were the most prevalent at 41%, followed by AD/HD at 31%.
- 11 % of a sample of 102 children and adolescents with ASD had suicidal ideation associated with depression (Matheis & Turygin, 2016).
  - Some published studies of children diagnosed with ASD, show an estimated 90% prevalence of eating problems (Kodak & Piazza, 2008).

Comorbid Medical Disorders:
- *Seizure disorder* – most common comorbid medical illness – 11 percent to 39 percent of individuals with ASD; onset before age 5 years and adolescence
- *Gastrointestinal problems* – commonly observed in patients with ASD (constipation and diarrhea)
- *Sleep disturbance* – underlying etiology or secondary to psychiatric illnesses.
- >70% of affected individuals have other concurrent conditions such as epilepsy (30%), gastrointestinal (GI) problems (9%–70%), immunodysregulation (38%), or sleep disorders (50%–80%). (Wasilewska & Klukowski, 2015)

Assessment
The primary care physician's (PCP's) role in identifying, managing, and supporting children with ASD is important and includes: "performing developmental surveillance, screening and referral; assisting in the diagnostic process; identifying and managing

co-occurring conditions; and supporting children and families across systems" (Ellerbeck et al., 2015). Authors discussed the family-centered (or patient-centered) medical home which requires substantial collaboration and coordination across systems. Diagnostic decision-making is challenging due to the substantial variability of symptoms of ASD. Children identified at risk for ASD may be referred to developmental-behavioral pediatricians, neurologists, child psychiatrists or licensed psychologists who have expertise in the area of ASD. They noted the significant role of the PCP in the medical management of the child with ASD; i.e., reviewing presenting medical issues co-occurring in ASD; reviewing co-occurring behavioral/psychiatric issues and collaborating with both medical and behavioral specialists.

Updated Review of Evidence-Based Practices for Children, Youth and Young Adults with ASD
In a recent study, researchers performed a comprehensive review of the intervention literature to identify evidence-based, *focused* intervention practices for children and youth with ASD (Wong et al., 2015). *Comprehensive* treatment models (CTMs), e.g., TEACCH program, Early Intensive Behavioral Intervention, Early Start Denver Model, and LEAP, are designed to achieve a broad learning or developmental impact on core deficits of ASD. In contrast, *focused* interventions, e.g., discrete trial teaching, pivotal response training, prompting and video modeling that are behavioral, developmental and/or educational in nature, address a single skill or goal of children or adolescents with ASD. Researchers focused on outcomes associated with social, communication, and challenging behaviors, and found 27 interventions that meet the criteria for being evidence-based. Six of the newest focused intervention practices include cognitive behavioral intervention, exercise, modeling, scripting, structured play groups, and technology-aided instruction and intervention practice. In this review, prompting and reinforcement had the most support and a clear trend was found showing combinations of evidence-based practices to address specific circumstances. Researchers suggested that the identified set of evidence-based practices is a tool in creating an individualized program for children and youth with ASD (Wong et al., 2015).

PLAY Project Home Consultation Intervention Program for Young Children With Autism Spectrum Disorders
A recent study evaluated the effectiveness of the Play and Language for Autistic Youngsters (PLAY) Project Home Consultation model combined with usual community services (CS) as an intervention for children with ASD and their parents (Solomon et al., 2014). Usual CS included speech/language and occupational therapy, and public education services. Parents were trained by PLAY consultants through coaching, modeling, and video feedback. PLAY emphasized social reciprocity while supporting parents in engaging their children (n=128) aged 32-71 months for at least two hours/day (15 hours/week). In this randomized controlled trial, families were randomized to PLAY combined with CS or to usual community services over 12 months. Researchers concluded that "PLAY children made greater improvements in their interactions, functional development and autism symptomatology than CS children" and "offers communities a relatively inexpensive effective treatment for children with ASD and their parents" (Solomon et al., p. 484).

Parent-Implemented Early Social Intervention (ESI) for Toddlers With Autism A recent randomized controlled trial compared results of two nine-month parent-implemented interventions for toddlers with ASD within the Early Social Interaction (ESI) Project (Wetherby et al., 2014). Children (n = 82) who had been diagnosed with

ASD at aged 16-20 months were randomly assigned to individual ESI or group ESI. In both groups, parents were taught the importance of intensive intervention and encouraged to utilize evidence-based strategies for improving social communication and adaptive behavior. Individual-ESI was offered two or three times per week at home or in the community whereas group-ESI was offered once per week in a clinic. Both groups used the manualized Social Communication, Emotional Regulation and Transactional Supports Curriculum. Results found that individual-ESI led to faster rate of improvement in social communication as well as greater improvement in measures of daily living and social skills than group-ESI. Noting this improvement, researchers suggested the importance of individualized parent coaching in natural environments. They concluded, "The efficacy of individual-ESI compared with group-ESI on many child outcomes is particularly important in light of the lack of main effects on child outcomes of most other parent-implemented interventions with toddlers with ASD" (Wetherby et al., p 1091. Researchers acknowledged that the potential to identify children with ASD by aged 18-24 months is within reach (Wetherby et al., 2014).

Implementation of Applied Behavior Analysis (ABA) using Telehealth Coaching of Parents
A recent study compared three delivery models for implementing ABA procedures in children (n=107) aged 21-84 months with autism: in-home therapy, clinic-based telehealth and home-based telehealth (Lindgren et al., 2016). Parents were taught by behavioral consultants in each group. Weekly treatments were over 25 or more weeks (based on decrease in problem behavior) with a similar number of weeks needed across treatment groups. Results found that problem behavior was reduced greater than 90 percent for all groups, with no significant differences between the three models. Researchers noted that the findings provide support for the use of telehealth as an alternative model to treat moderate to severe behavior problems associated with ASD in families with Internet access.

Parent Training Program Targeting School-Aged Children
In a recent study, authors examined data from a randomized trial evaluating outcomes of a social communication intervention (Joint Attention, Symbolic Play, Engagement, and Regulation [JASPER] and Enhanced Milieu Teaching [EMT] versus the same intervention plus the use of a speech-generating device in the treatment of minimally verbal children (n=61) with ASD (Shire et al., 2015). In the current study, using data from the randomized trial, authors examined the degree to which parents implemented the social communication intervention. Parents observed the intervention during the first three months while the therapist worked directly with the child and the parent watched through a one-way mirror. After the three-month period, parents received a combination of parent education and hands-on coaching. Authors found that parents were more successful in applying the intervention through direct coaching, with the greatest success during the first month of coaching. Data suggested hands-on training as the most effective approach, although observational learning and didactic workshops were also beneficial. Authors concluded that "children's joint engagement was associated with parents' implementation success across time demonstrating parents' implementation was relevant to children's social engagement" (Shire et al., p. 1712).

The Early Start Denver Model (ESDM)
A recent study prospectively examined evidence for sustained effects of the Early Start

Denver Model (ESDM) in children (n = 39) with ASD who participated in a randomized clinical trial where they were assigned to receive ESDM or the community-intervention-as-usual (COM) at aged 18-30 months for two years (Estes et al., 2015). ESDM, a naturalistic behavioral intervention integrating applied behavior analysis methods with developmental approaches and parent coaching, is designed for children as young as one year to promote learning, social reciprocity and affective engagement. The interventions, conducted in-home by clinicians (20 hours per week) over a period of two years, showed evidence of efficacy immediately posttreatment. In this follow-up study, the children were assessed across multiple domains of functioning two years after end of the intervention. The two groups received equivalent intervention hours during the original study while the ESDM group received fewer hours during the follow-up period. Gains from ESDM in areas including intellectual ability, adaptive behavior, autism symptoms and challenging behaviors, were maintained two years later. Compared to the COM group, the ESDM group demonstrated less severe overall ASD symptoms, better adaptive behavior and improved socialization ability. Researchers concluded that "early identification and intensive, early, ASD-specific intervention can improve long-term outcomes for children with ASD" (Estes et al., 2015).

Comprehensive Peer Network Intervention to Improve Social Communication of Children with ASD in Kindergarten and First Grade
A recent randomized trial including children (n = 93) with ASD, in kindergarten and first grade, examined the efficacy of a two-year comprehensive peer network intervention combining peer training and direct instruction by trained school personnel (Kamps et al., 2015). Children were randomized by a block randomization procedure (by ASD severity) to the experimental and comparison groups which resulted in closely balanced groups. The goals of the intervention were to improve reciprocal social communication in social groups, provide interaction with typical peers, and teach social and communication skills using toys and games. Skills taught included: "Ask and Share," "Tell about my toys," Tell about friends' toys, "Talk Nice," and "Ways to Play." Teachers used scripted lessons and written-text cues to teach specific communication skills, and provided feedback/reinforcement to children. The majority of children in the intervention group learned to communicate with peers during treatment sessions and showed significantly more growth in initiation to peers in generalization settings, e.g., recess, lunch, than children in the comparison group who did not receive weekly structured social skills instruction. Researchers noted that this result confirms "prior research indicating that social skills interventions for young children generally improve target skills and may promote generalization" (Kamps et al., p. 16).

A Computer Based Intervention (CBI) for High-Functioning Children with ASD
A recent controlled trial randomized children (n = 43), aged 7-12 years, with high functioning ASD (HFASD), to a computer based intervention, i.e., Mind Reading (MR), or to a waitlist control condition (Thomeer et al., 2015). MR, "an interactive software program designed to teach recognition of simple and complex emotions to children with ASD via facial-video and vocal-audio stimuli," was administered in a computer lab during 24 sessions over 12 weeks (Thomeer et al., p. 2121). Outcome measures, e.g., Cambridge Mindreading Face-Voice Battery for Children (CAM-C), Emotion Recognition and Display Survey (ERDS), and Social Responsiveness Scale (SRS), included the assessment of skills directly targeted by the treatment along with ASD features and broader social skills. Results of this intervention including both

instruction and reinforcement via computer software indicated that the children completing the treatment performed significantly better on a test of emotion regulation skills for both facial and vocal expressions than children in the control group. Moreover, the gains were maintained at five-week follow-up. Researchers noted that these results "lend support for the efficacy of MR as a promising CBI for children with HFASD" (Thomeer et al., p. 2125). They further suggested that the intervention improved both decoding and encoding skills and reduced ASD symptoms for children with HFASD.

Cognitive Behavioral Therapy for Early Adolescents with ASD and Clinical Anxiety
Past studies have shown that individually administered cognitive behavioral therapy (CBT) programs for treating anxiety in children and youth with ASD have demonstrated significant reductions in anxiety symptoms, improved rating of adaptive skills and reduced ASD symptom severity (Wood et al., 2015). A current study evaluated whether a CBT program, Behavioral Interventions for Anxiety in Children with Autism, adapted to address related adolescent-specific issues would result in the similar improvements. In this study, adolescents (n=33), aged 11-15 years and meeting criteria for both anxiety and ASD, were randomized to immediate treatment (CBT) or waitlist condition in 16 weekly format sessions including basic coping skills, e.g., behavioral activation, cognitive restructuring and in vivo exposure. Other areas, e.g., poor social skills, adaptive skills deficits, focused on fundamental concerns of anxious adolescents with ASD, were addressed. Results of the intervention found improvement in clinician reported anxiety severity as well as parent reported improvement in ASD symptom severity. Researchers noted the increasing recognition that anxiety and ASD symptom severity may be partially interdependent. They suggested that this treatment can be beneficial for early adolescents with ASD and indicated the need for future studies with an active control group, e.g., another form of psychotherapy, to determine specificity of intervention effects (Wood et al., 2015).

Behavioral Interventions Update – The Agency for Healthcare Research and Quality (AHRQ)
The 2014 update of AHRQ's systematic review of interventions for children with ASD focused on applied behavioral analysis (ABA) and included 65 studies. Authors of the report indicated that the strength of evidence from the studies remains low for many intervention/outcome pairs. Although high-intensity applied behavioral analysis interventions over extended timeframes were associated with improvement in cognitive functioning and language skills, the magnitude of effects varied across studies. Authors suggested that "early behavioral and developmental intervention based on the principles of ABA delivered in an intensive (0-24 hours of direct intervention) and comprehensive (25-40 hours of direct intervention), i.e., addressing numerous areas of functioning, approach can positively affect a subset of children with ASD" (Weitlauf et al, 2014). Noting significant methodological concerns limiting the strength of conclusions, authors indicated that in most of the studies, behavioral interventions were compared with nonspecific "treatment as usual" and studies used small samples. They stressed the need for improvements in methodological rigor and for studies of interventions across settings. Magellan Healthcare considers ABA in the treatment of ASD as evidence- informed (Magellan Healthcare, 2015).

Medical Management
A recent update on pharmacotherapy for ASD in children and adolescents emphasized the need for clinicians to understand current evidence-based pharmacotherapy, risks

and benefits, as well as pertinent updates from recent studies in order to guide patients and to make well informed decisions (Young et al., 2015). Noting the lack of known efficacious pharmacotherapy for core symptoms of ASD and the limited evidence-based pharmacotherapy options in children with ASD, authors reviewed current evidence-based pharmacotherapy options and updates from recent studies including psychotropic medications prescribed for behavioral/emotional symptoms associated with ASD. They recommended clinicians to weigh the risks and benefits of pharmacotherapy as a part of comprehensive treatment. Highlights from their review follow (Young et al., 2015):

- Antipsychotics – The only two medications approved by the FDA for children with ASD, risperidone and aripiprazole, have been shown to have efficacy in the treatment of aggression, self-injury and severe tantrums in children with ASD. However, regulatory approval limits the use of the medication to patients with problematic irritability and severe problem behavior. Adverse events include weight gain and metabolic changes. Studies have shown that risperidone combined with parent training was more efficacious than medication alone for problem behavior and adaptive functioning. Efficacy in decreasing problem behavior with the use of aripiprazole was comparable to risperidone in a systematic review of clinical data, and aripiprazole had a similar metabolic adverse event profile. Authors suggested more controlled studies of the use of ziprasidone and other newer agents that have less metabolic adverse events are needed.
- Methylphenidate, Atomoxetine, and Alpha-2 Agonists – In children with co-occurring attention deficit hyperactivity disorder (ADHD) and ASD, methylphenidate has been shown to be effective in improving symptoms of ADHD, although the medication was better tolerated in children with higher cognitive functioning. Atomoxetine and alpha-2 agonists, e.g., guanfacine, have also appeared to be effective in treating ADHD symptoms in children with ASD, especially when combined with parent training.
- Antidepressants – The conclusion of a recent Cochrane review of SSRI trials found no evidence of efficacy of SSRIs in children with ASD and found emerging evidence of harm.
- Antiepileptic Drugs – Studies have shown that valproate may be efficacious in treating irritability in children with ASD while topiramate in combination with risperidone may improve problem behavior. However, authors noted that further studies are necessary to define the efficacy of antiepileptic drugs as monotherapy or in combination with antipsychotics.
- Novel Drugs – In a quest to find a medication that is effective in treating the core symptoms of ASD, recent trials have investigated novel agents, e.g., glutamatergic agents and oxytocin which appear promising although with mixed results. Glutamatergic agents including amantadine, memantine and riluzole, as adjunctive therapy to risperidone, have been shown to improve behavioral measures when compared to risperidone plus placebo. Authors noted that they may be helpful when combined with antipsychotic treatment, but larger trials must replicate earlier results. Studies have also suggested that intranasal oxytocin as an adjunct to behavioral therapy for ASD may be beneficial.
- Future Directions in Pharmacotherapy for ASD – Authors concluded, "Future research investigating genotypic and/or phenotypic characteristics influencing medication response and tolerability will be valuable in further individualizing

pharmacotherapy" and "future research utilizing biomarkers such as eye-tracking, electrophysiological measures and/or functional neuroimaging may aid in capturing treatment benefits more accurately" (Young et al., p. 12).

Introduction

The guidelines Magellan has adopted to augment providers' clinical decision-making with members who have ASD are:

- *Practice Guideline for the Management of Children With Autism Spectrum Disorders* developed by the American Academy of Pediatrics (AAP) at http://pediatrics.aappublications.org/content/120/5/1162.full.pdf and published in *Pediatrics* 2007: 120(5); 1162-1182. Reaffirmed September 2010 (doi:10.1542/peds.2007-2362).
- Companion document to the guideline, *Clinical Report – Identification and Evaluation of Children With Autism Spectrum Disorders* developed by the American Academy of Pediatrics (AAP) at http://pediatrics.aappublications.org/cgi/reprint/120/5/1183 and published in *Pediatrics* 2007: 120(5); 1183-1215. Reaffirmed September 2010.[2]

This guideline and its companion report incorporate the rapidly evolving developments in pharmacotherapy, as well as developments in other areas of educational and clinical management of children with ASD. The AAP guideline and its companion report are evidence-based documents that cover all areas of management of patients with this disorder, from understanding the clinical features and screening/surveillance to medical/psychiatric treatment approaches, educational/behavioral interventions, planning and family support.

In addition to the guidelines referred to above, Magellan's Introduction also includes key recommendations from the American Academy of Child and Adolescent Psychiatry's (AACAP) new Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder (Volkmar et al., 2014).

Additional Recommendations Based on Recent Literature Review

The AAP guideline and companion report are based on a literature review through 2006. Prior to adopting the guideline, Magellan conducted an additional literature review on the assessment and treatment of ASD through May 2008. This guideline update is based on literature through April 2016. Key relevant recommendations from this more recent literature review are summarized below. Magellan encourages providers to be familiar with this information, as well as the information in both the guideline and the companion document.

Diagnosis of Autism Spectrum Disorder

In the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5™) autism spectrum disorder is classified as a neurodevelopmental disorder, encompassing the DSM-IV autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder, not otherwise specified. Individuals previously diagnosed with either of these diagnoses may now meet the criteria for ASD. Those with deficits in social communication whose symptoms do not

meet criteria for ASD should be evaluated for social communication disorder (American Psychiatric Association, 2013).

DSM-5 criteria for ASD include: 1) impairment in social communication and interaction, persistent and across multiple contexts, and 2) repetitive, restricted patterns of behavior, activities or interests. A severity scale must be recorded for each domain. Unlike the requirement in DSM-IV that onset must occur before age 3 years, the DSM-5 requires that individuals show symptoms that limit or impair everyday functioning in the early developmental period, encouraging earlier diagnosis of ASD. If ASD is accompanied by intellectual impairment, language impairment, catatonia or known medical, genetic or environmental factors, the diagnosis should specify "associated with a known medical/genetic or environmental/acquired condition" (American Psychiatric Association, 2013).

Epidemiology and Etiology

Prevalence. A recent report from the Centers for Disease Control Prevention (CDC) examined survey-based estimates of the lifetime prevalence of ASD and compared them with estimates from previous years (Zablotsky et al, 2015). The CDC's 2014 National Health Interview Survey (NHIS) reported an estimated parent-reported prevalence of ASD (based on 2014 data) of 2.24 percent, compared with a prevalence of 1.25 percent based on 2011-2013 data. However, authors acknowledged that revised question ordering and a new approach to inquiring about developmental disabilities in this survey may have affected the prevalence estimates. The overall prevalence of children with ASD, other developmental disability or intellectual disability was not significantly changed from 2011-2014. Authors suggested that the change may not be completely related to changes in the wording of the survey, but that the new survey was "more sensitive in capturing the full population of children with ASD than estimates based on the 2011-2013 data" (Zablotsky et al, P.5). In the 2014 survey, the ASD questions included Asperger's disorder and pervasive developmental disorder (PDD). In a recent review, Yu et al. discussed the steady increase in prevalence of ASD from 2006 through 2010 while noting variability from state to state (Yu et al., 2016). They suggested that the increase may be related to increased awareness and availability of services for ASD, as well as to potential environmental factors.

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According to a National Health Statistics Report, the prevalence of parent-reported ASD increased by 78 percent between 2002 and 2008 (CDC, 2013). The report also indicates that the prevalence of parent-reported ASD among U.S. children aged 6-17 increased from 1.16 percent to 2.00 percent from 2007 to 2011-2012, with the greatest increase for boys and for adolescents aged 14-17. Researchers found that school-aged children who were diagnosed in 2008 or later were more likely to be diagnosed with milder ASD than those diagnosed in 2007 or earlier. Researchers concluded that much of the increase in prevalence from 2007 to 2011-2012 resulted from the diagnoses of children with previously unrecognized ASD (CDC, 2013). The AACAP practice parameter notes that although ASD is four times more common in males than in females, more severe intellectual disabilities are associated in ASD in females. It also suggests potential under diagnosis of ASD in disadvantaged inner-city children in the U.S. (Volkmar et al., 2014). DSM-5 indicates that the age at which a diagnosis of ASD is recognized may be related to cultural and socioeconomic factors (American Psychiatric Association, 2013).

Neurobiologic factors. The DSM-5 notes that symptoms may be seen earlier than 1 year of age, although they are typically recognized during the second year of life. Almost 25 percent of individuals with ASD have electroencephalographic abnormalities and seizure disorder, suggesting an association between ASD and neurobiologic factors (Volkmar et al., 2014). Although definitive data are lacking, abnormalities that have been associated with ASD include increased overall brain size and the elevation of peripheral levels of serotonin. The immune system has also been suggested as playing a role in ASD. The AACAP practice parameter discusses the neuropsychological correlates of ASD, i.e., impairments in executive functioning, weak central coherence and deficits in theory-of-mind tasks (Volkmar et al., 2014).

Genetic Factors. Genetics is also important in the etiology of ASD. In a recent study, researchers "demonstrated differences related to morphological stratification of ASD probands based on clinical examination" (Tammimies et al., 2015, p. 901). Researchers performed chromosomal microarray analysis (CMA) and whole-exome sequencing (WES) in a group of children with ASD (n = 258 probands). They found comparable molecular diagnostic yields of CMA and WES among the heterogeneous sample of children with ASD, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes. Researchers noted that "the broad phenotype spectrum of ASD is also reflected in the underlying genetic etiology" and suggested that "medical evaluation of ASD children may help identify populations more likely to achieve a molecular diagnosis with genetic testing" (Tammimies et al., p. 901). They concluded that more study is required on the use of genome-wide tests to provide molecular diagnosis for children with ASD.

In a 2014 study, researchers analyzed 25 genes in postmortem brain tissue from children (n=22), between age 2 years and 15 years, with and without autism (Stoner et al., 2014). Researchers focused on genes implicated in autism and control genes, finding that the development of six distinct layers of the cortex beginning in prenatal life had been disrupted in 91 percent of children with autism compared to 9 percent of those without ASD. The brain regions affected by the absent gene markers were those associated with communication and language. In addition to suggesting a prenatal origin of autism, these findings support the idea that early focal defects may sometimes be circumvented as the brain may be able to rewire connections in children with autism. Researchers suggested that the findings may lead to exploring how that improvement occurs (Stoner et al., 2014).

The AACAP practice parameter notes the higher rates of autism in siblings of affected children and in identical twins, providing strong support for genetic factors in autism. Other risk factors for ASD include advanced maternal or paternal age, premature birth and closer spacing of pregnancies. A meta-analysis of epidemiological studies investigating the association between maternal age and autism found that the risk of autism increased with increasing maternal age, even after the effects of paternal age and other potential confounders had been considered (Sandin et al., 2012). Authors suggested possible explanation for the maternal age effect may be an increased occurrence of genomic alteration or an accumulated exposure to environmental toxins over the life course of an older mother.

Environmental factors. A recent study evaluated the association between ASD prevalence, at the census tract level, and proximity to sources of pollution, i.e., industrial facilities releasing arsenic, lead or mercury (Dickerson et al., 2015). To estimate prevalence of ASD among children age 8 years, researchers used 2000 to 2008 surveillance data from five sites of the Autism and Developmental Disabilities Monitoring (ADDM) network and 2000 census data. Reported on-site air releases of arsenic, lead and/or mercury were obtained from the U.S. Environmental Protection Agency Toxics Release Inventory (TRI). Results showed greater ASD prevalence with closer proximity to TRI sites in existence during birth years, consistent with results of prior studies. Additionally the results suggested that exposure to arsenic, lead or mercury released from the industrial facilities may have had an impact from a further distance than in past studies. Researchers concluded that the results are suggestive

of the association between urban residential proximity to industrial facilities emitting arsenic, lead and mercury and higher ASD prevalence (Dickerson et al., 2015).

In a 2014 study, environmental factors were found to be as important as genetic factors in ASD (Sandin et al., 2014). Based on the results of this study including children with ASD (n=14516), investigators estimated that genetic factors are 50 percent and the other 50 percent is explained by non-shared environmental factors, e.g., birth complications or medication received during pre- or perinatal periods. Studies have shown conflicting findings regarding the associations between prenatal use of selective serotonin reuptake inhibitors (SSRIs) and ASD. In a population-based case-control study, children with ASD and their mothers (n=492), mother-child pairs including a child with developmental delay (n=154), and children with typical development and their mothers (n=320) were evaluated to determine whether there was an association between antidepressant use during pregnancy and ASD in the offspring, while considering confounding factors (Harrington et al., 2014). Findings showed that mother's reported use of SSRIs during pregnancy was associated with an increased risk of ASD in boys, with the greatest association during first-trimester SSRI exposure. Researchers pointed out that the findings from other published studies continue to be inconsistent and "these results must be viewed in the context of the disorder they are used to treat and, particularly, with the risks associated with failure to treat the condition" (Harrington et al., p. 1246). The DSM-5 names a variety of nonspecific risk factors including advanced parental age, low birth weight and fetal exposure to valproate that may contribute to the risk of ASD (American Psychiatric Association, 2013). A population-based study including children born alive in Denmark from 1996 to 2006 (n=655,615) identified children exposed to valproate during pregnancy and diagnosed with ASD. Analysis of the data found that maternal use of valproate during pregnancy was significantly associated with increased of risk of ASD in offspring, even after adjusting for maternal epilepsy and psychiatric disease. Researchers cautioned that the findings should be balanced against the benefits of treatment for women who require valproate for control of epilepsy (Christensen et al., 2013).

A population-based case-control study examined the relationship between traffic-related air pollution, air quality, and autism in preschool children (n=424). The researchers used data, e.g., traffic volume and meteorological data, to build models of traffic-related air pollution in the locations where the children lived and to look for association between traffic air pollution and autism. Findings showed that children with autism were three times more likely to have been exposed to traffic-related pollution during the first year of life than children with typical development. An association between exposure during pregnancy and autism was also found. Researchers suggested the need for additional research to replicate these findings (Volk et al., 2013).

Differential Diagnosis

The AACAP practice parameter states that ASD must be differentiated from developmental disabilities, sensory impairment disorders, reactive attachment disorder, obsessive-compulsive disorder, anxiety disorders, ADHD, schizophrenia (child-onset) and other conditions. ASD is diagnosed after determining that the DSM-5 symptoms are present and ruling out other disorders (Volkmar et al., 2014). The

practice parameter notes that two behaviors may differentiate children with ASD from language-impaired peers at age 20 months and 42 months: pointing for interest and use of conventional gestures (Volkmar et al., 2014).

Comorbidity

In a recent clinical synthesis, authors reported common psychiatric disorders and medical disorders for individuals with ASD as follows (Yu et al., 2016):

Comorbid Psychiatric disorders:
- *Intellectual disability* (ID) – 20 percent to 53 percent of individuals with ASD
- *Psychiatric disorders*, e.g., attention-deficit hyperactivity disorder (ADHD), anxiety disorders, obsessive-compulsive disorder (OCD), depression and schizophrenia – approximately 70 percent of individuals with ASD
- *Two or more psychiatric disorders* – Nearly 40 percent of individuals with ASD
- *Anxiety spectrum disorders* – most common psychiatric condition comorbid with ASD (may be byproduct of core symptoms instead of comorbid condition)
- *Obsessive Compulsive Disorder* – 44 percent of individuals with ASD
- *Catatonia* – highest risk in adolescence.

Comorbid Medical Disorders:
- *Seizure disorder* – most common comorbid medical illness – 11 percent to 39 percent of individuals with ASD; onset before age 5 years and adolescence
- *Gastrointestinal problems* – commonly observed in patients with ASD (constipation and diarrhea)
- *Sleep disturbance* – underlying etiology or secondary to psychiatric illnesses.

ASD is known to be a heterogeneous disorder, complicated by associated behavioral, neurological and medical issues. Medical conditions, e.g., gastrointestinal conditions and epilepsy, often occur in patients with ASD. A meta-analysis evaluated the evidence regarding GI symptoms in children with ASD (n=2215). Results of this study showed that children with ASD experience significantly more general GI symptoms, diarrhea, constipation and abdominal pain than children without ASD (McElhanon et al., 2013). Investigators suggested future research to address causes and long-term impact of GI symptoms in ASD. Epilepsy occurs in approximately 25 percent of individuals with ASD over the life span, with higher prevalence in those with severe intellectual disability (American Academy of Pediatrics, 2012). In up to 70 percent of children with ASD, epileptiform abnormalities on electroencephalogram (EEG) are common and present, although many children with abnormal EEGs have no history of clinical seizures. Epilepsy in treated in children with ASD with anticonvulsant medications using the same criteria used for other children with epilepsy (American Academy of Pediatrics, 2012).

Comorbid Mental disorders. DSM-5 states that approximately 70 percent of individuals with ASD have one comorbid mental disorder while 40 percent may have two mental disorders. A study using large-population data from the 2007 National Survey on Children's Health (NSCH) found that 66.2 percent of children with ASD also had a comorbid psychiatric condition (CPC) and 61.8 percent of those with ASD and CPC had more than one CPC. The study also showed that children with ASD and a CPC had significantly poorer health outcomes than chose with ASD alone. Investigators

suggested that screening and referral to specialized treatment practices should be increased for children with both ASD and CPC (Ahmedani et al., 2012). ADHD symptoms occur in 41 percent to 78 percent of children with ASD (Mahajan et al., 2012). In a study evaluating co-occurring ADHD symptoms in children with ASD, investigators found greater impairment in adaptive functioning and a poorer quality of life in children with both ASD and ADHD symptoms in comparison with children with ASD and fewer ADHD symptoms (Sikora et al., 2012). They suggested providers should screen for symptoms of ADHD in their patients with ASD, and consider these symptoms in developing a plan of treatment. A practice pathway for the identification, evaluation and management of insomnia in children and adolescents with ASD was developed by the Sleep Committee of the Autism Treatment Network (ATN) (Malow et al., 2012). Key points of this pathway are: 1) all children with ASD should be screened for insomnia (parents do not often volunteer sleep information); 2) evaluate possible medical contributors affecting sleep, e.g., gastrointestinal disorders, epilepsy, psychiatric comorbidities, medicines; 3) 1st line of treatment should be educational/behavioral interventions, after excluding medical contributors; 4) pharmacologic treatment should be considered if behavioral approach not feasible; and 5) monitor progress and resolution of insomnia (Malow el al., 2012).

There continues be a co-morbidities of autism and other disorders (e.g. intellectual disability, sensory processing disorder, bipolar disorder, etc.). It is important for the treatment provider to work collaboratively with the member's PCP, psychologist, and other practitioners within the medical model to ensure that the comorbidities are being addressed by the qualified licensed professionals.

Assessment

The primary care physician's (PCP's) role in identifying, managing and supporting children with ASD is important and includes: "performing developmental surveillance, screening and referral; assisting in the diagnostic process; identifying and managing co-occurring conditions; and supporting children and families across systems" (Ellerbeck et al., 2015). Authors discussed the family-centered (or patient-centered) medical home which requires substantial collaboration and coordination across systems. Diagnostic decision-making is challenging due to the substantial variability of symptoms of ASD. Children identified at risk for ASD may be referred to developmental-behavioral pediatricians, neurologists, child psychiatrists or licensed psychologists who have expertise in the area of ASD. They noted the significant role of the PCP in the medical management of the child with ASD; i.e., reviewing presenting medical issues co-occurring in ASD; reviewing co-occurring behavioral/psychiatric issues; and collaborating with both medical and behavioral specialists.

The AACAP recommendations for assessment of ASD include the following (Volkmar et al., 2014):

- Developmental and psychiatric assessment of children should include screening for the core symptoms of ASD using screening instruments applicable to the age range and the method of administration. Examples of screening tools are the Modified Checklist for Autism in Toddlers (M-CHAT), Social Communication Questionnaire, Childhood Autism Rating Scale (CARS) and High Functioning Autism Spectrum Screening Questionnaire. Screening instruments supplement, but do not replace clinical judgment.

- To determine the presence of ASD, a thorough diagnostic evaluation, including a psychiatric assessment, interviews with child and family, review of past records, and historical information, should be performed if the screening indicates significant symptoms of ASD. DSM-5 criteria should be considered in the evaluation.

- An appropriate multidisciplinary assessment of all children with ASD should be coordinated by clinicians. A medical assessment including physical examination should be performed and a chromosomal microarray is recommended by medical geneticists for the initial evaluation of children with ASD. Additional evaluations should be performed to assess unusual features, e.g., staring spells. Developmental disorders, e.g., Landau-Kleffner syndrome, should be ruled out. The assessment should also include both a psychological and communication assessment.

Treatment of Children and Adolescents with Autism Spectrum Disorder

The AACAP practice parameter recommends an evidence-based, multidisciplinary treatment plan for children and adolescents with ASD (Volkmar et al., 2014). The treatment plan may include a combination of therapies, e.g., structured educational and behavioral interventions. Other forms of psychosocial interventions, e.g., cognitive behavioral therapy, may be effective in treating high functioning youth with ASD, but for most other forms of psychosocial interventions, there is a lack of evidence. Pharmacologic interventions may be effective in treating associated comorbid conditions, e.g., depression and anxiety, and may also treat specific target symptoms such as repetitive or stereotypic behaviors and sleep disturbances. The practice parameter notes the growing body of controlled evidence for pharmacologic intervention, and especially for combining medication with parent training.

Educational and Behavioral Interventions

The AACAP practice parameter recommends evidence-based and structured educational and behavioral interventions for children with ASD while noting that further studies using more rigorous randomized group comparisons are needed. Although treatments have been shown to have efficacy for groups of children, they note that no treatment models have emerged as superior (Volkmar et al., 2014).

Updated Review of Evidence-Based Practices for Children, Youth, and Young Adults with ASD
In a recent study, researchers performed a comprehensive review of the intervention literature to identify evidence-based, *focused* intervention practices for children and youth with ASD (Wong et al., 2015). *Comprehensive* treatment models (CTMs), e.g., TEACCH program, Early Intensive Behavioral Intervention, Early Start Denver Model and LEAP, are designed to achieve a broad learning or developmental impact on core deficits of ASD. In contrast, *focused* interventions, e.g., discrete trial teaching, pivotal response training, prompting and video modeling that are behavioral, developmental and/or educational in nature, address a single skill or goal of children or adolescents with ASD. Researchers focused on outcomes associated with social, communication and challenging behaviors, and found 27 interventions that meet the criteria for being evidence-based. Six of the newest focused intervention practices include cognitive

behavioral intervention, exercise, modeling, scripting, structured play groups and technology-aided instruction and intervention practice. In this review, prompting and reinforcement had the most support and a clear trend was found showing combinations of evidence-based practices to address specific circumstances. Researchers suggested that the identified set of evidence-based practices is a tool in creating an individualized program for children and youth with ASD (Wong et al., 2015).

PLAY Project Home Consultation Intervention Program for Young Children With Autism Spectrum Disorders
A recent study evaluated the effectiveness of the Play and Language for Autistic Youngsters (PLAY) Project Home Consultation model combined with usual community services (CS) as an intervention for children with ASD and their parents (Solomon et al., 2014). Usual CS included speech/language and occupational therapy, and public education services. Parents were trained by PLAY consultants through coaching, modeling, and video feedback. PLAY emphasized social reciprocity while supporting parents in engaging their children (n=128) aged 32-71 months for at least two hours/day (15 hours/week). In this randomized controlled trial, families were randomized to PLAY combined with CS or to usual community services over 12 months. Researchers concluded that "PLAY children made greater improvements in their interactions, functional development and autism symptomatology than CS children" and "offers communities a relatively inexpensive effective treatment for children with ASD and their parents" (Solomon et al., p. 484).

Applied Behavioral Analysis - Interventions Update
The 2014 update of *The Agency for Healthcare Research and Quality's (AHRQ's)* systematic review of interventions for children with ASD focused on applied behavioral analysis (ABA) and included 65 studies. Authors of the report indicated that the strength of evidence from the studies remains low for many intervention/outcome pairs. Although high-intensity applied behavioral analysis interventions over extended timeframes were associated with improvement in cognitive functioning and language skills, the magnitude of effects varied across studies. Authors suggested that "early behavioral and developmental intervention based on the principles of ABA delivered in an intensive (≥15 hours per week) and comprehensive (i.e., addressing numerous areas of functioning) approach can positively affect a subset of children with ASD" (Weitlauf et al, 2014). Noting significant methodological concerns limiting the strength of conclusions, authors indicated that in most of the studies, behavioral interventions were compared with nonspecific "treatment as usual" and studies used small samples. They stressed the need for improvements in methodological rigor and for studies of interventions across settings. Magellan Healthcare considers ABA in the treatment of ASD as evidence-informed (Magellan Healthcare, 2015).

Based on a thorough review of the literature and evaluation of published research studies in peer-reviewed clinical journals, Magellan considers Applied Behavior Analysis (ABA) used in the treatment of autism to be an evidence- informed treatment for which more treatment research is needed (Magellan Healthcare, 2012). Current findings from well-designed studies are insufficient to firmly establish ABA as a proven effective treatment since there are currently only two published randomized controlled studies. Magellan's Technology Assessment concludes that "more treatment research is needed with strict empirical designs that can allow for sound inferences regarding the parameters of treatment effectiveness and can answer

current questions about features of children who are most likely to respond" (Magellan Healthcare, 2012, p. 9).

Nonetheless, ABA has been safely used to treat children with autism outside of the investigational setting since the 1960's. The use of ABA has grown dramatically in the past decade due to the increased prevalence of the disorder and lack of other viable therapeutic psychosocial treatment alternatives to treat this serious neurodevelopmental condition. In light of this widespread use, more well-designed studies of ABA will provide a greater understanding of which children are most likely to benefit. According to a Comparative Effectiveness Review (Number 26) issued by the Agency for Healthcare Research and Quality (AHRQ), *Therapies for Children with Autism Spectrum Disorders*, the current evidence is promising, but confusing because "not all children receiving intensive intervention demonstrate rapid gains and many children continue to display substantial impairment" (AHRQ, 2011, pp. vi, ES-7).

An independent Technical Expert Panel (TEP) performed a systematic review of the scientific evidence for ABA in the treatment of children with ASD. Moderate effects in language, adaptive skills and cognition were reported in most of the 16 systematic reviews and meta-analyses. Except for two randomized controlled trials, the studies were observational trials or nonrandomized trials (Maglione et al., 2012). Additionally, the TEP reviewed a meta-analysis that suggested ABA has medium to large positive effects in language development, social functioning, acquisition of daily living skills and intellectual functioning in children with ASD. This study showed that better outcomes result from more intense intervention (hours per week) and higher duration (months or years) (Maglione et al., 2012).

A later study examined early intervention outcomes in toddlers with ASD (n=48) who received a six month intervention using instructional strategies, e.g., pivotal response training, that included ABA (Landa and Kalb, 2012). Results showed significant gains in cognitive and communication ability between pre-intervention assessment and follow-up at a mean of 37.6 months after completion of intervention. ASD severity decreased significantly between pre-intervention and immediately following the six-month treatment, but returned to the pre-intervention level by the follow-up period (37.6 months after completion of intervention). Investigators suggested further research to determine whether initial reduction in the severity of ASD can be sustained through targeted interventions (Landa and Kalb, 2012).

A recent study compared three delivery models for implementing ABA procedures in children (n=107) aged 21-84 months with autism: in-home therapy, clinic-based telehealth and home-based telehealth (Lindgren et al., 2016). Parents were taught by behavioral consultants in each group. Weekly treatments were delivered over 25 or more weeks (based on decrease in problem behavior) with a similar number of weeks needed across treatment groups. Results found that problem behavior was reduced greater than 90 percent for all groups, with no significant differences between the three models. Researchers noted that the findings provide support for the use of telehealth as an alternative model to treat moderate to severe behavior problems associated with ASD in families with Internet access.

Social Skills Training and Social Communication Treatments - Parent- Implemented Early Social Intervention (ESI) for Toddlers With Autism.
A recent randomized controlled trial compared results of two nine-month parent-implemented interventions for toddlers with ASD within the Early Social Interaction

(ESI) Project (Wetherby et al., 2014). Children (n = 82) who had been diagnosed with ASD at aged 16-20 months were randomly assigned to individual ESI or group ESI. In both groups, parents were taught the importance of intensive intervention and encouraged to embed evidence-based strategies for child targets for 25 or more hours per week. Individual-ESI was offered two or three times per week at home or in the community whereas group-ESI was offered once per week in a clinic. Both groups used the manualized Social Communication, Emotional Regulation and Transactional Supports Curriculum. Results found that individual-ESI led to faster rate of improvement in social communication as well as greater improvement in measures of daily living and social skills than group-ESI. Noting this improvement, researchers suggested the importance of individualized parent coaching in natural environments. They concluded, "The efficacy of individual-ESI compared with group-ESI on many child outcomes is particularly important in light of the lack of main effects on child outcomes of most other parent-implemented interventions with toddlers with ASD" (Wetherby et al., p. 1091). Researchers acknowledged that the potential to identify children with ASD by aged 18-24 months is within reach (Wetherby et al., 2014).

Parent Training Program Targeting School-Aged Children
In a recent study, authors examined data from a randomized trial evaluating outcomes of a social communication intervention (Joint Attention, Symbolic Play, Engagement, and Regulation [JASPER] and Enhanced Milieu Teaching [EMT] versus the same intervention plus the use of a speech-generating device in the treatment of minimally verbal children (n=61) with ASD (Shire et al., 2015). In the current study, using data from the randomized trial, authors examined the degree to which parents implemented the social communication intervention. Parents observed the intervention during the first three months while the therapist worked directly with the child and the parent watched through a one-way mirror. After the three-month period, parents received a combination of parent education and hands-on coaching. Authors found that parents were more successful in applying the intervention through direct coaching, with the greatest success during the first month of coaching. Data suggested that hands-on training was the most effective approach, although observational learning and didactic workshops were also beneficial. Authors concluded that "children's joint engagement was associated with parents' implementation success across time demonstrating parents' implementation was relevant to children's social engagement" (Shire et al., p. 1712).

Comprehensive Peer Network Intervention to Improve Social Communication of Children with ASD in Kindergarten and First Grade
A recent randomized trial including children (n = 93) with ASD, in kindergarten and first grade, examined the efficacy of a two-year comprehensive peer network intervention combining peer training and direct instruction by trained school personnel (Kamps et al., 2015). Children were randomized by a block randomization procedure (by ASD severity) to the experimental and comparison groups which resulted in closely balanced groups. The goals of the intervention were to improve reciprocal social communication in social groups, provide interaction with typical peers, and teach social and communication skills using toys and games. Skills taught included: "Ask and Share," "Tell about my toys," Tell about friends' toys, "Talk Nice," and "Ways to Play." Teachers used scripted lessons and written-text cues to teach specific communication skills, and provided feedback/reinforcement to children. The majority of children in the intervention group learned to communicate with peers during treatment sessions and showed significantly more growth in initiation to peers

in generalization settings, e.g., recess, lunch, than children in the comparison group who did not receive weekly structured social skills instruction. Researchers noted that this result confirms "prior research indicating that social skills interventions for young children generally improve target skills and may promote generalization" (Kamps et al., p. 16).

Based on a review of the literature and evaluation of published research studies in peer-reviewed clinical journals, Magellan considers Social Skills Training (SST) used in the treatment of autism to be an investigational treatment. This determination is based on an evaluation of research findings, e.g., currently insufficient data related to the efficacy of SST compared to other modalities used in the educational setting; very small amount of evidence supporting improvement in clinical/educational outcomes; improvements in health outcomes not established in an investigational setting or outside such a setting; and the need for additional studies with improved design to meet accepted methodological standards for clinical research (Magellan Healthcare, 2012).

There is currently a very small amount of scientific data to support improvement in clinical/education outcomes – i.e., language acquisition, child-initiated joint engagement, mother-child interaction and play. Rigorous scientific research using appropriate empirical designs are in the early stages and just beginning to be published. Despite the widespread clinical use of this educational intervention, the empirical support for SST programs for children with autism is in its infancy (Rao et al., 2008; Kasari et al., 2008). Similarly, future research should incorporate the use of standardized and validated outcome measures in the reporting of SST behavioral changes against other existing alternatives. To date, autism researchers are using a wide variety of SST programs from diverse theoretical foundations, with disparate program designs, differing levels of intensity and variable duration of treatment (Rao et al., 2008).

The adopted AAP *Practice Guideline on the Management of Children With Autism Spectrum Disorders* guideline indicates that the other social skill formats and related modalities, i.e., social skills groups, social stories, visual cueing, social games, video modeling, scripts, peer-mediated techniques and play/leisure curricula, that are used in the field "are supported primarily by descriptive and anecdotal literature, but the quantity and quality of research is increasing" (p. 1166).

Since then, there has been a newly published report of a non-randomized matching group comparison study on the use of a one hour per week group therapy intervention, i.e., cognitive-behavioral and social skills instruction techniques within a stage-based, cognitive-developmental framework, in the treatment of 18 children diagnosed with ASDs (Cotugno, 2009). This study used a pre- and post-test analysis on two subgroups of children (aged 7-8 and 10-11) in order to measure clinical improvements. Results showed that for both the 7-8 and 10-11 year-old intervention groups, teacher ratings on the Walker-McConnell Scale (WMS) showed significant gains as well as improvements in anxiety management, joint attention and flexibility/transitions. The study also evaluated 10 non-ASD children of the same ages, who did not receive the treatment but were attending regular public school classes, in order to obtain normative comparison data on the measurement tools. Researchers noted that further investigation is necessary due to this study's small size, lack of

randomization and comparison against a true, no treatment control group of children diagnosed with ASDs (Cotugno, 2009).

The adopted AAP *Practice Guideline on the Management of Children With Autism Spectrum Disorders* indicates that the therapeutic modality, *Social Stories*™, is supported primarily by descriptive and anecdotal literature, but that the quantity and quality of research is increasing. *Social Stories*™ uses short stories that have been written for an individual with ASD and describe a difficult social situation, skill or a concept and the expected behavior for that situation. The goal of the intervention is to improve social skills/outcomes of children with ASD. Eighteen studies (15 published articles and three dissertations), using a single-subject design with demonstration of the experimental control, were included in a meta-analysis examining the effectiveness of *Social Stories*™ as the sole treatment of children (total n=47) aged 3-15 years with ASD (Kokina and Kern, 2010). Results of the analysis showed questionable outcomes of the intervention which confirmed previous findings. Limitations of the study included very small sample sizes (n $\leq$ 5 in each study) and lack of statistical procedures, e.g., nonparametric tests and arbitrary interpretation of differences in the outcome metrics. Preliminary findings suggest that although Social Stories™ have low to questionable overall effectiveness, it may be more effective when addressing inappropriate behaviors than when teaching social skills (Kokina and Kern, 2010).

Interpersonal Synchrony (IS) is a developmental social curriculum targeting socially synchronous behavior on social outcomes of toddlers (aged 21-33 months) with ASD. The investigative team of Landa et al. conducted this first randomized controlled trial of IS, which was delivered as a supplemental modality to a comprehensive intervention, i.e., 10 hours per week classroom instruction, 1.5 hours/month home-based parent training and 38 hours parent education, designed to evaluate the impact of IS on social outcomes. In this study, toddlers (n=50) with ASD were assigned to one of two interventions: (IS) or Non-Interpersonal Synchrony (non-IS). The interventions were comparable except that the IS group received a supplementary social curriculum targeting joint attention, affect sharing and socially engaged imitation. During the six-month intervention period, toddlers in both groups made improvements in social, cognitive and language skills, particularly within the IS group. The most significant effect of the supplemental intervention in the IS group was found for socially engaged imitation with an increase in imitated acts paired with eye contact after the intervention. This study contributes to a very small body of literature about deficits of social functioning and communication in small children with autism. The researchers indicated a need for further research in this area (Landa et al., 2011).

Social Skills Group Intervention-High Functioning Autism (S.S. GRIN-HFA) is a new social skills intervention developed to provide effective treatments for the social difficulties in children with high functioning ASD. The efficacy of S.S.GRIN-HFA was tested in a study designed to improve social behaviors in children between age 8 years and 12 years with high functioning ASD (DeRosier et al., 2010). Children (n=55) were randomly assigned to the S.S. GRIN-HFA treatment group or to the control group (S.S. GRIN). The original S.S. GRIN program's goal was to build social skills and peer relationships for children who are socially at-risk using combined cognitive-behavioral and social learning techniques. The S.S. GRIN-HFA manualized program preserved elements of the S.S. GRIN treatment and addressed specific social deficits of children with high functioning ASDs. This modality included features such as the progressive

introduction of skills, i.e., communication, working with others and friendship behaviors, with socially relevant goals and structure/ predictability in the group environment. Parents were also involved in the program with their children. Children in the S.S.GRIN-HFA group showed treatment benefits across multiple outcomes, and unexpectedly, children in the S.S.GRIN group showed worsening outcomes in this study. The researchers cautioned that although this study provided evidence for the efficacy of the S.S.GRIN-HFA treatment program for improving the social skills of children with high functioning ASD, this study is limited by the homogeneity of the sample as well as to the small sample size. They concluded that the S.S. GRIN-HFA group intervention, with its active engagement of parents, use of community exercises to promote generalization, and focused social skills training, offers advantages compared to more generic social skills training (DeRosier et al., 2010).

A later replication randomized clinical trial examined the efficacy of a psychosocial treatment including social skills training for children with high-functioning ASD. Children with high functioning ASD, aged 7-12 years (n=35) were randomized to a treatment or wait-list control group. Treatment in group format occurred over five weeks, five days per week, with five 70-minutes cycles of treatment per day. In the first 20 minutes of each 70-minute cycle, participants received social skills instruction which was followed by 50 minutes of practicing and reinforcing social interaction. Both the initial and replication randomized controlled trial supported the efficacy of social skills training, including direct instruction, modeling, role-play rehearsal and repeated practice. The direct child measures as well as parent ratings reflected significant improvements in social performance posttreatment favoring the treatment group (Thoemeer and Lopata, 2012).

Parent-assisted interventions to improve social skills among children with autism include Children's Friendship Training (CFT), which teaches social etiquette and rules of behavior used by the peer group. A randomized controlled study of CFT in children with ASD evaluated the effects of CFT on parent measures including social skills and play date behavior as well as child measures of popularity and loneliness (Frankel et al., 2010). Children with ASD (n=68) from second to fifth grade (regular classrooms) were randomized to the CFT condition or the delayed treatment control group (DTC) during 12 weeks of CFT training. The study's purpose was to test whether children participating in CFT showed greater improvement in social skills than the DTC group and whether the CFT group would maintain improvement after a three-month follow period. Parents of children in the CFT group reported a difference in how children filled their time on play dates after treatment with an increase in social interaction and decrease in electronic media use. Investigators also reported that children maintained more self-control. In addition, children in the CFT group reported decreased feelings of loneliness and increased feelings of popularity. Conversely, teachers did not report a decrease in aggressiveness or withdrawal for the CFT group. Follow-up results (three months post treatment) reported by parents revealed less conflict and disengaged behavior in hosted play dates and less internalizing behavior when compared with baseline. Researchers suggested that parental involvement in the implementation of treatment may have influenced their report. Moreover, only children who were very high-functioning were included in the study and this may limit the results of the study. Teachers did not report significant improvement for the CFT group as a whole in aggression or withdrawal (Frankel et al., 2010).

In another study, Green et al. investigated the efficacy of a parent-mediated, communication- focused treatment (Preschool Autism Communication Trial [PACT]) in a randomized controlled trial conducted in the United Kingdom which included children (n=152) aged 2-4 years and 11 months with ASD. Subjects were assigned to the PACT intervention targeting social interactive and communication impairments in autism while the control group was assigned to treatment as usual. PACT's aim was to increase parental sensitivity and responsiveness to child communication and increase development of the child's communication. The researchers concluded that on the basis of their findings, they could not recommend the addition of the PACT intervention to treatment as usual for the reduction of autism symptoms, but they noted a benefit for parent-child dyadic social communication (Green et al., 2010).

The AAP guideline discusses the significant deficits in social communication that people with ASD possess which require treatment by a speech-language pathologist. The adopted guideline stresses that "traditional, low-intensity, pull-out service delivery models often are ineffective" but they can be improved with the involvement of teachers, support personnel, peers and family (p. 1165). A randomized controlled trial of toddlers (n=62) less than age 21 months were assigned either to the parent-mediated *Hanen's More Than Words* (HMTW) program or to a treatment-as-usual program. In the HMTW treatment group, parents learned strategies to help their toddlers communicate, for example by modeling simple sentences from the child's perspective. Investigators concluded that HMTW did not result in treatment effects on child outcomes after the parent-implemented treatment. However, there were some conditional effects for children, who at the beginning of the study had more limited object interest, and appeared to have benefitted from HMTW (Carter et al., 2011).

Theory of Mind (ToM) training is another type of social skills training sometimes used to improve the social skills of children with ASD by focusing children on the "mastering of social situations" (Begeer et al., 2011). This modality was studied in a randomized, controlled trial, including children (n=40), aged 8-13, with high-functioning ASD. Children were randomized into an intervention group and a waiting list control group. The 16-week ToM treatment trained children on perception, imitation, emotion recognition, pretense, belief and false belief understanding, second order reasoning, and the use of irony and humor. Parents were also actively involved in the training. ToM was ineffective in improving children's social skills although it was effective in improving their conceptual understanding. Investigators suggested that ToM treatment requires further study and may enhance children's self-esteem (Begeer et al., 2011).

The Early Start Denver Model (ESDM)
A recent study prospectively examined evidence for sustained effects of the Early Start Denver Model (ESDM) in children (n = 39) with ASD who participated in a randomized clinical trial where they were assigned to receive ESDM or the community-intervention-as-usual (COM) at aged 18-30 months for two years (Estes et al., 2015). ESDM, a naturalistic behavioral intervention integrating applied behavior analysis methods with developmental approaches and parent coaching, is designed for children as young as age 1 year to promote learning, social reciprocity, and affective engagement. The interventions, conducted in-home by clinicians (20 hours per week) over a period of two years, showed evidence of efficacy immediately posttreatment. In this follow-up study, the children were assessed across multiple domains of

functioning two years after end of the intervention. The two groups received equivalent intervention hours during the original study while the ESDM group received fewer hours during the follow-up period. Gains from ESDM in areas including intellectual ability, adaptive behavior, autism symptoms and challenging behaviors, were maintained two years later. Compared to the COM group, the ESDM group demonstrated less severe overall ASD symptoms, better adaptive behavior and improved socialization ability. Researchers concluded that "early identification and intensive, early, ASD-specific intervention can improve long-term outcomes for children with ASD" (Estes et al., 2015).

The AAP guideline specifies that The Denver Model program is no longer delivered primarily in treatment centers but rather has shifted to service delivery in homes and schools. This particular developmental approach fosters symbolic thought in order to teach the power of communication. The guideline also notes that while studies for this particular intervention have demonstrated improvements for children with autism in such areas as cognition, motor/socials skills and play, there were no controlled clinical trials.

Since the guideline's release, there has been an important published randomized controlled trial where 48 toddlers with ASDs (between age18-30 months) were randomly assigned to either the Early Start Denver Model (ESDM) or to interventions commonly available in the community (Dawson et al., 2010). The ESDM intervention integrates ABA with developmental and relationship-based approaches and was based on a detailed manual and curriculum whereby one or both parents were trained on the techniques. The intensity of the ESDM was two-hour sessions, twice per day, five days/week for two years – averaging 15.2 hours of therapist-guided and 16.3 hours of parent-guided therapy interventions per week. The comparison community intervention averaged 9.1 hours/week of individual therapy and 9.3 hours/week of group interventions tailored to preschoolers (Dawson et al., 2010).

Researchers reported that compared with children who received community intervention, children who received ESDM showed significant improvements in IQ, adaptive behavior and autism diagnosis. Two years after entering treatment, the ESDM group on average improved 17.8 standard score points on IQ, compared with 7.0 points in the comparison group relative to baseline. They also reported that the ESDM group maintained its rate of growth in adaptive behavior compared with a normative sample of typically developing children, whereas the comparison group showed greater delays in adaptive behavior. Additionally, the ESDM children were more likely to experience a change in diagnosis from autism to pervasive developmental disorder not otherwise specified (PPD-NOS), than the comparison group (Dawson et al., 2010).

Dawson et al. later reported data on EEG activity collected in children with ASD who participated in the randomized trial discussed above while they viewed faces (social) and non-social objects. EEG measurements reflected that children who had received ESDM allotted greater attentional and cognitive resources during viewing of the social stimuli (faces) than to the nonsocial stimuli comparable to age-matched typical children and different from children with ASD who received the community intervention. Increased cortical activation occurred in the children who received the ESDM intervention as well as in typically developing children while viewing faces

compared with objects. In the children receiving community intervention, increased cortical activation occurred during viewing of objects compared with faces. Researchers concluded that this trial demonstrated that early behavioral intervention is associated with normalized patterns of brain activity, and improvements in social behavior in young children with ASD (Dawson et al., 2012).

The AACAP practice parameter reports although efficacy has been shown for the Early Start Denver Model as well as the Treatment and Education of Autism and related Communication Handicapped Children Program, disseminating knowledge about effective interventions to educators is a challenge (Volkmar et al., 2014).

The Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) Program
The adopted guideline reports the TEACCH method, also called "structured teaching", which emphasizes "organization of the physical environment, predictable sequence of activities, visual schedules, routines with flexibility, structured work/activity systems, and visually structured activities" (AAP, 2007). The structured teaching is for individuals of all ages and at all developmental levels of ASD, and can be provided in a variety of educational settings. The TEACCH program, considered as an emerging practice for autism, emphasizes a relationship of parents and practitioners working closely together. Making use of structured teaching experiences, the intervention is adapted to the particular characteristics of the individual (Virues-Ortega et al, 2013). In a meta-analysis including 13 studies, of which only two were randomized controlled trials and all included small samples, of individuals with autism (n=172), researchers evaluated the impact of TEACCH on perceptual and motor skills, social behavior, activities of daily living, maladaptive behavior, cognition and language (Virues-Ortega et al, 2013). Three age groups were included in this study: 0-5, 6-17, and ≥18. The results of this analysis suggested that TEACCH results in moderate to large gains in social behavior and maladaptive behavior while effects on perceptual, motor, verbal and cognitive skills are small. Likewise, TEACCH effects on communication, activities of daily living and motor functioning were negligible to small. Across the age groups, results were generally consistent although effects of TEACCH were of less magnitude among young children compared to school-age children. Researchers noted that results should be considered exploratory due to the limited pool of studies in each age group (Virues-Ortega, et al, 2013).

The Picture Exchange Communication System
The adopted guideline notes that the Picture Exchange Communication System (PECS) is a widely used method having scant evidence to support its effectiveness. PECS incorporates both ABA and developmental principles used to teach a child to initiate a picture request of a highly desired item and continue appropriate communication until the other person responds. A published clinical review of some 27 studies by Preston and Carter summarized findings for PECS used in the treatment of autism and found that most studies were single subject or other group designs (Preston and Carter, 2009). Only three studies evaluated in this report were randomized controlled trials. The two trials conducted by Yoder and Stone (2006) that were reviewed compared two treatments (PECS vs. Responsive Education and Prelinguistic Milieu Teaching [RMPT]) but did not have a control arm. While the third trial by Howlin et al. (2007) used random assignment of classes to immediate treatment, delayed treatment or no treatment, these investigators did not provide any information on treatment fidelity.

Moreover, their design focused on the effectiveness of a consultancy technique used to deliver PECS rather than on the efficacy of PECS itself. Therefore, authors cautioned that the nature and quality of data arising from the randomized controlled trials discussed in their review were insufficient to draw firm conclusions about the PECS intervention as a treatment for this population. However, authors suggested that these early findings may provide some preliminary positive data on the ease of learning this modality for use in children with ASDs and other developmental disabilities with little or no functional speech (Preston and Carter, 2009).

The therapeutic efficacy of PECS in the treatment of children with ASD was tested again in a later randomized controlled study when the same sample/design from the aforementioned Yoder study (2006) was used again to compare the intervention with RMPT. Investigators reported results showing support for their hypothesis that PECS can teach children with ASD the generalized means to show coordinated attention to objects and persons without requiring eye contact. Additionally, authors suggested that teaching a generalized picture exchange, "may be one way to help a child begin to use coordinated attention to object and person to communicate" (Yoder and Lieberman, 2010, p. 632).

Another randomized controlled trial by Gordon, et al. (2011) used the same sample from the aforementioned 2007 trial by Howlin. Children with ASD (n=84/73 boys) aged between 4 years and 10 years were studied to answer questions about whether PECS training acted specifically to increase children's spontaneous communication using the picture cards and if its effect supported greater spontaneity using speech as well. Accessing data from three time points and in the three different experimental groups (immediate treatment, delayed treatment and no treatment), the authors found that classroom-based spontaneous communication using picture cards, speech or both increased significantly following PECS training. The improvement in spontaneous communication was only to request objects, such as snacks or toys, but requesting for social routine or commenting did not improve. In addition, researchers found that less severe baseline autism symptomatology and expressive language impairment demonstrated larger increases in improvement (Gordon et al., 2011).

A meta-analysis by Flippin et al. (2010) reviewed current evidence for PECS in affecting communication and speech outcomes for children with ASD. Eleven studies were included in this systematic review, including three group studies (total n=160) and eight single-subject experiments (n=18) to evaluate the quality of the research as well as the effectiveness of the PECS approach. The investigators found that these data provided small to moderate evidence that PECS improved communication skills for children with autism, but the outcomes in speech ability ranged from small gains to negative. Investigators suggested that PECS is a promising evidence-based practice but is not yet established for promoting communication in children with ASD and acknowledged that further studies are needed. It is noteworthy that this meta-analysis included studies with participants who were also diagnosed with pervasive developmental disorder, not otherwise specified, children/adolescents with neurological disorders other than autism, and comorbid physical or neurological diagnoses, e.g., attention-deficit/hyperactivity disorder (Flippin et al., 2010).

The AACAP practice parameter notes children who do not yet use words may receive benefit from the use of alternative communication modalities including PECS and

voice output communication aids, e.g., speech generating devices. It also stated that the focus should be on pragmatic language skills training for individuals who are highly verbal but have impaired pragmatic language skills (Volkmar et al., 2014).

Speech-Generating Device
The speech generating device (SGD), like PECS, is another form of augmentative and alternative communication (AAC) used to address communication deficits in ASD. Individuals with little to no functional speech can activate the SGD via various methods, e.g., keyboard or touch screen, producing electronic voice output through speech synthesis or digitized recordings. Speech production is similar to natural speech production in that the speech is immediately available to the person being addressed, providing additional feedback for the user.

An experimental research study investigated the comparative efficacy of PECS versus a new type of SGD, using digitized speech providing a verbal model of selected picture cards, in the development of requesting skills in children (n=3) aged 4-12 with severe autism (Boesch et al., 2012). The new type of SGD has the added benefit of speech output. Based on results of this study demonstrating increased requesting behavior for all participants when receiving either treatment, researchers suggested that PECS and SGD are equally appropriate for developing initial requesting skills and that successful implementation of either PECS or SGD requires appropriate instructional strategies (Boesch et al., 2012). Another study compared the speed at which children (n=9) with ASD learned manual signs, PECS, and iPad®/iPod®-based SGD as well as whether the children showed a preference for one of these options (Couper, et al., 2014). Results demonstrated that all children learned to request preferred stimuli using either manual signs, picture exchange, or the iPad®/iPod®-based SGD and that most showed a preference for the SGD. Fewer sessions were needed to learn the SGD than the manual signs or picture exchange. Researchers suggested that when learning a preferred option, the technology may be a promising option (Couper et al., 2014).

A larger study examined the effect of adding a SGD to another behavioral-based intervention, i.e., joint-attention and engagement with enhanced milieu training (JAE/EMT), to improve spontaneous, communicative verbal communication in school-aged, minimally verbal children (n=61) with autism (Kasari et al., 2014). The children were randomized to two sessions per week of JAE/EMT or an adaptive intervention, i.e., JAE/EMT + SGD over six months, with a three-month follow-up. Results showed that the gain in socially communicative utterances was significantly higher among children randomly assigned to the augmented condition compared with that of children receiving the behavioral intervention alone. Researchers concluded that school-aged children with minimal verbal abilities can make significant gains rapidly in spoken spontaneous language with an intervention focusing on joint engagement and play skills and incorporating an SGA (Kasari et al., 2014). Dawson notes that "an early behavioral intervention can be very helpful in improving a number of outcomes, including social ability, but despite early intervention, some 20 percent to 30 percent of children do not acquire language, so it's important to modify interventions to teach children how to communicate" (Medscape, 2014). She further suggested that adding the SGA was "really encouraging," noting that it improves communications generally while also helping children learn spoken language.

Computer Assisted Instruction
A recent controlled trial randomized children (n=43), aged 7-12 years, with high functioning ASD (HFASD), to a computer based intervention, i.e., Mind Reading (MR), or to a waitlist control condition (Thomeer et al., 2015). MR, "an interactive software program designed to teach recognition of simple and complex emotions to children with ASD via facial-video and vocal-audio stimuli," was administered in a computer lab during 24 sessions over 12 weeks (Thomeer et al., p. 2121). Outcome measures, e.g., Cambridge Mindreading Face-Voice Battery for Children (CAM-C), Emotion Recognition and Display Survey (ERDS), and Social Responsiveness Scale (SRS), included the assessment of skills directly targeted by the treatment along with ASD features and broader social skills. Results of this intervention including both instruction and reinforcement via computer software indicated that the children completing the treatment performed significantly better on a test of emotion regulation skills for both facial and vocal expressions than children in the control group. Moreover, the gains were maintained at five-week follow-up. Researchers noted that these results "lend support for the efficacy of MR as a promising CBI for children with HFASD" (Thomeer et al., p. 2125). They further suggested that the intervention improved both decoding and encoding skills and reduced ASD symptoms for children with HFASD.

Computer assisted instruction (CAI) is not discussed in the AAP guideline but is becoming more popular for use in children with ASD. After receiving parental consent for inclusion in a study, preschool and K-1 students (n=47) aged 3-6 years with ASD were randomly assigned classrooms to the *TeachTown: Basics* CAI group or to a control group in a study designed to assess the efficacy of CAI in children with autism. Over a period of three months, children in the *TeachTown: Basics* group received computer lessons incorporating principles of ABA with instruction using the discrete trial format (within-stimulus prompting procedure) for approximately 20 minutes per day as well as 20 minutes per day in supplementary off-computer connection activities. Students received reinforcement for correct responses in the form of animated reward games along with verbal praise and graphics. Researchers found that students in the *TeachTown: Basics* group showed more improvement on language and cognitive outcome measures compared to their counterparts in the control group. Investigators suggested that although the findings were not conclusive, they offer future possibilities in the use of CAI for remediating deficits for children with ASD (Whalen et al., 2010).

In a study by Tanaka et al. (2010), children, adolescents, and young adults (n=79) with ASD who were significantly impaired in face processing abilities were randomly assigned to either an active treatment group or to a waitlist control group to determine whether face recognition skills can be enhanced through the *Let's Face It!* (LFI!) computer-based skills battery/games program. Children in the LFI! Intervention group received 20 hours of face training in seven computer games targeting various face processing skills. Researchers found that 20 hours of *Let's Face It!* training improved both analytic, i.e., isolated eye or mouth part, and holistic processing, i.e., whole face recognition, skills of children with ASD. They suggested further research to test the long-term benefits of face training and whether the training transfers to everyday social skills (Tanaka et al., 2010).

In a review of the use of computer-assisted technologies (CAT) to enhance social, communicative and language development in children with ASD, the authors concluded that research has not answered the question of whether CAT has been demonstrated to be more effective than traditional teaching and training methods. They suggested that computer-assisted technologies may be advantageous in helping children gain skills for increased adaptive functioning, but they also noted that poorly designed programs using this technology can socially isolate a child. Authors suggested follow-up controlled trials involving comparisons of the effects of different treatment approaches, i.e., comparison to traditional non-CAT methods (Ploog et al., 2013).

Cognitive Behavioral Therapy (CBT)

The AAP guideline does not address the utility of cognitive behavioral therapy (CBT) as a treatment for co-morbid anxiety disorders and their resultant significant impairment on children with autism. Nevertheless, there has been a clinical review and findings of a randomized clinical trial published on this therapeutic modality employed with these individuals that are noteworthy and warrant attention.

Cognitive Behavioral Therapy for Early Adolescents with ASD and Clinical Anxiety
Past studies have shown that individually administered cognitive behavioral therapy (CBT) programs for treating anxiety in children and youth with ASD have demonstrated significant reductions in anxiety symptoms, improved rating of adaptive skills and reduced ASD symptom severity (Wood et al., 2015). A current study evaluated whether a CBT program, Behavioral Interventions for Anxiety in Children with Autism, adapted to address related adolescent-specific issues would result in the similar improvements. In this study, adolescents (n=33), aged 11-15 years and meeting criteria for both anxiety and ASD, were randomized to immediate treatment (CBT) or waitlist condition in 16 weekly format sessions including basic coping skills, e.g., behavioral activation, cognitive restructuring and in vivo exposure. Other areas, e.g., poor social skills, adaptive skills deficits, focused on fundamental concerns of anxious adolescents with ASD, were addressed. Results of the intervention found improvement in clinician reported anxiety severity as well as parent reported improvement in ASD symptom severity. Researchers noted the increasing recognition that anxiety and ASD symptom severity may be partially interdependent. They suggested that this treatment can be beneficial for early adolescents with ASD and indicated the need for future studies with an active control group, e.g., another form of psychotherapy, to determine specificity of intervention effects (Wood et al., 2015).

In one study, 40 children (7-11 years old) diagnosed with autism, Asperger syndrome or PDD-NOS and either separation anxiety disorder, social phobia or obsessive-compulsive disorder were randomly assigned to 16 sessions of CBT or a three-month wait list (Wood et al., 2008). The CBT model followed a manualized protocol which emphasized behavioral experimentation, parent-training and school consultation. Researchers described using specific interventions such as coping skills training, e.g., affect recognition, cognitive restructuring and exposure principles, followed by in vivo exposure (facing fear situations repeatedly and using coping skills until habituation is learned). The reported results were very encouraging because in the intent-to-treat analysis, 78.5 percent of the CBT group met Clinical Global Impression-Improvement

Scale criteria for positive treatment response at post-treatment, as compared to only 8.7 percent of the wait-list group. Also, CBT outperformed the wait-list on diagnostic outcomes and parents reports of child anxiety, but researchers acknowledged that this did not hold true for children's self-reports of anxiety (Wood et al., 2008).

In a comprehensive clinical psychology review of anxiety in children and adolescents with ASDs, authors also reported on two other randomized clinical trials where children who received CBT showed significant reduction in anxiety symptoms (White et al., 2008). Specifically, a trial by Chalfant et al. (2006) studied 47 school age children, and another trial by Sofronoff, Attwood, and Hinton (2005) evaluated 71 children in the same age range. The latter study also incorporated a child plus parent combined intervention study arm where the parents were trained in all aspects of the intervention and subsequently served as their children's co-therapists. While both intervention groups in the Sofronoff et al. study developed more coping strategies compared to the wait-list group, the combined intervention group developed more coping strategies than the child-only condition (White et al., 2009). Authors argued that findings such as these provide emerging evidence that coexisting anxiety may be effectively managed. Nonetheless, they emphasized that it remains critically important for the clinician to determine if "an anxiety problem represents a true co-morbid condition or if the anxiety is secondary to, or reflective of, the deficits associated directly with the ASDs diagnosis" (White et al., 2009, p. 228).

A randomized controlled study of children (n=50) between age 7 years and 14 years with high-functioning ASD and clinical anxiety were assigned to group CBT or "treatment as usual" (TAU) for 12 weeks (Reaven et al., 2011). Results showed that participants who received the group CBT intervention met diagnostic criteria for a significantly fewer number of anxiety diagnoses post-intervention when compared with the TAU group. Limitations in this study included the small sample, lack of a control group comparable in facilitator time and attention to treatment, and statistical comparisons based on the small number of participants. Investigators stated the need for more research to identify the extent to which observed short-term treatment gains are maintained as children with ASD transition into more complex social and academic environments (Reaven et al., 2011).

A family-based CBT intervention for anxiety in ASD was studied in order to determine its impact on parental perceptions of children's personal daily living skills and related parental intrusiveness (Drahota et al., 2009). In this trial, children with ASD and an anxiety disorder (n=40), aged 7-11, were randomly assigned to either a treatment condition or three-month wait-list condition. Treatment included therapists working with families for 16 weekly sessions (30 minutes with the child and 60 minutes with the family) implementing a CBT program. A manual including coping skills training was used as well as the actual practice of such skills. Researchers suggested that family-based CBT techniques may produce clinically significant improvement in daily living skills among children with ASD and parents may reduce their intrusion in their children's private daily routines. They also indicated the need for future research on daily living skills interventions for ASD to determine if parents and children are able to maintain improvement over a longer period of time, i.e., years, not months, (Drahota et al, 2011).

A meta-analysis including eight randomized controlled trials that involved children and adolescents with high-functioning autism (n=469) systematically reviewed evidence of CBT to treat anxiety in these children. Participants were randomized to CBT, wait list condition, treatment as usual or an attention control condition (social recreation). All participants were allowed to continue ongoing treatments, e.g., psychoeducational services or pharmacotherapy. Parent and clinician ratings showed that CBT was more effective in reducing anxiety than treatment as usual or wait list condition in children with high-functioning ASD. No difference was evidenced between CBT and the social recreation condition using child self-report measure of anxiety. Researchers noted the need for randomized studies with larger samples as well as more studies evaluating CBT for anxiety against attention control conditions (Sukhodolsky et al., 2013).

Other Psychosocial Interventions
The AACAP practice parameter indicates the lack of evidence for most other forms of psychosocial intervention, e.g., auditory integration training, sensory integration therapy and touch therapy/massage (Volkmar et al., 2014). Limited evidence exists for the developmental, social-pragmatic models of intervention, e.g., Developmental-Individual Difference-Relationship Based/Floortime and Relationship Development Intervention (Volkmar et al., 2014; Magellan Healthcare, 2013).

Medical Management – Psychopharmacology

A recent update on pharmacotherapy for ASD in children and adolescents emphasized the need for clinicians to understand current evidence-based pharmacotherapy, risks and benefits, as well as pertinent updates from recent studies in order to guide patients as well as to make well informed decisions (Young et al., 2015). Noting the lack of known efficacious pharmacotherapy for core symptoms of ASD and the limited evidence-based pharmacotherapy options in children with ASD, authors reviewed current evidence-based pharmacotherapy options and updates from recent studies including psychotropic medications prescribed for behavioral/emotional symptoms associated with ASD. They recommended clinicians to weigh the risks and benefits of pharmacotherapy as a part of comprehensive treatment. Highlights from their review follow (Young et al., 2015):

- Antipsychotics – The only two medications approved by the FDA for children with ASD, risperidone and aripiprazole, have been shown to have efficacy in the treatment of aggression, self-injury and severe tantrums in children with ASD. However, regulatory approval limits the use of the medication to patients with problematic irritability and severe problem behavior. Adverse events include weight gain and metabolic changes. Studies have shown that risperidone combined with parent training was more efficacious than medication alone for problem behavior and adaptive functioning. Efficacy in decreasing problem behavior with the use of aripiprazole was comparable to risperidone in a systematic review of clinical data, and aripiprazole had a similar metabolic adverse event profile. Authors suggested more controlled studies of the use of ziprasidone and other newer agents that have less metabolic adverse events are needed.
- Methylphenidate, Atomoxetine, and Alpha-2 Agonists – In children with co-occurring attention deficit hyperactivity disorder (ADHD) and ASD,

methylphenidate has been shown to be effective in improving symptoms of ADHD, although the medication was better tolerated in children with higher cognitive functioning. Atomoxetine and alpha-2 agonists, e.g., guanfacine, have also appeared to be effective in treating ADHD symptoms in children with ASD, especially when combined with parent training.

- Antidepressants – The conclusion of a recent Cochrane review of SSRI trials found no evidence of efficacy of SSRIs in children with ASD and found emerging evidence of harm.
- Antiepileptic Drugs – Studies have shown that valproate may be efficacious in treating irritability in children with ASD while topiramate in combination with risperidone may improve problem behavior. However, authors noted that further studies are necessary to define the efficacy of antiepileptic drugs as monotherapy or in combination with antipsychotics.
- Novel Drugs – In a quest to find a medication that is effective in treating the core symptoms of ASD, recent trials have investigated novel agents, e.g., glutamatergic agents and oxytocin which appear promising although with mixed results. Glutamatergic agents including amantadine, memantine and riluzole, as adjunctive therapy to risperidone, have been shown to improve behavioral measures when compared to risperidone plus placebo. Authors noted that they may be helpful when combined with antipsychotic treatment, but larger trials must replicate earlier results. Studies have also suggested that intranasal oxytocin as an adjunct to behavioral therapy for ASD may be beneficial.
- Future Directions in Pharmacotherapy for ASD – Authors concluded, "Future research investigating genotypic and/or phenotypic characteristics influencing medication response and tolerability will be valuable in further individualizing pharmacotherapy" and "future research utilizing biomarkers such as eye-tracking, electrophysiological measures and/or functional neuroimaging may aid in capturing treatment benefits more accurately" (Young et al., p. 12).

A retrospective observational study examining rates and predictors of psychotropic use and multiclass polypharmacy among children (n=33,565) aged 0-20 years with ASD reported that 64 percent of the children used at least one psychotropic medication while 35 percent had evidence of psychotropic polypharmacy (Spencer et al., 2013). Drug combinations included: antidepressants and ADHD medications; antipsychotics and ADHD medications; antipsychotics and antidepressants; and combinations of antipsychotics, antidepressants, and ADHD medications. The time period over which the study subjects were observed was greater than three years on average and the median length of polypharmacy was almost one year (Spencer et al., 2013). The strongest predictors of psychotropic use and polypharmacy were co-occurring conditions, with seizures, ADHD and bipolar disorder highly associated. Investigators noted that clinicians may not be aware of the extent of the psychotropic use of their patients as many of the children may be seeing multiple providers. They stressed the need for a multidisciplinary approach and standards of care around the prescription of psychotropic medications based on best evidence to improve the health and quality of life of children with ASD and their families (Spencer et al., 2013).

The AACAP Practice Parameter recommends that pharmacotherapy be offered to children with ASD to treat a specific target symptom, e.g., aggression, hyperactivity, inattention, sleep disturbances, or comorbid condition, e.g., anxiety or depression

(Volkmar et al., 2014). The practice parameter recommends that medications be used judiciously and that best evidence must guide the prescribing of these medications. A growing body of controlled evidence for pharmacologic intervention in the treatment of children with ASD is included in the discussion below.

Antipsychotics
In a systematic review of evidence for the use of psychotropic medications in children with ASD, findings from randomized controlled trials (n=33) suggested that only a few medications have obtained a rating of "Established Evidence," and they were all within the antipsychotic class. Aripiprazole and risperidone have evidence for irritability and hyperactivity and aripiprazole also has established evidence for stereotypy. Haloperidol has established evidence for treatment of negative behavioral symptoms (Siegel and Beaulieu, 2012).

The AAP guideline indicates that the Food and Drug Administration (FDA) approved atypical antipsychotic risperidone is now widely used to treat symptomatic irritability, aggressive behavior, deliberate self-injury and temper tantrums in children and adolescents with autism. A current systematic review of published randomized controlled trials of typically prescribed medications, including antipsychotics, reported three trials including children (n=281), age 18 years or younger, with ASD who were randomized to risperidone or placebo. Results demonstrated preliminary evidence for risperidone's efficacy in reducing repetitive behavior and stereotypy and established evidence for its efficacy in the treatment of irritability and hyperactivity in children with ASD (Siegel and Beaulieu, 2012).

In a study of children with ASD (n=32), aged 5-16 years, the contribution of genetic factors to the susceptibility of weight gain in children treated with risperidone was evaluated (Hoekstra et al., 2010). Investigators found that children and adolescents with a variant T allele have some protection against risperidone-induced weight gain. Consequently, researchers suggested genotyping the HTR2C promoter – 759C/T polymorphism when considering treating children and adolescents with risperidone since younger children and those treated with higher doses may be at increased risk for drug induced weight gain. They suggested future studies with larger sample size to further investigate the possible contribution of genetic factors in risperidone-related weight gain and to investigate the effectiveness of weight gain prevention programs in children treated with antipsychotic medications (Hoekstra et al., 2010).

Since publication of the guideline, the FDA also approved an expanded indication for the oral formulation of aripiprazole for treatment of irritability associated with ASDs in children aged 6-17 years in November 2009. This approval was based on positive results for two large eight-week, randomized, placebo-controlled multi-center studies (Owen et al, 2009; Marcus et al, 2009). Recommended starting dose is 2 mg/day, increasing to 5 mg/day, with subsequent increases to 10-15mg/day as needed. The FDA also specified that the efficacy of aripiprazole for the maintenance treatment of autistic irritability has not been evaluated and that patients should be periodically reassessed to determine the need for continued treatment (Waknine, 2009). A further exploratory, post-hoc analysis of data from the aforementioned Owen and Marcus studies also concluded that aripiprazole is efficacious in the treatment of irritability in children and adolescents with ASD, having its most consistent effects on symptoms associated with tantrums (Aman et al., 2010). The long-term safety and tolerability of aripiprazole was studied again by Marcus et al. in children with ASD (n=330), aged 6-

17 years, finding that the drug was generally safe and well tolerated in the long-term treatment of irritability associated with ASD in children. The most commonly reported adverse condition was weight gain requiring proactive monitoring during the long-term use of the drug (Marcus et al., 2011).

The AAP guideline acknowledges that the atypical or second-generation antipsychotic (SGA) drugs aripiprazole, olanzapine, quetiapine and ziprasidone currently are being investigated for use in treating such behaviors as hyperactivity, impulsivity, inattention, aggression and explosive outburst and self-injury.[1] In a published clinical review on the role of antipsychotics in managing behavioral symptoms in autism, the investigative team of Malone and Waheed stressed that these particular agents should be used as an adjunctive treatment to other psychosocial or education interventions. They also found that most SGAs cause weight gain and associated metabolic syndrome, with ziprasidone and aripiprazole appearing to have the lesser risk of metabolic adverse effects. Consequently, the authors recommended regular monitoring of weight, blood pressure, glucose and lipids in patients with autism being treated with these drugs (Malone et al., 2009). More recently, a small (n=11) open-label clinical trial of low-dose quetiapine (50-150 mg/day) showed effectiveness in reducing aggression and improving sleep quality in high-functioning adolescents with high-functioning ASD and prominent aggressive behavior. Investigators attempted to minimize adverse effects of quetiapine – e.g., excessive sedation and weight gain, and recommended additional large-scale, double-blind, placebo controlled studies with long-term follow-up as necessary before widespread adaptation to practice (Golubchik et al., 2011). In a systematic review of psychotropic medications in children with ASD, Siegel and Beaulieu cautioned that due to the high frequency of weight gain in studies of olanzapine in treating children with ASD, olanzapine should not be a first-line agent at this time (Siegel and Beaulieu, 2012).

Other published evidence from systematic reviews of randomized controlled trials have shown that risperidone, methylphenidate, tianeptine (a selective serotonin enhancer available in Europe), clonidine and naltrexone have produced significant results in reducing aggression or self-injury in children with autism. Authors indicated that these positive findings were particularly noteworthy for risperidone and methylphenidate since they were replicated across at least two studies (Parikh et al., 2008).

In a published review of antipsychotic treatment of autism, Posey et al. note that with the widespread use of SGA agents, the use of conventional antipsychotics, like haloperidol, became and continue to become less frequent, although prior randomized controlled trials have shown that they too are efficacious in young children with autism.[14] Researchers have suggested that more controlled studies are needed to assess efficacy of both classes of agents on a short- and long-term basis along with head-to-head comparison studies of antipsychotics in order to address differences and safety profiles in treating this population (Malone et al., 2009).

Most of the clinical studies on the use of conventional antipsychotics occurred in the decade spanning 1965-1975. These studies were well-designed controlled studies of haloperidol in doses of 1 to 2 mg/day, where the drug was found to be more efficacious than placebo for withdrawal, stereotypy, hyperactivity, affective lability, anger and temper outbursts (Posey et al., 2008; McDougle et al., 2002). Posey concluded that while multiple studies found haloperidol efficacious for improving a

variety of behavioral symptoms in young children with autism, there was less robust evidence for the efficacy of other conventional antipsychotics. Posey also concluded that since haloperidol treatment frequently leads to acute dystonic reactions, withdrawal dyskinesias and tardive dyskinesia, this high risk of extrapyramidal symptoms has limited the use of these medications to only the most treatment-refractory patients.

Antidepressants
The AAP guideline indicates that current clinical trial data support the use of SSRIs for target symptoms, i.e., repetitive behaviors, irritability, depressive symptoms, tantrums, anxiety, aggression, difficulty with transitions and aspects of social interaction and language, and in coexisting psychiatric disorders or the depressive phenotype. Since publication of the guideline, a large randomized clinical trial of 149 participants with ASDs was conducted comparing citalopram against placebo for the treatment of repetitive behaviors (King et al., 2009). The research team found that citalopram was not an effective treatment for these children with moderate or greater repetitive behavior. Results also showed that citalopram use was more likely to be associated with adverse events, e.g., increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia and dry skin or pruritus. This study team and others have highlighted the urgent need for more well-designed studies of medications commonly used in this population in order to determine whether the risks of the drugs substantially outweigh their benefit (King et al., 2009; Volkmar, 2009).

The adopted guideline also mentions the use of the tetracyclic antidepressant, mirtazapine, as a possible agent to treat symptoms of anxiety or depression citing one open label trial for this particular drug. Another small study (n=10) was conducted in order to evaluate the efficacy of mirtazapine in the treatment of excessive masturbation and other inappropriate sexual behaviors in individuals with a diagnosis of autistic disorder with ages ranging from 5-16 years. Researchers noted that they chose mirtazapine for its previously reported antilibidinal effects and noted very encouraging results for this serious problem that often interferes with the social and educational activities considered vital in this population (Coskun et al., 2009).

Although the FDA has approved certain SSRIs for some children in the treatment of clinical indications that may co-occur with autism, such as obsessive-compulsive disorder (OCD) and depression, SSRIs have not been specifically approved for treatment of autism in children. A systematic review was performed by Williams et al. in order to evaluate the effectiveness and safety of three SSRIs: fluoxetine, fluvoxamine, and citalopram and one serotonin releasing agent (SRA), fenfluramine (not available in the U.S.) in treating the "core features" of ASD, i.e., social interaction, communication stereotypy or restricted, repetitive patterns of behavior, interest or activities, in children. The investigators selected seven randomized controlled trials (total n=271) for their review which showed no evidence that SSRIs are effective as a treatment for children with autism. Limitations of the study included lack of medium- and long-term follow-up (maximum duration was 12 weeks). In addition, there were no trials of sertraline, paroxetine or escitalopram although these SSRIs are used in clinical practice to treat problems associated with ASD. Study authors recommended replication of the citalopram study and at least one other SSRI, fluoxetine, because of its favorable safety profile (Williams et al., 2010).

An updated Williams et al. study (2013) included nine randomized controlled trials (n=320) for a review evaluating the effectiveness and safety of four SSRIs, i.e., fluoxetine, fluvoxamine, fenfluramine and citalopram, in the treatment of ASD (Williams et al., 2013). Five of the studies included only children. Findings showed no evidence that SSRIs are an effective treatment of ASD in children and showed emerging evidence of harm from side effects. No trials evaluated sertraline, paroxetine or escitalopram. Researchers advised that although SSRIs are not supported by evidence to treat ASD in children, decisions about their use for clinical indications that may co-occur with ASD, e.g., obsessive-compulsive disorder and depression, should be based on the individual case (Williams et al., 2013).

Anticonvulsant Mood Stabilizers
Anticonvulsant mood stabilizers are suggested in the adopted AAP guideline to treat either the target symptom cluster of aggression, explosive outbursts and self-injury or behaviors associated with a bipolar phenotype, i.e., behavioral cycling with rages and euphoria, decreased need for sleep, manic-like hyperactivity, irritability, aggression, self-injury or sexual behaviors. A double-blind, placebo controlled trial (n=27) examined the effect of divalproex sodium compared to placebo in the treatment of children with ASD, children aged 5-17 years. Efficacy was evaluated using the CGI-I Scale and the Irritability Subscale of the Aberrant Behavior Checklist. Results of the study suggested that divalproex sodium may be effective in treating irritability in ASD in that 62.5 percent of divalproex subjects versus 9 percent of placebo subjects were responders. Researchers suggested the small sample size as a limitation of their study and noted that a larger follow-up is warranted (Hollander et al., 2010).

Another agent in the anticonvulsant class, topiramate, was used as an adjuvant to risperidone in the treatment of children with ASD and studied in an eight-week, double-blind, placebo-controlled trial (Rezaei et al., 2010). The study (n=40) showed that treatment of children, aged 4-12, with topiramate augmentation of risperidone resulted in a significantly greater reduction in irritability compared with placebo plus risperidone. Topiramate was not found to induce cognitive difficulties in children and adolescents as reported in an earlier study of its use in bipolar disorder in this population. Investigators suggested that a slow titration of topiramate minimized the risk of cognitive difficulties. Researchers suggested that a limitation of the study is its small size where results of this study should be confirmed in larger randomized controlled trials (Rezaei et al., 2010).

In a later published meta-analysis including results of seven randomized, placebo controlled trials of antiepileptic drugs (AEDs), i.e., valproate, lamotrigine, levetiracetam and tomiramate, for treatment in children with ASD (n=171), researchers found AEDs were not significantly more effective than placebo in reducing irritability/agitation or in global improvement (Hirota et al., 2014). Researchers concluded that AEDs appear to lack a large effect size to treat behavioral symptoms in ASD although further studies are needed involving patients with epileptiform abnormalities.

Cognitive/Memory Enhancers
Since publication of the AAP guideline, there has been much interest in studying off-label uses for memantine (1-amino-3, 5-dimethyladamanantate), a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease and currently

under study as an agent that targets "the imbalance between excitatory and inhibitory signaling suspected to be part of the basis of autism" (Webb, 2010). There have been five open label trials conducted for the indication of pervasive developmental disorder identified in a published systematic review (Zdanys et al., 2008). Authors purported that memantine may be efficacious in the treatment of other conditions resulting from underlying glutamatergic dysfunction. These preliminary studies were encouraging since all reported positive findings and improvements in a range of behaviors – e.g., memory, behavioral change, irritability, lethargy, stereotypy, self-stimulatory stereotypy, hyperactivity and inappropriate speech for patients with autistic disorder, Asperger's disorder and PDD-NOS (Zdanys et al., 2008). Other clinical trials are currently underway to study the effect of memantine in children with ASD. Subjects (n=60) aged 6-12, who are verbal, will be randomized to memantine or placebo for six months in this trial. These children will be assessed for memory function, expressive language output and motor skills/praxis at staged intervals while the drug's efficacy and safety will be examined (U.S. National Institutes of Health, 2012).

In a review of literature regarding the pharmacology of memantine and potential benefits for treatment in children, Hosenbocus and Chahal reported a ten-week, randomized double-blind, placebo-controlled study of memantine as an adjunctive treatment to risperidone in children (n=40), aged 4-12 years, with ASD. Children were randomized to risperidone plus memantine or risperidone plus placebo with the dose of risperidone and memantine titrated up to 3 mg/d and 20 mg/d respectively. The group receiving risperidone plus memantine reported significant improvement in irritability, stereotypic behavior and hyperactivity than the group receiving risperidone plus placebo. This study demonstrated memantine to be a potential adjunctive treatment for autism in children. Authors concluded that although memantine has demonstrated beneficial effects in treatment ASD symptoms, the evidence is limited and further studies are needed (Hosenbocus and Chahal, 2013).

Another cognitive enhancing drug, donepezil, a cholinesterase inhibitor, has been of interest as a possible treatment for cognitive functioning deficits in ASD. A ten-week, double-blind, placebo-controlled trial was conducted to assess the tolerability, safety, and efficacy of donepezil on executive functioning deficits in a sample of children and adolescents (n=34), aged 8-17, with ASD (Handen et al., 2011). Subjects who received either the placebo or donepezil tended to improve, and differences between the groups were not statistically significant. Researchers suggested that cognitive enhancers, like donepezil, may be more effective in younger children with ASD. In addition, investigators reported that few subjects displayed global deficits in cognitive functioning at baseline, making improvement after treatment more difficult to obtain. Researchers concluded that donepezil may have limited impact on cognitive functioning in ASD (Handen et al., 2011).

Medical Management – Other Drugs and Treatments

Along with addressing challenging behaviors, the AAP guideline also provides the evidence basis for medical management strategies for the unique needs of children with autistic disorders to include seizures, gastrointestinal problems and sleep disturbances. In the discussion of sleep disturbances, it notes that there is little empirical information available on the pharmacological management of this problem and acknowledges the need for well-designed studies on its treatment. Since

publication of the guideline, there has been one important randomized placebo-controlled crossover trial of melatonin on sleep problems for children with ASD and fragile X syndrome. Findings from this trial supported the efficacy and tolerability of melatonin (3 mg.) and resulted in longer sleep duration, shorter sleep-onset latency and earlier sleep-onset time for melatonin than placebo (Wirojanan et al. 2009).

Other more recent evidence comes from a double-blind, randomized, controlled crossover trial including children with ASD and severe dyssomnias (Wright et al., 2011). Children (n=22) received either three months of placebo or melatonin (maximum dose of 10 mg). The results of this study showed that melatonin significantly improved sleep latency and total sleep compared to placebo, but did not improve the number of night awakenings (Wright et al., 2011). A 2011 systematic review of thirty-five studies investigating melatonin-related findings in ASD identified five studies that used a randomized double-blind, placebo-controlled design. A meta-analysis performed on these five studies of melatonin treatment in children with ASD (total n=57) found that the use of the drug improved sleep duration and sleep onset latency while having minimal to no side effects. However, these studies were limited by small sample sizes and variability in the protocols measuring changes in sleep parameters, and investigators recommended additional studies of melatonin to confirm and expand these findings (Rossignol and Frye, 2011). In addition, an open-label dose-escalation study involving 24 children with ASD assessed the effects of melatonin for sleep latency in children with autism, contributing to the growing literature on melatonin for insomnia in ASD. This study found that melatonin improved sleep latency in the first week of treatment and over several months. Improvement in behavior and parenting stress was also noted. Researchers also emphasized the need for a large randomized trial in this population (Malow, 2011).

Researchers carried out a later open-label dose escalation study of supplemental melatonin to evaluate its possible therapeutic effectiveness for sleep in children with ASD (Malow et al., 2012). Children (n=24), aged 3-10, with ASD who experienced sleep onset delay of 30 minutes or more on three or more nights per week (reported by parents) were administered supplemental melatonin after a week of structured sleep education followed by a two-week acclimation phase (inert liquid administered before bedtime). Melatonin was then administered according to an optional escalating dose protocol, based on five three-week periods to determine lowest possible dose that was well tolerated as well as effective. A majority of participants had improved sleep latency within the first week of dosing at a 1 mg or 3 mg dose administered 30 minutes before bedtime; however, there was no significant improvement in sleep duration or night wakings as measured by actigraphy. Researchers suggested large randomized controlled trials are needed to establish the impact of melatonin on sleep duration and night wakings (Malow et al., 2012).

 The AAP guideline does not address hyperbaric treatment and its potential role in treating these disorders. Since release of the guideline, the first multi-center, randomized, double-blind controlled study of hyperbaric treatment was conducted on 62 children with autism aged 2-17 years. The research compared 40 hourly treatments of either hyperbaric treatment at 1.3 atmosphere (atm) and 24 percent oxygen against the control condition of slightly pressurized room air at 1.03 atm and 21 percent oxygen. The published findings indicated that children with autism who received the hyperbaric treatment had significant improvements in overall functioning,

receptive language, social interaction, eye contact and sensory/cognitive awareness compared to children who received slightly pressurized air (Rossignol et al., 2009). However, later studies have questioned the use of the Autism Treatment Evaluation Checklist (ATEC) which was used in Rossignol's 2009 study, stating that is has not been validated in the scientific community and researchers point to conflicting results in the study (Jepson et al, 2011). Another research team evaluated the effects of hyperbaric oxygen therapy on a wide variety of behaviors, i.e., adaptive behavior, stereotypy and aberrant behavior, at the level of the individual participant, using a single-subject design. The evaluation was replicated across a sample of participants including 16 children with ASD. Results of this study showed no evidence suggesting that hyperbaric oxygen therapy, delivered at 24 percent oxygen and 1.3 ATA is effective in treating the behavior symptoms of autism (Jepson et al., 2011).

In August 2013, the FDA issued a consumer health information notification for consumers informing them that hyperbaric oxygen therapy (HBOT) has not been clinically shown to be effective in the treatment of autism and has not been cleared or approved by FDA. The agency warned consumers that the use of HBOT may cause them to forgo or delay proven medical therapies. Risks of using HBOT may include sinus pain, ear pressure, painful joints, paralysis and air embolism. The FDA also warned of the risk of fire, advising patients to discuss all possible options with their health care professional (FDA, 2013).

In a double-blind, randomized, placebo-controlled trial children aged 3-11 years with ASD (n=54) were randomized to receive either bumetanide or placebo. The aim of the study was to test the adverse effects of long-term treatment on child behavior as well as the therapeutic actions of bumetanide. Findings showed that bumetanide reduced the severity of the symptoms as measured on the Childhood Autism Rating Scale (CARS) with only a small hypokalaemia in 30 percent of the children who were provided potassium supplements. Researchers suggested bumetanide as a promising novel therapeutic approach to treat ASD children although it does not cure autism. They suggested larger trials to determine best dosage (Lemonnier et al., 2012).

Magellan's adopted guideline provides a significant amount of information on both biological and non-biological complementary and alternative medical therapies (CAM) used to treat ASDs and emphasizes that their usage in this population is quite high. Moreover, the guideline urges physicians to become knowledgeable about CAM therapies in order to assist families in evaluating the scientific merits of such interventions. The AACAP practice parameter recommends that clinicians be knowledgeable about the use of alternative/complementary treatments in order to discuss these treatments with parents who may be motivated to seek all possible treatments (Volkmar et al., 2014). The AACAP notes that "in most instances, these treatments have little or no proved benefit but also have little risk" (Volkmar et al., 2014, P 252). Treatments for which the practice parameter indicates have little or no proved benefit include intravenous infusion of secretin, oral vitamin B6 and magnesium, a gluten-free, casein-free diet, fatty acids and oral human immunoglobulin.
The adopted guideline indicates that there have been both positive and negative findings from small, methodologically flawed studies of intravenous immunoglobulin. A newer, large (n=125), double-blind, placebo-controlled trial of *oral* human immunoglobulin (IGOH 140, 420 or 840 mg./day for 12 weeks) for gastrointestinal

dysfunction in children with autistic disorder revealed no significant differences compared to placebo and across treatment groups in global improvement, number of daily bowel movements, days of constipation or severity of problems (Handen et al., 2009).

The AAP guideline also notes that there is a paucity of evidence on the efficacy of omega-3 fatty acids for this population but suggests a trend on their superiority over placebo for hyperactivity. This was not substantiated in a newly published systematic review of one randomized controlled trial, four uncontrolled studies and one case report examining the value of omega-3 fatty acids for the treatment of ASD where insufficient evidence was found on both its safety and efficacy (Bent et al. 2009).

Despite its popularity and widespread usage, the AAP guideline does not address acupuncture in the treatment of ASD. In a double-blind, randomized, controlled trial, children aged 3-18 years with ASD (n=55) were randomly assigned either to an electro-acupuncture group or a sham electro-acupuncture group where they received treatment during 12 sessions over four weeks. In addition to the significant improvements in language comprehension and self-care ability, the group receiving electro-acupuncture also showed better social initiation, receptive language, motor skills, coordination and attention span. Side effects of acupuncture treatment included minor superficial bleeding or irritability during acupuncture treatment. Researchers noted that there have been few randomized, controlled trials studying the efficacy and safety of electro-acupuncture in ASD and suggested further studies to increase the knowledge base in this field (Wong et al., 2010). Another study utilizing a single-blind randomized design compared tongue acupuncture versus sham acupuncture in children aged 3-11 (n=50) with ASD. The study consisted of 40 sessions over eight weeks. Children were randomly assigned either to a treatment group with tongue acupuncture or the control group (sham acupuncture). In this study, both the treatment group and the control group participants showed improvement in assessed measures including developmental, behavioral, language and mental age. Participants in the treatment group however, also showed significant improvement in self-care and cognition domains as compared to the control group. The authors noted the need for further exploration of the long-term efficacy of acupuncture treatment in ASD as well as an increased understanding of the significant "placebo effect" seen in the sham comparison (Wong and Sun, 2010).

Qigong Sensory Training (QST) is the application of qigong massage, a branch of traditional Chinese medicine utilizing massage. The QST Home Program, a training and support program for parents of children with autism, was designed and its efficacy was evaluated against a wait-list control group in a pilot study using a randomized control group design (Silva et al, 2011). The QST Home Program consists of daily, parent- mediated massage, including a sequence of 12 patting, shaking, or pressing movements, delivered to their preschool children over a period of five months. Children with ASD (n=47), aged 3-6 years, were randomly assigned to one of two groups: intervention group (28 children) and wait-list control group (19 children). Their parents received group QST training in how to deliver Qigong massage to their children. Results showed that parents learned how to give the treatment correctly and to incorporate it into daily routine of the family. The QST Home Program demonstrated improvement in measures of autism (medium effect sizes) and self-regulatory responses (large effect size) for children with less severe pathology (and their

correspondingly less stressed parents) by providing an intervention for autism that can be delivered at home (Silva et al., 2011).

The AAP guideline includes music therapy as an example of non-biological CAM that has shown some short-term benefit on communication skills but not on behavior problems of children with ASDs. Since publication of the guideline, a study by Lim (2010) explored how the perception and production of speech in children with ASD may be impacted by the perception of organized musical patterns, and examined the effect of music as part of developmental speech language training for this population. In this study, children (n=50) aged 3-5 years were assigned to one of three groups: music, speech or control (no-intervention). Training consisted of two sessions per day for three days; music training involved watching a 9-minute music video and speech training required listening to an almost 6-minute speech video. Findings suggested enhanced speech production in both music and speech training compared to the no-training condition. Greater improvement was found for music training than speech training in low functioning participants (Lim, 2010). A review of 20 small experimental studies provided only limited evidence to support the effectiveness of music as an intervention with children with ASD (Simpson and Keen, 2011). Music interventions reported in the studies included improvisational music therapy and the use of composed song, with both techniques demonstrating some support for the use of music to facilitate target skills in communication and socialization. Authors suggested that future studies are needed to investigate the types of interventions and the training required to implement them.

Auditory integration training (AIT) is included in the examples of CAM in the AAP guideline for which the most recent and most appropriately designed trials have demonstrated no significant benefit. Based on a review of the literature, Sinha et al. concluded that there is no evidence to support the use of AIT, i.e., Tomatis sound therapy, Somonas therapy, or other sound therapies as treatment for ASD. The authors reviewed six randomized controlled trials of AIT and one of Tomatis therapy, involving a total of 182 individuals aged 3-39 with ASD. Five trials had less than 20 participants. Authors reported that studies were relatively small, measured different outcomes and reported mixed results. Results in some studies did not reach statistical significance and some results were of questionable validity. The team of investigators concluded that "given the lack of evidence of AIT or other sound therapies are effective as a treatment for autism, future research is discouraged." In addition, authors concluded that AIT "must be considered experimental and care must be taken not to risk hearing loss. Parents need to be aware of the cost involved in pursuing these treatments" (Sinha et al., 2011).

Sensorimotor enrichment was investigated as a treatment for autism in a randomized controlled trial including children aged 3-12 (n=28) with autism (Lee and Leon, 2013). Children were randomized to either a sensorimotor group receiving daily olfactory/tactile stimulation/classical music or to a control group. Members of both groups continued receiving standard treatment, e.g., ABA, throughout the six month trial period. The study found that children receiving the in-home sensorimotor enrichment therapy improved significantly in both symptom severity and cognition compared to controls. Researchers concluded that environmental enrichment may be effective in ameliorating some of the symptoms of autism in children and suggested future studies to determine whether the improvements are long-lasting and whether

beginning the enrichment therapy at an earlier age, i.e., 18-months, would further enhance its efficacy (Woo and Leon, 2013).

Relationship Development Intervention (RDI) is a "cognitive-developmental" parent training program with a goal to impact "experience sharing" in autistic individuals. Parents function as facilitators for their children's mental development through guided interactions in daily activities to improve the child's critical emotional, social and "metacognitive abilities" (Magellan Healthcare, 2013). Only one small study has been published using a one group pretest-posttest design and it did not offer convincing evidence that the treatment was the sole reason for changes in patient outcomes measures. The AACAP practice parameter notes that there is limited evidence for developmental, social-pragmatic models of intervention, e.g., Developmental-Individual Difference-Relationship Based/Floortime, Relationship Development Intervention, Social Communication Emotional Regulation and Transactional Support, and Play and Languate for Autistic Youths (Volkmar et al., 2014).

Exercise Interventions/Physical Activity

While the AAP guideline discusses various educational/behavioral interventions that may focus on play and leisure skills in children with autism, it does not directly address the need for exercise interventions and their role in an overall treatment program. The effects of exercise interventions on stereotypic behaviors in children with ASDs were studied in a published systematic review (Petrus et al., 2008). The authors noted that although physical exercise is included in many regular school programs, it is not routinely used in children with autism. Petrus et al. speculated that aerobic exercise may physiologically modulate stereotypic behaviors through the release of neurotransmitters or simply through physical exertion and increased fatigue. Their review evaluated seven studies, where children's ages ranged from aged 4-15 years, and the methods of exercise used were either jogging or hydrotherapy. In their analysis, researchers rated the quality and rigor of the evidence as ranging from weak to moderately strong. Nonetheless, their findings did suggest that exercise produced short-term decreases in stereotypic behaviors and that higher-intensity exercise may be more effective than lower-intensity activity in decreasing self-stimulation (Petrus et al., 2009).

A later study found that aerobic exercise prior to classroom activities may improve academic responding in young children (n=24) aged 3-6 years with ASD. In this study, two of four classrooms were assigned randomly to the treatment condition and two to the control condition for the first three weeks. Each classroom received the opposite condition in the following three weeks. Children in the treatment condition ran or jogged for 15 minutes before a classroom task whereas those in the control condition did not do any aerobic exercise before participating in a classroom task. This study found statistically significant improvements in academic responding following the aerobic exercise and this improvement continued for 30 minutes following aerobic exercise. There was, however, no significant decrease in on-task behavior or stereotypic behaviors following exercise (Oriel et al, 2011).

Healthcare Effectiveness Data and Information Set (HEDIS)
Measure: Follow-Up after Hospitalization for Mental Illness (FUH)

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). The HEDIS measure that includes autism spectrum disorder diagnoses is Follow-Up after Hospitalization for Mental Illness (FUH). This measure, like almost all HEDIS measures, focuses on processes, rather than on outcome measures. Children age 6 years and older with ASD 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.

Obtaining Copies of the American Academy of Pediatrics (AAP) Guideline

Copies of the *Practice Guideline for the Management of Children With Autism Spectrum Disorders* may be obtained through the AAP at http://pediatrics.aappublications.org/content/120/5/1162.full.pdf or by obtaining this article as published in *Pediatrics* 2007: 120; 1162-1182. (doi:10.1542/peds.2007-2362).

Copies of the companion document to the guideline, *Clinical Report – Identification and Evaluation of Children With Autism Spectrum Disorders*, may be obtained through the AAP at http://pediatrics.aappublications.org/cgi/reprint/120/5/1183 or by obtaining this article as published in *Pediatrics* 2007: 120; 1183-1215.

Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. We take all suggestions and recommendations into consideration in our ongoing review of the guidelines. Comments may be submitted to:

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