



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

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Table of Contents

Purpose of This Document.....	3
Introduction.....	3
Additional Recommendations Based on Recent Literature Review.....	3
Educational Interventions	4
Cognitive Behavioral Therapy (CBT)	6
Medical Management – Psychopharmacology.....	7
Medical Management – Other Drugs and Treatments.....	9
Exercise Interventions/Physical Activity	10
Obtaining Copies of the American Academy of Pediatrics (AAP) Guideline.....	11
Provider Feedback	11
References	12

Purpose of This Document

This document is an introduction to Magellan Health Services' (Magellan) adopted clinical practice guideline (CPG) for the treatment of children with an autistic spectrum disorder. As with all CPGs, this 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.

Introduction

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

- ***Practice Guideline for the Management of Children With Autism Spectrum Disorders*** developed by the American Academy of Pediatrics (AAP) at <http://www.pediatrics.org/cgi/content/full/120/5/1162> and as published in *Pediatrics* 2007; 120; 1162-1182. (doi:10.1542/peds.2007-2362) ¹
- 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 as published in *Pediatrics* 2007; 120; 1183-1215. 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 autism. 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.

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 autism spectrum disorders through May 2008. This guideline update is based on literature through March 2010. 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.

Educational Interventions

Applied Behavior Analysis

Based on an extensive 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 investigational treatment. This determination is based on an evaluation of the research findings where the evidence did not support ABA's effect on health outcomes, its safety and efficacy against existing alternative treatments, and its ability to demonstrate that benefits outweigh the risks.³

Only recently have controlled trials on ABA been published. Two of these studies are randomized controlled study designs.^{4,5,6,7,8,9,10} 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.¹¹ To date, most of the published literature on ABA involves studies that have several methodological problems, including lack of a clear definition of the ABA treatment and its protocols (e.g., many studies refer to using the Lovaas method manual and video), lack of control groups using established treatment alternatives, poorly chosen or poorly specified samples, outcomes measured only in limited areas (e.g., IQ), and outcome measures giving little information regarding the totality of the treatment impact. Use of a battery of assessments, both specific and global, is needed to give a comprehensive and detailed picture of treatment effects.^{11,12} Additionally, most research on ABA programs has focused on preschoolers with autistic spectrum disorders and therefore research on comprehensive programs for older children and adults with autism is needed.

In addition to the limited research evidence on efficacy, there are other limitations to the use of ABA treatments in children with autism:^{11,12,13}

- ABA is very intense and intrusive in its format and delivery. Stressful reactions by the recipient of the procedure need to be carefully monitored. Sensitive and knowledgeable interventionists are essential in observing adverse outcomes.
- “Setting results” may occur with autistic individuals responding to stimuli in one environment, but unable to generalize learning to other contexts. Great care needs to be taken in selecting natural environments for instruction in order to promote skills in real world situations.
- The use of a single treatment may not be advisable – given the spectrum of difficulties, range of abilities, age of the child, culture of the family and characteristics of the patient.

Social Skills Training

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 the research

findings where the evidence did not support SST's effect on health outcomes, its safety and efficacy against existing alternative treatments; and its ability to demonstrate that benefits outweigh the risks. (Magellan, 2009)

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 (ages 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 Denver Model

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 one important published randomized controlled trial where 48 toddlers with ASDs (between 18-30 months of age) 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 pre-schoolers (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)

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 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 who have little or no functional speech. (Preston and Carter, 2009)

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. 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 3-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 posttreatment, 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)

Medical Management – Psychopharmacology

Antipsychotics

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.¹ 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 ages 6-17 years in November 2009. This approval was based on positive results for two large 8-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)

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 more recent 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)

Other more recently 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.^{14,15} Posey concludes 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 concludes 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.¹⁴

Along with other studies comparing SGAs to placebo in the treatment of autism, in 2001 Malone et al. conducted an open-label trial of 12 children with autistic disorders who were randomly assigned to treatment with either olanzapine or haloperidol for six weeks following a one-week period with no treatment.¹⁶ The children studied ranged in age from 4.9 to 11.8 years. The primary outcome measure used was the Clinical Global Impressions Improvement (CGI-I) scale; secondary measure was the Children's Psychiatric Rating Scale (CPRS) with four factors (autism, anger/uncooperativeness, hyperactivity and speech deviance).¹⁶

Researchers found no significant difference in CGI-I scores between the two treatment groups. For CGI-Severity of Illness (CGI-S) scores, both treatments resulted in non-significant improvement from baseline. Both olanzapine and haloperidol were associated with significant improvement from baseline in CPRS autism factor scores (hyperactivity, anger/uncooperativeness). No significant effect of treatment was seen for CPRS speech deviance factor. Drowsiness and weight gain were the most common adverse events reported, with patients given olanzapine reporting a higher weight gain compared with those who received haloperidol.^{16,17}

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 (i.e., 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. More recently, 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)

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. 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)

Medical Management – Other Drugs and Treatments

Along with 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)

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 ages 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)

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 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 (IGH 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)

Our 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)

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 4-15 years old, 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)

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://www.pediatrics.org/cgi/content/full/120/5/1162> 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. Questions or comments may be submitted via mail or e-mail to:

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