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CLINICAL REPORT

Management of Children With Autism Spectrum Disorders

Guidance for the Clinician in Rendering Pediatric Care

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ABSTRACT

Pediatricians have an important role not only in early recognition and evaluation of autism spectrum disorders but also in chronic management of these disorders. The primary goals of treatment are to maximize the child's ultimate functional independence and quality of life by minimizing the core autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. To assist pediatricians in educating families and guiding them toward empirically supported interventions for their children, this report reviews the educational strategies and associated therapies that are the primary treatments for children with autism spectrum disorders. Optimization of health care is likely to have a positive effect on habilitative progress, functional outcome, and quality of life; therefore, important issues, such as management of associated medical problems, pharmacologic and nonpharmacologic intervention for challenging behaviors or coexisting mental health conditions, and use of complementary and alternative medical treatments, are also addressed.

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words
autism, autism spectrum disorders, Asperger syndrome, pervasive developmental disorders, complementary and alternative medicine, early intervention

Abbreviations
ASD—autism spectrum disorder
TEACCH—Treatment and Education of Autistic and Related Communication Handicapped Children
ABA—applied behavior analysis
DTT—discrete trial training
DIR—developmental, individual-difference, relationship-based
RDI—relationship-development intervention
RT—responsive teaching
SI—sensory integration
EEG—electroencephalography
SSRI—selective serotonin-reuptake inhibitor
CAM—complementary and alternative medicine

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INTRODUCTION

The term autism spectrum disorders (ASDs) has been used to include the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*[1] diagnostic categories autistic disorder, Asperger disorder, and pervasive developmental disorder–not otherwise specified.[2] Recent estimates of the prevalence of ASDs are in the range of 6.5 to 6.6 per 1000, and pediatricians, therefore, are likely to care for children and adolescents with these diagnoses.[3–5] In the companion document to this clinical report,[2] the American Academy of Pediatrics has summarized pertinent background information on ASDs and emphasized the importance of surveillance and screening as well as other potential physician roles in the diagnostic process. However, the role of the primary health care professional extends beyond recognizing signs of ASDs, referring for diagnostic evaluation, conducting an etiologic investigation, providing genetic counseling, and educating caregivers about ASDs and includes ongoing care and management.

ASDs, similar to other neurodevelopmental disabilities, are generally not "curable," and chronic management is required. Although outcomes are variable and specific behavioral characteristics change over time, most children with ASDs remain within the spectrum as adults and, regardless of their intellectual functioning, continue to experience problems with independent living, employment, social relationships, and mental health.[6–8] The primary goals of treatment are to minimize the core features and associated deficits, maximize functional indepen-

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dence and quality of life, and alleviate family distress. Facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families can help accomplish these goals. Ideally, interventions should help mitigate the core features of ASDs, which include impairment in social reciprocity, deficits in communication, and restricted, repetitive behavioral repertoire.

Educational interventions, including behavioral strategies and habilitative therapies, are the cornerstones of management of ASDs. These interventions address communication, social skills, daily-living skills, play and leisure skills, academic achievement, and maladaptive behaviors.

Optimization of medical care is also likely to have a positive impact on habilitative progress and quality of life. In addition to routine preventive care and treatment of acute illnesses, management of sleep dysfunction, coexisting challenging behaviors or psychiatric conditions, and associated medical problems, such as seizures, may be particularly important. Medications have not been proven to correct the core deficits of ASDs and are not the primary treatment. However, associated maladaptive behaviors or psychiatric comorbidities may interfere with educational progress, socialization, health or safety, and quality of life. These behaviors may be amenable to psychopharmacologic intervention or, in some cases, treatment of underlying medical conditions that are causing or exacerbating the behaviors. Effective medical management may allow a child with an ASD to benefit more optimally from educational interventions.

EDUCATIONAL INTERVENTIONS

Education has been defined as the fostering of acquisition of skills and knowledge to assist a child to develop independence and personal responsibility; it encompasses not only academic learning but also socialization, adaptive skills, communication, amelioration of interfering behaviors, and generalization of abilities across multiple environments.[9] Physicians and other clinicians are often in a position to guide families to empirically supported practices and help them evaluate the appropriateness of the educational services that are being offered.

Comprehensive Programs for Young Children

In the last 2 decades, research and program development in the area of educational intervention have focused largely on very young children with ASDs because of earlier identification and evidence that early intensive intervention may result in substantially better outcomes.[9,10] Model early childhood educational programs for children with ASDs have been described in thorough reviews.[9,11,12] These model programs are often categorized as behavior analytic, developmental, or structured teaching on the basis of the primary philosophical orientation. Although the approaches have important differences, they also overlap. For example, contemporary comprehensive behavioral curricula borrow from developmental or cognitive approaches (such as addressing joint attention, reciprocal imitation, symbolic play, and theory of mind and using indirect language stimulation and contingent imitation techniques), and some developmental models (eg, the Denver model) and the structured teaching approach of the Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) program use behavioral techniques to fulfill their curriculum goals.[10,13]

Although programs may differ in philosophy and relative emphasis on particular strategies, they share many common goals, and there is a growing consensus that important principles and components of effective early childhood intervention for children with ASDs include the following[9,10,14–16]:

- entry into intervention as soon as an ASD diagnosis is seriously considered rather than deferring until a definitive diagnosis is made;
- provision of intensive intervention, with active engagement of the child at least 25 hours per week, 12 months per year, in systematically planned, developmentally appropriate educational activities designed to address identified objectives;
- low student-to-teacher ratio to allow sufficient amounts of 1-on-1 time and small-group instruction to meet specific individualized goals;
- inclusion of a family component (including parent training as indicated);
- promotion of opportunities for interaction with typically developing peers to the extent that these opportunities are helpful in addressing specified educational goals;
- ongoing measurement and documentation of the individual child's progress toward educational objectives, resulting in adjustments in programming when indicated;
- incorporation of a high degree of structure through elements such as predictable routine, visual activity schedules, and clear physical boundaries to minimize distractions;
- implementation of strategies to apply learned skills to new environments and situations (generalization) and to maintain functional use of these skills; and
- use of assessment-based curricula that address:
  - functional, spontaneous communication;
  - social skills, including joint attention, imitation, reciprocal interaction, initiation, and self-management;

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- functional adaptive skills that prepare the child for increased responsibility and independence;
- reduction of disruptive or maladaptive behavior by using empirically supported strategies, including functional assessment;
- cognitive skills, such as symbolic play and perspective taking; and
- traditional readiness skills and academic skills as developmentally indicated.

Specific Strategies

A variety of specific methodologies are used in educational programs for children with ASDs. Detailed reviews of intervention strategies to enhance communication,[9,17–20] teach social skills,[21–24] and reduce interfering maladaptive behaviors[21,25,26] have been published in recent years. Brief descriptions of selected methodologies are provided below.

Applied Behavior Analysis

Applied behavior analysis (ABA) is the process of applying interventions that are based on the principles of learning derived from experimental psychology research to systematically change behavior and to demonstrate that the interventions used are responsible for the observable improvement in behavior. ABA methods are used to increase and maintain desirable adaptive behaviors, reduce interfering maladaptive behaviors or narrow the conditions under which they occur, teach new skills, and generalize behaviors to new environments or situations. ABA focuses on the reliable measurement and objective evaluation of observable behavior within relevant settings including the home, school, and community. The effectiveness of ABA-based intervention in ASDs has been well documented through 5 decades of research by using single-subject methodology[21,25,27,28] and in controlled studies of comprehensive early intensive behavioral intervention programs in university and community settings.[29–40] Children who receive early intensive behavioral treatment have been shown to make substantial, sustained gains in IQ, language, academic performance, and adaptive behavior as well as some measures of social behavior, and their outcomes have been significantly better than those of children in control groups.[31–40]

Highly structured comprehensive early intervention programs for children with ASDs, such as the Young Autism Project developed by Lovaas[35,41] at the University of California Los Angeles, rely heavily on discrete trial training (DTT) methodology, but this is only one of many techniques used within the realm of ABA. DTT methods are useful in establishing learning readiness by teaching foundation skills such as attention, compliance, imitation, and discrimination learning, as well as a variety of other skills. However, DTT has been criticized because of problems with generalization of learned behaviors to spontaneous use in natural environments and because the highly structured teaching environment is not representative of natural adult-child interactions. Traditional ABA techniques have been modified to address these issues. Naturalistic behavioral interventions, such as incidental teaching and natural language paradigm/pivotal response training, may enhance generalization of skills.[13]

Functional behavior analysis, or functional assessment, is an important aspect of behaviorally based treatment of unwanted behaviors. Most problem behaviors serve an adaptive function of some type and are reinforced by their consequences, such as attainment of (1) adult attention, (2) a desired object, activity, or sensation, or (3) escape from an undesired situation or demand. Functional assessment is a rigorous, empirically based method of gathering information that can be used to maximize the effectiveness and efficiency of behavioral support interventions.[42] It includes formulating a clear description of the problem behavior (including frequency and intensity); identifying the antecedents, consequences, and other environmental factors that maintain the behavior; developing hypotheses that specify the motivating function of the behavior; and collecting direct observational data to test the hypothesis. Functional analysis also is useful in identifying antecedents and consequences that are associated with increased frequency of desirable behaviors so that they can be used to evoke new adaptive behaviors.

Structured Teaching

The TEACCH method, developed by Schopler and colleagues,[43] emphasizes structure and has come to be called "structured teaching." Important elements of structured teaching include organization of the physical environment, predictable sequence of activities, visual schedules, routines with flexibility, structured work/activity systems, and visually structured activities.[43] There is an emphasis on both improving skills of individuals with ASDs and modifying the environment to accommodate their deficits. Several reports have documented progress in children who have received TEACCH services as well as parent satisfaction and improvement in parent teaching skills, but these reports were not from controlled studies of treatment outcomes.[44–49] In a controlled trial, Ozonoff and Cathcart[50] found that children treated with a TEACCH-based home program for 4 months in addition to their local day treatment programs improved significantly more than children in the control group who received local day treatment services only.

Developmental Models

Developmental models are based on use of developmental theory to organize hypotheses regarding the fundamental nature of ASDs and design approaches to address

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the deficits. The Denver model, for example, is based largely on remediating key deficits in imitation, emotion sharing, theory of mind, and social perception by using play, interpersonal relationships, and activities to foster symbolic thought and teach the power of communication.[12] This program has shifted from a center-based treatment unit to service delivery in homes and inclusive school environments. Several studies have demonstrated improvements in cognitive, motor, play, and social skills beyond what would be expected on the basis of initial developmental rates in children who are treated according to the Denver model, but controlled trials are lacking.[51–54]

Relationship-focused early intervention models include Greenspan and Wieder's developmental, individual-difference, relationship-based (DIR) model,[55] Gutstein and Sheely's relationship-development intervention (RDI),[56] and the responsive-teaching (RT) curriculum developed by Mahoney et al.[57,58] The DIR approach focuses on (1) "floor-time" play sessions and other strategies that are purported to enhance relationships and emotional and social interactions to facilitate emotional and cognitive growth and development and (2) therapies to remediate "biologically based processing capacities," such as auditory processing and language, motor planning and sequencing, sensory modulation, and visual-spatial processing. Published evidence of the efficacy of the DIR model is limited to an unblinded review of case records (with significant methodologic flaws, including inadequate documentation of the intervention, comparison to a suboptimal control group, and lack of documentation of treatment integrity and how outcomes were assessed by informal procedures[55]) and a descriptive follow-up study of a small subset (8%) of the original group of patients.[59] RDI focuses on activities that elicit interactive behaviors with the goal of engaging the child in a social relationship so that he or she discovers the value of positive interpersonal activity and becomes more motivated to learn the skills necessary to sustain these relationships.[56] Some reviewers have praised the face validity of this model, which targets the core impairment in social reciprocity. However, the evidence of efficacy of RDI is anecdotal; published empirical scientific research is lacking at this time. One study reported beneficial effects of RT on young children with ASDs or other developmental disabilities.[58] Parents were taught to use RT strategies to encourage their children to acquire and use pivotal developmental behaviors (attention, persistence, interest, initiation, cooperation, joint attention, and affect). Children in both groups improved significantly on nonstandardized play-based measures of cognition and communication and standardized parent ratings of socioemotional functioning. Although a control group was lacking and the potential role of concurrent educational services was unclear, the improvements were beyond what the authors expected from maturational factors alone.[58]

Speech and Language Therapy

A variety of approaches have been reported to be effective in producing gains in communication skills in children with ASDs.[9,17,20] Didactic and naturalistic behavioral methodologies (eg, DTT, verbal behavior, natural language paradigm, pivotal response training, milieu teaching) have been studied most thoroughly, but there is also some empirical support for developmental-pragmatic approaches (eg, Social Communication Emotional Regulation Transactional Support, Denver model, RDI, Hanen model).

People with ASDs have deficits in social communication, and treatment by a speech-language pathologist usually is appropriate. Most children with ASDs can develop useful speech, and chronologic age, lack of typical prerequisite skills, failure to benefit from previous language intervention, and lack of discrepancy between language and IQ scores should not exclude a child from receiving speech-language services.[60] However, traditional, low-intensity pull-out service delivery models often are ineffective, and speech-language pathologists are likely to be most effective when they train and work in close collaboration with teachers, support personnel, families, and the child's peers to promote functional communication in natural settings throughout the day.[60]

The use of augmentative and alternative communication modalities, including gestures, sign language, and picture communication programs, often is effective in enhancing communication.[17,20,61] The Picture Exchange Communication System (PECS)[62,63] is used widely. The PECS method incorporates ABA and developmental-pragmatic principles, and the child is taught to initiate a picture request and persist with the communication until the partner responds. Some nonverbal people with ASDs may benefit from the use of voice-output communication aids, but published evidence for these aids is scant.[20,64] Introduction of augmentative and alternative communication systems to nonverbal children with ASDs does not keep them from learning to talk, and there is some evidence that they may be more stimulated to learn speech if they already understand something about symbolic communication.[61,62,65]

Social Skills Instruction

There is some objective evidence to support traditional and newer naturalistic behavioral strategies and other approaches to teaching social skills.[22–24,66–68] Joint attention training may be especially beneficial in young, preverbal children with ASDs, because joint attention behaviors precede and predict social language development.[69,70] A recent randomized, controlled trial demonstrated that joint attention and symbolic play skills can be taught and that these skills generalize to different

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settings and people.[71] Families can facilitate joint attention and other reciprocal social interaction experiences throughout the day in the child's regular activities. Examples of these techniques are described in the American Academy of Pediatrics parent booklet "*Understanding Autism Spectrum Disorders*."[72]

A social skills curriculum should target responding to the social overtures of other children and adults, initiating social behavior, minimizing stereotyped perseverative behavior while using a flexible and varied repertoire of responses, and self-managing new and established skills.[10] Social skills groups, social stories, visual cueing, social games, video modeling, scripts, peer-mediated techniques, and play and leisure curricula are supported primarily by descriptive and anecdotal literature, but the quantity and quality of research is increasing.[10,15,73] A number of social skills curricula and guidelines are available for use in school programs and at home.[10,66,74,75]

Occupational Therapy and Sensory Integration Therapy

Traditional occupational therapy often is provided to promote development of self-care skills (eg, dressing, manipulating fasteners, using utensils, personal hygiene) and academic skills (eg, cutting with scissors, writing). Occupational therapists also may assist in promoting development of play skills, modifying classroom materials and routines to improve attention and organization, and providing prevocational training. However, research regarding the efficacy of occupational therapy in ASDs is lacking. Sensory integration (SI) therapy often is used alone or as part of a broader program of occupational therapy for children with ASDs. The goal of SI therapy is not to teach specific skills or behaviors but to remediate deficits in neurologic processing and integration of sensory information to allow the child to interact with the environment in a more adaptive fashion. Unusual sensory responses are common in children with ASDs, but there is not good evidence that these symptoms differentiate ASDs from other developmental disorders, and the efficacy of SI therapy has not been demonstrated objectively.[76–78] Available studies are plagued by methodologic limitations, but proponents of SI note that higher-quality SI research is forthcoming.[79] "Sensory" activities may be helpful as part of an overall program that uses desired sensory experiences to calm the child, reinforce a desired behavior, or help with transitions between activities.

Comparative Efficacy of Educational Interventions for Young Children

All treatments, including educational interventions, should be based on sound theoretical constructs, rigorous methodologies, and empirical studies of efficacy.[15] Proponents of behavior analytic approaches have been the most active in using scientific methods to evaluate their work, and most studies of comprehensive treatment programs that meet minimal scientific standards involve treatment of preschoolers using behavioral approaches.[16,38] However, there is still a need for additional research, including large controlled studies with randomization and assessment of treatment fidelity. Empirical scientific support for developmental models and other interventions is more limited, and well-controlled systematic studies of efficacy are needed.

Most educational programs available to young children with ASDs are based in their communities, and often, an "eclectic" treatment approach is used, which draws on a combination of methods including applied behavior analytic methods such as DTT; structured teaching procedures; speech-language therapy, with or without picture communication or related augmentative or alternative communication strategies; SI therapy; and typical preschool activities. Three studies that compared intensive ABA programs (25–40 hours/week) to equally intensive eclectic approaches have suggested that ABA programs were significantly more effective.[31,32,34] Another study that involved children with ASDs and global developmental delay/mental retardation retrospectively compared a less intensive ABA program (mean: 12 hours) to a comparably intensive eclectic approach and found statistically significant but clinically modest outcomes that favored those in the ABA group.[33] Although the groups of children were similar on key dependent measures before treatment began, these studies were limited because of parent-determined rather than random assignment to treatment group. Additional studies to evaluate and compare educational treatment approaches are warranted.

Programs for Older Children and Adolescents

Some model programs provide programming throughout childhood and into adulthood.[11] More commonly, the focus of specialized programs is on early childhood, and published research evaluating comprehensive educational programs for older children and adolescents with ASDs is lacking. However, there is empirical support for the use of certain educational strategies, particularly those that are based on ABA, across all age groups to increase and maintain desirable adaptive behaviors, reduce interfering maladaptive behaviors or narrow the conditions under which they occur, teach new skills, and generalize behaviors to new environments or situations.[13,21,28]

When children with ASDs move beyond preschool and early elementary programs, educational intervention continues to involve assessment of existing skills, formulation of individualized goals and objectives, selection and implementation of appropriate intervention strategies and supports, assessment of progress, and adaptation of teaching strategies as necessary to enable students to acquire target skills. The focus on achieving social communication competence, emotional and be-

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havioral regulation, and functional adaptive skills necessary for independence continues. Educational programs should be individualized to address the specific impairments and needed supports while capitalizing on the child's assets rather than being based on a particular diagnostic label.

Specific goals and objectives and the supports that are required to achieve them are listed in a child's individualized education plan and should be the driving force behind decisions regarding the most appropriate, least restrictive classroom placement. Appropriate settings may range from self-contained special education classrooms to full inclusion in regular classrooms. Often, a mix of specialized and inclusive experience is appropriate. Even highly functioning students with ASDs often require accommodations and other supports such as provision of explicit directions, modification of classroom and homework assignments, organizational supports, access to a computer and word-processing software for writing tasks, and social communication skills training. When a paraprofessional aide is assigned, it is important that there be an infrastructure of expertise and support for the child beyond the immediate presence of the aide.[80] The specific duties of the aide should be outlined, the strategies to be used should be defined, and the aide should receive adequate training.

In adolescence, the term "transition" is used to describe the movement from child-centered activities to adult-oriented activities. The major transitions are from the school environment to the workplace and from home to community living. In schools, transition-planning activities may begin at as early as 14 years of age, and by 16 years of age, the individualized education plan should include an individualized transition plan. The emphasis may shift from academic to vocational services and from remediating deficits to fostering abilities. A vocational assessment is often conducted to evaluate the adolescent's interests and strengths and to determine the services and supports needed to promote independence in the workplace and in the community. Comprehensive transition planning involves the student, parents, teachers, the medical home, and representatives from all concerned community agencies. Depending on the individual's cognitive level, social skills, health condition, work habits, and behavioral challenges, preparation for competitive, supported, or sheltered employment is targeted. Regardless of the type of employment, attention to skill development should never stop. Skills necessary for independent living should be taught to the degree possible given the abilities of the person. Sexuality education instruction should be included, and there is a growing body of literature that has addressed the topic.[81–83]

MEDICAL MANAGEMENT

Children with ASDs have the same basic health care needs as children without disabilities and benefit from the same health-promotion and disease-prevention activities, including immunizations. In addition, they may have unique health care needs that relate to underlying etiologic conditions, such as fragile X syndrome or tuberous sclerosis, or to other conditions, such as epilepsy, that often are associated with ASDs. Those with pica or persistent mouthing of fingers or objects should be monitored for elevated blood lead concentrations, particularly if the history suggests potential for environmental exposure.[84] These health care needs are most appropriately met within the context of a medical home.[85,86]

To deliver appropriate and effective medical care, the history, approach to the patient, physical evaluation, and treatment options must be considered in the context of the patient's ASD.[87,88] Familiarizing the patient with the office setting and staff, allowing ample time while talking before touching the patient, allowing the child to manipulate instruments and materials, keeping instructions simple, using visual cues and supports, slowing down the pace, exaggerating social cues, and having family and/or familiar staff available may be helpful in reducing the obstacles to health care provision presented by patients' difficulties with social interaction, communication, and accepting novelty.[88] Often, more time is required for outpatient appointments. In a nationally representative sample, it was found that children with ASDs spent twice as much time with the physician per outpatient visit compared with children in control groups.[89]

Associated Morbidity and Mortality

Health care utilization and costs are substantially higher for children and adolescents with ASDs compared with children without ASDs,[89–91] and available data suggest that mortality is increased as well (standardized mortality ratio: 2.4–2.6).[92,93] The increased mortality in ASDs is thought to be largely, but not completely, accounted for by the increased mortality associated with mental retardation and epilepsy. Cases of suicide in higher-functioning individuals have been reported.[6]

Seizures

The reported prevalence of epilepsy among people with ASDs ranges from 11% to 39%.[94] Comorbid severe global developmental delay/mental retardation and motor deficits are associated with a high prevalence of seizures (42%),[95] whereas the prevalence of seizures is only 6% to 8% in children with ASDs without severe mental retardation, a motor deficit, an associated etiologic medical disorder, or a positive family history of epilepsy.[95,96] The prevalence of epilepsy also was higher in studies that included adolescents and young adults, because the onset of epilepsy in ASDs has 2 peaks: 1 before 5 years of age and another in adolescence.[97] Anticonvulsant treatment in children with ASDs is based on the same criteria that are used for other children with

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epilepsy, including accurate diagnosis of the particular seizure type.[98]

Epileptiform abnormalities on electroencephalography (EEG) are common in children with ASDs, with reported frequencies ranging from 10% to 72%.[99] Some studies have suggested that epileptiform abnormalities on EEG[100] and/or epilepsy[101] are more common in the subgroup of children with ASDs who have a history of regression, whereas other studies have not demonstrated this association.[102,103] Autistic regression with epileptiform abnormalities on EEG has been compared by analogy with Landau-Kleffner syndrome and electrical status epilepticus in sleep, but there are important differences between these conditions, and the treatment implications are unclear.[94,104] Whether subclinical seizures have adverse effects on language, cognition, and behavior is debated, and there is no evidence-based recommendation for the treatment of children with ASDs and epileptiform abnormalities on EEG, with or without regression.[104] Universal screening of patients with ASDs by EEG in the absence of a clinical indication is not currently supported.[2,99] However, because of the increased prevalence of seizures in this population, a high index of clinical suspicion should be maintained, and EEG should be considered when there are clinical spells that might represent seizures.

Gastrointestinal Problems

The relationship between gastrointestinal problems and ASDs is unclear, because most studies have not examined representative groups of children with ASDs compared with appropriate controls.[105,106] Surveys published in the gastroenterology literature have stated that gastrointestinal problems, such as chronic constipation or diarrhea, occur in 46% to 85% of children with ASDs.[107–109] Lower rates in the range of 17% to 24% have been reported in other population-based studies,[110–112] and a nested case-control study in the United Kingdom found that only 9% of children with ASDs and the same percentage of controls had a history of gastrointestinal complaints.[113] However, in a recent cross-sectional study that used structured interviews and matched control groups, a lifetime history of gastrointestinal symptoms (including abnormal stool pattern, frequent constipation, frequent vomiting, and frequent abdominal pain) was elicited in 70% of the children with ASDs, compared with 42% of the children with other developmental disabilities ($P = .03$) and 28% of the children without developmental disabilities ($P < .001$).[114]

In children with ASDs undergoing endoscopy, who may or may not be representative of the general population of children with ASDs, high rates of lymphoid nodular hyperplasia and, often, histologically subtle esophagitis, gastritis, duodenitis, and colitis have been described, and preliminary evidence suggests that some immunohistochemical features may be unique to inflammation associated with ASDs.[105,115,116] The existing literature does not support routine specialized gastroenterological testing for asymptomatic children with ASDs.[105] However, if a child with an ASD presents with symptoms such as chronic or recurrent abdominal pain, vomiting, diarrhea, or constipation, it is reasonable to evaluate the gastrointestinal tract. Occult gastrointestinal discomfort also should be considered in a child who presents with a change in behavior, such as outbursts of aggression or self-injury. Radiographic evidence of constipation has been found to be more common in children with ASDs than in controls with abdominal pain (36% vs 10%),[117] and effective management may provide global benefit.

Sleep Disturbance

Sleep problems are common in children and adolescents with ASDs at all levels of cognitive functioning.[118–122] Sleep problems correlate with family distress and may have significant effects on daytime functioning and quality of life of children with ASDs.[123–125] In some cases, there may be an identifiable etiology such as obstructive sleep apnea or gastroesophageal reflux; assessment and treatment are guided by history and physical examination. When there is not an identifiable medical cause, behavioral interventions including sleep-hygiene measures, restriction of daytime sleep, positive bedtime routines, and extinction procedures often are effective.[118,126–129]

Relatively little empirical information is available regarding pharmacologic management of sleep problems in children with ASDs or other developmental disabilities. Recommendations typically are based on case reports and open-label trials, extrapolation from the adult literature, and expert consensus (Table 1).[128] There is some evidence of abnormality of melatonin regulation in children with ASDs,[125,130] and melatonin may be effective for improving sleep onset in children with ASDs as well as children with other developmental disabilities[131–134] and otherwise healthy children with sleep/wake disorders.[135] A recent open-label study suggested that controlled-release melatonin improved sleep in a group of 25 children with ASDs and that treatment gains were maintained at 1- and 2-year follow-up,[136] but randomized, double-blind, placebo-controlled studies are needed. Recently, a child and a young adult with ASDs with significant insomnia were reported to have responded well, with no apparent adverse effects, to open-label treatment with the high-affinity melatonin receptor agonist ramelteon.[137] Antihistamines, α_2-agonists, benzodiazepines, chloral hydrate, trazodone, and newer nonbenzodiazepine hypnotic agents, such as zolpidem and zaleplon, sometimes are used to treat pediatric insomnia.[128] In some cases, other conditions or symptoms, such as epilepsy, depression, anxiety, or aggressive outbursts, warrant pharmacologic treatment, and an agent that also may assist with sleep can be chosen.[118]

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TABLE 1 **Selected Potential Medication Options for Common Target Symptoms or Coexisting Diagnoses in Children With ASDs**

Target Symptom Cluster	Potential Coexisting Diagnoses	Selected Medication Considerations	Selected References
Repetitive behavior, behavioral rigidity, obsessive-compulsive symptoms	Obsessive-compulsive disorder, stereotypic movement disorder	SSRIs (fluoxetine,[a] fluvoxamine,[a] citalopram, escitalopram, paroxetine, sertraline)	McDougle et al,[158,b] Buchsbaum et al,[180,b] Sugie et al,[159,b] Hollander et al,[157,b] Moore et al,[160,c] Namerow et al,[181,d] Owley et al[182,d]
		Atypical antipsychotic agents (risperidone,[a] aripiprazole, olanzapine, quetiapine, ziprasidone)	McDougle et al[164,b]
		Valproic acid[a]	Hollander et al[183,b]
Hyperactivity, impulsivity, inattention	Attention-deficit/hyperactivity disorder	Stimulants (methylphenidate,[a] dextroamphetamine, mixed amphetamine salts)	Quintana et al,[168,b] Handen et al,[169,b] RUPP Autism Network[170,b]
		α_2-agonists (clonidine,[a] guanfacine)	Fankhauser et al,[172,b] Jaselskis et al,[173,b] Posey et al,[175,d] Scahill et al (RUPP Autism Network)[174,d]
		Atomoxetine[a]	Arnold et al,[178,b] Jou et al,[176,d] Posey et al[177,d]
		Atypical antipsychotic agents (risperidone,[a] aripiprazole, olanzapine,[a] quetiapine, ziprasidone)	McCracken et al,[162,b] Arnold et al,[163,b] Shea et al,[165,b] RUPP Autism Network,[166,b] Troost et al[167,d]
Aggression, explosive outbursts, self-injury	Intermittent explosive disorder	Atypical antipsychotic agents (risperidone,[a] aripiprazole, olanzapine, quetiapine, ziprasidone)	McCracken et al,[162,b] Arnold et al,[163,b] Shea et al,[165,b] RUPP Autism Network,[166,b] Troost et al[167,d]
		α_2-agonists (clonidine,[a] guanfacine)	Fankhauser et al,[172,b] Jaselskis et al,[173,b] Posey et al[175,d]
		Anticonvulsant mood stabilizers (levetiracetam, topiramate, valproic acid)	Hollander et al[184,d], Rugino and Samsock[185,d], Hardan et al[186,d], Myers[148,c], Myers and Challman[149,c]
		SSRIs (fluoxetine,[a] fluvoxamine,[a] citalopram, escitalopram, paroxetine, sertraline)	McDougle et al,[158,b] Moore et al,[160,c] Namerow et al,[181,d] Owley et al[182,d]
		β-blockers (propranolol, nadolol, metoprolol, pindolol)	Connor et al,[187,d] Ratey et al,[188,d] Myers and Challman[149,c]
Sleep dysfunction	Circadian rhythm sleep disorder, dyssomnia–not otherwise specified	Melatonin	Giannotti et al,[136,d] Jan and Freeman,[131,c] Phillips and Appleton,[133,c] Turk,[134,c] Owens et al[128,c]
		Ramelteon	Stigler et al[137,e]
		Antihistamines (diphenhydramine, hydroxyzine)	Reed and Findling,[189,c] Owens et al[128,c]
		α_2-agonists (clonidine, guanfacine)	Mehta et al,[190,d] Ingrassia and Turk,[191,d] Posey et al,[175,d] Owens et al[128,c]
		Mirtazapine	Posey et al[192,d]
Anxiety	Generalized anxiety disorder, anxiety disorder–not otherwise specified	SSRIs (fluoxetine,[a] fluvoxamine,[a] citalopram, escitalopram, paroxetine, sertraline)	McDougle et al,[158,b] Buchsbaum et al,[180,b] Sugie et al,[159,b] Hollander et al,[157,b] Moore et al,[160,c] Namerow et al,[181,d] Owley et al[182,d]
		Buspirone	Buitelaar et al[193,d]
		Mirtazapine	Posey et al[192,d]
Depressive phenotype (marked change from baseline including symptoms such as social withdrawal, irritability, sadness or crying spells, decreased energy, anorexia, weight loss, sleep dysfunction)	Major depressive disorder, depressive disorder–not otherwise specified	SSRIs (fluoxetine,[a] fluvoxamine,[a] citalopram, escitalopram, paroxetine, sertraline)	McDougle et al,[158,b] Moore et al,[160,c] Namerow et al,[181,d] Owley et al[182,d]
		Mirtazapine	Posey et al[192,d]

Evaluation of Challenging Behaviors

Problematic emotional reactions and behaviors such as aggression and self-injury are common in children and adolescents with ASDs. In some cases, medical factors may cause or exacerbate maladaptive behaviors, and recognition and treatment of medical conditions may eliminate the need for psychopharmacologic agents. For example, in the case of an acute onset or exacerbation of aggressive or self-injurious behavior, a source of pain or discomfort may be identified and treated.[138] Sources of discomfort may include otitis media, otitis externa, pharyngitis, sinusitis, dental abscess, constipation, urinary

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TABLE 1 **Continued**

Target Symptom Cluster	Potential Coexisting Diagnoses	Selected Medication Considerations	Selected References
Bipolar phenotype (behavioral cycling with rages and euphoria, decreased need for sleep, manic-like hyperactivity, irritability, aggression, self-injury, sexual behaviors)	Bipolar I disorder, bipolar disorder–not otherwise specified	Anticonvulsant mood stabilizers (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproic acid)	Kowatch and DelBello,[194,c] Myers and Challman[149,c]
		Atypical antipsychotic agents (risperidone, aripiprazole, olanzapine, quetiapine, ziprasidone)	Cheng-Shannon et al,[195,c] Kowatch and DelBello,[194,c] Myers,[148,c] Myers and Challman[149,c]
		Lithium	DeLong,[196,e] Kerbeshian et al,[197,e] Steingard and Biederman,[198,e] Myers,[148,c] Myers and Challman[149,c]

RUPP indicates Research Units on Pediatric Psychopharmacology.
[a] At least 1 published double-blind, placebo-controlled trial supports use in patients with an ASD.
[b] Double-blind, placebo-controlled trial.
[c] Review article.
[d] Open-label trial or retrospective chart study.
[e] Case report.

tract infection, fracture, headache, esophagitis, gastritis, colitis, allergic rhinitis, and others. When behavioral deterioration is temporally related to menstrual cycles in an adolescent female,[139] use of an analgesic or oral or injectable contraceptive may be helpful. Obstructive sleep apnea may contribute to behavioral deterioration and may be amenable to weight reduction, tonsillectomy and adenoidectomy, or continuous positive airway pressure.[140] Extreme food selectivity has the potential to lead to protein-calorie malnutrition or specific vitamin or mineral deficiencies; however, most studies that evaluated nutritional status in children with ASDs have suggested that despite dietary selectivity, malnutrition is uncommon.[105,141] Although the prevalence in children with ASDs is unknown, pica related to iron or zinc deficiency may respond to supplementation with the appropriate mineral. It should be noted that it is not clear how frequently medical factors cause or exacerbate serious maladaptive behaviors in children with ASDs, and the efficacy of these interventions is based on anecdotes, case reports, and conventional clinical practice rather than empirical support from clinical trials.

It is also important to consider environmental factors that may precipitate challenging behaviors. Parents, teachers, or other caregivers may inadvertently reinforce maladaptive behaviors, and in such cases, the most appropriate and effective interventions are behavioral. In some instances, a mismatch between educational or behavioral expectations and cognitive ability of the child is responsible for disruptive behavior (eg, when the diagnosis of mental retardation has not been recognized), and adjustment of expectations is the most appropriate intervention. In both situations, a functional analysis of behavior, completed by a behavior specialist in the settings in which the problems occur, will identify factors in the environment that exacerbate or maintain the problematic behavior. A strategy for intervention through behavioral techniques and environmental manipulations can then be formulated and tested.

Psychopharmacology

Pharmacologic interventions may be considered for maladaptive behaviors such as aggression, self-injurious behavior, repetitive behaviors (eg, perseveration, obsessions, compulsions, and stereotypic movements), sleep disturbance, mood lability, irritability, anxiety, hyperactivity, inattention, destructive behavior, or other disruptive behaviors. After treatable medical causes and modifiable environmental factors have been ruled out, a therapeutic trial of medication may be considered if the behavioral symptoms cause significant impairment in functioning and are suboptimally responsive to behavioral interventions. In some cases, the diagnosis of a comorbid disorder, such as major depression, bipolar disorder, or an anxiety disorder, can be made reasonably and the patient can be treated with medications that are useful for treating these conditions in otherwise typically developing children and adolescents. Modifications of diagnostic criteria may be necessary to account for clinical presentations of psychiatric conditions in individuals with developmental disabilities,[142,143] and tools such as behavior checklists[144] and structured interviews[145] may be helpful. In other cases, clinicians opt to target specific interfering maladaptive behaviors or symptom clusters in the absence of a clear comorbid psychiatric diagnosis (a target-symptom approach).[146–151]

Recent surveys indicate that approximately 45% of children and adolescents[152–154] and up to 75% of adults[8,155] with ASDs are treated with psychotropic medication. Greater age, lower adaptive skills and social competence, and higher levels of challenging behavior are associated with the likelihood of medication use.[154] The evidence regarding the efficacy of psychopharmacologic interventions in patients with ASDs has been de-

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tailed in recent reviews.[148,150,151,156] Although most psychotropic medications have been used in children with ASDs, there is currently insufficient literature to establish consensus regarding an evidence-based approach to pharmacologic management. However, in recent years, there has been an increase in publication of randomized, double-blind, placebo-controlled clinical trials to guide clinical practice.

Surveys performed in the United States suggest that selective serotonin-reuptake inhibitors (SSRIs), atypical antipsychotic agents, stimulants, and α_2-adrenergic agonist antihypertensive agents are the most commonly prescribed classes of psychotropic medications for children with ASDs.[152,153] Double-blind, placebo-controlled trials have demonstrated efficacy of the SSRIs fluoxetine[157] and fluvoxamine[158,159] in the treatment of repetitive and other maladaptive behaviors in patients with ASDs, and open-label trials of these and other SSRIs have shown improvements in target symptoms, including repetitive behaviors, irritability, depressive symptoms, tantrums, anxiety, aggression, difficulty with transitions, and aspects of social interaction and language.[157–161] Potential adverse effects of SSRIs include but are not limited to nausea, drowsiness, sexual dysfunction, constipation, abdominal discomfort, fatigue, headache, dizziness, dry mouth, agitation, behavioral activation, hypomania or mania, apathy, suicidal ideation, and alteration of sleep.

Risperidone has become the first medication with US Food and Drug Administration–approved labeling for the symptomatic treatment of irritability (including aggressive behavior, deliberate self-injury, and temper tantrums) in children and adolescents with ASDs. Two large, multisite, randomized, controlled trials have confirmed the short-term efficacy of risperidone for these severe disruptive behaviors in youth with ASDs,[162–165] and 2 open-label studies, each with a double-blind discontinuation component, have suggested long-term benefits and tolerance.[166,167] Potential adverse effects include but are not limited to excessive appetite and weight gain, insulin resistance, dyslipidemia, hyperprolactinemia, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, QTc prolongation, dry mouth, urinary retention, constipation, seizures, hematologic abnormalities, and sedation.

Although early studies of the effects of stimulants yielded negative results, recent double-blind, placebo-controlled trials of methylphenidate have demonstrated improvement in hyperactivity, impulsivity, and inattention in children with ASDs.[168–170] Methylphenidate is effective in some children with ASDs, but the response rate is lower than that in children with isolated attention-deficit/hyperactivity disorder, adverse effects are more frequent, and it is unclear whether the results can be generalized to other stimulants.[170,171] Potential adverse effects of stimulant medications include but are not limited to appetite reduction, inhibition of growth, delayed sleep onset, jitteriness, exacerbation of tics, abdominal discomfort, increased blood pressure, increased heart rate, irritability, increased anxiety, and repetitive behaviors.

Two small double-blind, placebo-controlled trials have documented modest benefits of clonidine in reducing hyperarousal symptoms including hyperactivity, irritability and outbursts, impulsivity, and repetitive behaviors in children with ASDs.[172,173] A prospective open-label trial[174] and a retrospective record review[175] have suggested that guanfacine was similarly effective in some patients. Potential adverse effects of these centrally acting α_2-agonists include but are not limited to drowsiness, sedation, dry mouth, decreased blood pressure, dizziness, constipation, and irritability, and these drugs can be dangerous in overdose. Recently, a retrospective study,[176] an open-label trial,[177] and a small double-blind, placebo-controlled crossover trial[178] suggested that atomoxetine may be effective for attention-deficit/hyperactivity disorder–like symptoms in children and adolescents with ASDs, and additional research is warranted. Appetite suppression, nausea, fatigue, mood swings, suicidal ideation, dizziness, and liver injury are among the potential adverse effects of atomoxetine.

A summary of selected target symptoms, potential psychiatric diagnoses, and medication options is provided in Table 1. Pediatricians and other practitioners should only prescribe medications with which they have sufficient expertise, including knowledge of indications and contraindications, dosing, potential adverse effects, drug-drug interactions, and monitoring requirements. It will be important for future research to address the need for more rigorous evaluation of safety and efficacy of psychotropic agents in children with ASDs; the value of combining behavioral and medical interventions; the practice of polypharmacy; delineation of clinical and biological subgroups of patients who may be responsive to particular treatments; the role of drugs in treating deficits in language and nonlanguage cognition, social interaction, and behavioral rigidity; and the potential to alter the neural substrate during early critical periods to affect brain development and future function. Several multisite trials are underway, and others undoubtedly will be forthcoming.[179]

Principles to guide the approach to psychopharmacologic management of ASDs in clinical practice have been proposed by several authors in recent years, and an approach is outlined in Table 2.[148–151] When medications are used, potential benefits and adverse effects should be explained, informed consent should be obtained, baseline data regarding behaviors and somatic complaints should be collected, and potential strategies for dealing with treatment failure or partial response should be reviewed. It is important to have some quantifiable means of assessing the efficacy of the medication and to

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TABLE 2 **Clinical Approach to Psychopharmacologic Management**

- Identify and assess target behaviors
  - Parent/caregiver interview
    - Intensity
    - Duration
    - Exacerbating factors/triggers (time, setting/location, demand situations, denials, transitions, etc)
    - Ameliorating factors and response to behavioral interventions
    - Time trends (increasing, decreasing, stable)
    - Degree of interference with functioning
  - Consider baseline behavior-rating scales and/or baseline performance measures/direct observational data
  - Include input from school staff and other caregivers
- Assess existing and available supports
  - Behavioral services and supports
  - Educational program, habilitative therapies
  - Respite care, family psychosocial supports
- Search for medical factors that may be causing or exacerbating target behavior(s)
  - Consider sources of pain or discomfort (infectious, gastrointestinal, dental, allergic, etc)
  - Consider other medical causes or contributors (sleep disorders, seizures, menstrual cycle, etc)
- Complete any medical tests that may have a bearing on treatment choice
- Consider psychotropic medication on the basis of the presence of
  - Evidence that the target symptoms are interfering substantially with learning/academic progress, socialization, health/safety (of the patient and/or others around him or her), or quality of life
  - Suboptimal response to available behavioral interventions and environmental modifications
  - Research evidence that the target behavioral symptoms or coexisting psychiatric diagnoses are amenable to pharmacologic intervention
- Choose a medication on the basis of
  - Likely efficacy for the specific target symptoms
  - Potential adverse effects
  - Practical considerations such as formulations available, dosing schedule, cost, and requirement for laboratory or electrocardiographic monitoring
  - Informed consent (verbal or written) from parent/guardian and, when possible, assent from the patient
- Establish plan for monitoring of effects
  - Identify outcome measures
  - Discuss time course of expected effects
  - Arrange follow-up telephone contact, completion of rating scales, reassessment of behavioral data, and visits accordingly
  - Outline a plan regarding what might be tried next if there is a negative or suboptimal response or to address additional target symptoms
    - Change to a different medication
    - Add another medication to augment a partial or suboptimal therapeutic response to the initial medication (same target symptoms)
    - Add a different medication to address additional target symptoms that remain problematic
  - Obtain baseline laboratory data if necessary for the drug being prescribed and plan appropriate follow-up monitoring
- Explore the reasonable dose range for a single medication for an adequate length of time before changing to or adding a different medication
- Monitor for adverse effects systematically
- Consider careful withdrawal of the medication after 6–12 mo of therapy to determine whether it is still needed

Adapted from Myers SM. The status of pharmacotherapy for autism spectrum disorders. *Expert Opin Pharmacother*. 2007;8:1579–1603; and Myers SM, Challman TD. Psychopharmacology: an approach to management in autism and intellectual disabilities. In: Accardo PJ, ed. *Capute & Accardo's Neurodevelopmental Disabilities in Infancy and Childhood*. 3rd ed. Baltimore, MD: Paul H. Brookes; 2007: In press.

obtain input from a variety of sources, such as parents, teachers, therapists, and aides. Consistent use of validated, treatment-sensitive rating scales and medication adverse-effect scales is desirable. A wide variety of outcome measures have been used in research trials and in clinical practice to measure maladaptive behavior treatment effects.[199] Among the most common are the Clinical Global Impression Scale, Aberrant Behavior Checklist, and Nisonger Child Behavior Rating Form.

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) is defined by the National Center for Complementary and Alternative Medicine as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[200] The definition of CAM adopted by the Cochrane Collaboration is "a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health systems of a particular society or culture in a given historical period."[201] Detailed reviews of CAM as related to developmental disabilities and ASD-specific CAM have been published recently.[202–204]

Use of CAM is common in children with ASDs.[152,205–207] Levy et al[206] reported that by the time their clinical population received a formal diagnostic evaluation for a suspected ASD, almost one third of the children already had received a complementary or alternative therapy, and a survey conducted in a predominantly white, middle-to-upper socioeconomic-status private-practice population found that 92% of parents who responded had used CAM therapies for their children with ASDs.[205]

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Another recent parent survey found that 52% of the children with an ASD had been treated with at least 1 CAM therapy, compared with 28% of a group of control children without disabilities.[207] Surveys indicate that only 36% to 62% of caregivers who used CAM therapies for their children with ASDs had informed the child's primary care physician,[207,208] although more information on CAM is something that families indicate that they want from their child's primary health care professionals.[209]

It is important that health care professionals understand how to evaluate the evidence used to support all treatments, including CAM, psychopharmacologic, and other interventions. Ideally, the evidence supporting or refuting a treatment should include peer-reviewed studies with appropriately diagnosed, well-defined homogeneous study populations; a randomized, double-blind, placebo-controlled design; an adequate sample size to support the statistical analysis presented; control for confounding factors; and use of appropriate, validated outcome measures. When evaluating the efficacy of studies, it is particularly important to keep in mind confounding factors, such as the placebo effect, and the natural history of the disorder. Participation in a study may alter the way a parent interacts with a child and confound the perceived outcome,[210] and improvements are expected with maturation and educational interventions. Only appropriately controlled studies are helpful in proving that an effect is attributable to the intervention being studied.

The practitioner should encourage families to seek additional information when they encounter the following claims or situations[211]:

- treatments that are based on overly simplified scientific theories;
- therapies that are claimed to be effective for multiple different, unrelated conditions or symptoms;
- claims that children will respond dramatically and some will be cured;
- use of case reports or anecdotal data rather than carefully designed studies to support claims for treatment;
- lack of peer-reviewed references or denial of the need for controlled studies; or
- treatments that are said to have no potential or reported adverse effects.

To help to describe their proposed rationales and mechanisms, CAM therapies used to treat ASDs have been categorized as "nonbiological" or "biological."[204] Examples of nonbiological interventions include treatments such as auditory integration training, behavioral optometry, craniosacral manipulation, dolphin-assisted therapy, music therapy, and facilitated communication. Examples of biological therapies include immunoregulatory interventions (eg, dietary restriction of food allergens or administration of immunoglobulin or antiviral agents), detoxification therapies (eg, chelation), gastrointestinal treatments (eg, digestive enzymes, antifungal agents, probiotics, "yeast-free diet," gluten/casein-free diet, and vancomycin), and dietary supplement regimens that are purported to act by modulating neurotransmission or through immune factors or epigenetic mechanisms (eg, vitamin A, vitamin C, vitamin B_6 and magnesium, folic acid, folinic acid, vitamin B_{12}, dimethylglycine and trimethylglycine, carnosine, omega-3 fatty acids, inositol, various minerals, and others).[203,204]

For most of the aforementioned CAM interventions, there is not enough scientific evidence yet to support or refute their use as treatment for ASDs. However, evaluation of treatments is possible, and a few CAM treatments have been appropriately studied. For example, more than a dozen randomized, double-blind, placebo-controlled trials involving more than 700 patients have demonstrated that secretin (a biological treatment) is not an effective treatment for ASDs.[212,213] Evaluation of nonbiological treatments also is feasible. This has been demonstrated in the case of facilitated communication, a technique that uses a trained facilitator to provide physical support to a nonverbal person's hand or arm while that person uses a computer keyboard or other device to spell. Evidence suggests that the communications produced actually originate from the facilitator[214,215] and that facilitated communication is not a valid treatment for ASDs.[216–218]

Because of methodologic flaws, insufficient numbers of patients, or lack of replication, many CAM therapies have been inadequately evaluated; therefore, evidence-based recommendations for their use are not possible. The most recent and most appropriately designed trials have demonstrated no significant benefit of dimethylglycine,[219,220] vitamin B_6 and magnesium,[221,222] or auditory integration training.[223–225] Both positive[226] and negative[227,228] results have been described for small, methodologically flawed studies of intravenous immunoglobulin. A recent double-blind, placebo-controlled trial revealed no statistically significant differences on Aberrant Behavior Checklist subscale scores between small groups of children with ASDs who were given omega-3 fatty acids and those who were given placebo.[229] However, the investigators noted a trend toward superiority of omega-3 fatty acids over placebo for hyperactivity, which suggests that further investigation may be warranted.[229] The gluten/casein-free diet is based on a hypothesis of abnormal gut permeability and exogenous opiate excess. Although use of the gluten/casein-free diet for children with ASDs is popular, there is little evidence to support or refute this intervention, and reviewers have determined that meaningful conclusions cannot be drawn from the existing literature.[230,231] Subsequent to these reviews, a randomized, double-blind

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pilot study demonstrated no significant benefit.[232] Double-blind, placebo-controlled elimination and challenge studies are in progress, and it is anticipated that these studies will provide substantially more useful information regarding the efficacy of the gluten/casein-free diet.[204,230] Measurement of urinary peptides has not been proven to be clinically useful as a marker for ASDs or as a tool to determine if dietary restriction is warranted or would be effective.

Many popular interventions, such as chelation of heavy metals, antifungal agents to decrease presumed yeast overgrowth, and antiviral agents to modulate the immune system, have not yet been studied in people with ASDs; their popularity is based on unproven theories and anecdotes or case reports. None of these interventions can be endorsed as treatment for ASDs outside of well-designed and appropriately monitored clinical trials. Some treatments, such as intravenous chelation, may be particularly dangerous and should be discouraged. One child with autism died as a result of chelation with edetate disodium (Na_2EDTA) despite the facts that a causal association between mercury and ASDs has not been demonstrated, there is no scientific evidence that chelation is an effective treatment for ASDs, and the effectiveness of chelation therapy to improve nervous system symptoms of chronic mercury toxicity has not been established.[233] Unless there is clear evidence of current heavy metal toxicity, chelation by any method is not indicated outside of monitored clinical trials.

In some cases, interesting findings await replication or further investigation. For example, in a double-blind, placebo-controlled trial of vitamin C, improvement was found in total and sensory motor scores on the Ritvo-Freeman Real Life Rating Scale,[234] and several small studies have suggested that music therapy had some short-term benefit on communication skills but not on behavior problems of children with ASDs.[235] Recently, a group of 20 children with ASDs were compared with children without ASDs and found to have an imbalance of methionine and homocysteine metabolism, which was interpreted to represent impaired capacity for methylation and increased oxidative stress.[236] Treatment with trimethylglycine, folinic acid, and methylcobalamin resulted in normalization of laboratory findings. The study did not measure clinical response to the intervention, but anecdotal improvements were noted. Interpretation of these preliminary findings awaits further investigation.

Health care practitioners who diagnose and treat children with ASDs should recognize that many of their patients will use nonstandard therapies. The importance of becoming knowledgeable about CAM therapies, inquiring about current and past CAM use, providing balanced information and advice about treatment options, identifying risks or potential harmful effects, avoiding becoming defensive or dismissing CAM in ways that convey a lack of sensitivity or concern, maintaining open communication, and continuing to work with families even if there is disagreement about treatment choices has been emphasized.[237] It also is essential to critically evaluate the scientific merits of specific therapies and share this information with families, educate families about how to evaluate information and recognize pseudoscience, and insist that studies that examine CAM be held to the same scientific and ethical standards as all clinical research.[202,238]

Parents of children with ASDs will understandably pursue interventions that they believe may present some hope of helping their child, particularly if the therapies are viewed as being unlikely to have any adverse effects. Unfortunately, families are often exposed to unsubstantiated, pseudoscientific theories and related clinical practices that are, at best, ineffective and, at worst, compete with validated treatments or lead to physical, emotional, or financial harm. Time, effort, and financial resources expended on ineffective therapies can create an additional burden on families. Health care professionals can help parents and other caregivers to distinguish empirically validated treatment approaches from treatments that have been proven to be ineffective and those that are unproven and potentially ineffective and/or harmful.

FAMILY SUPPORT

Management should focus not only on the child but also on the family. Although parents once were viewed erroneously as the cause of a child's ASD, it is now recognized that parents play a key role in effective treatment.[9] Having a child with an ASD has a substantial effect on a family. Parents and siblings of children with ASDs experience more stress and depression than those of children who are typically developing or even those who have other disabilities.[239–243] Supporting the family and ensuring its emotional and physical health is an extremely important aspect of overall management of ASDs.

Physicians and other health care professionals can provide support to parents by educating them about ASDs; providing anticipatory guidance; training and involving them as cotherapists; assisting them in obtaining access to resources; providing emotional support through traditional strategies such as empathetic listening and talking through problems; and assisting them in advocating for their child's or sibling's needs.[244] In some cases, referral of parents for counseling or other appropriate mental health services may be required. The need for support is longitudinal, although the specific needs may vary throughout the family life cycle.

One of the chief strategies for helping families raise children with ASDs is helping to provide them with access to needed ongoing supports and additional services during critical periods and/or crises. Natural supports include spouses, extended family members, neigh-

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bors, religious institutions, and friends who can help with caregiving and who can provide psychological and emotional support. Informal supports include social networks of other families of children with ASDs and community agencies that provide training, respite, social events, and recreational activities. Formal supports include publicly funded, state-administrated programs such as early intervention, special education, vocational and residential/living services, respite services, Medicaid, in-home and community-based waiver services, Supplemental Security Income benefits, and other financial subsidies. The breadth and depth of services vary, even within the same state or region. Few services exist in many rural areas, and public programs may have long waiting lists.

Sibling support groups offer the opportunity to learn important information and skills while sharing experiences and connecting with other siblings of children with ASDs.[244] Although the research on support groups for siblings of children with disabilities is difficult to interpret because of study-design problems and inconsistent outcome effects on sibling adjustment, these groups generally have been evaluated positively by participating siblings and parents,[244] and there is some evidence of beneficial effects for siblings of children with ASDs.[245]

Because each state has organized its services and access mechanisms differently, physicians and families must learn their own state's unique rules to access supports by contacting the state or county offices of the states' Department of Health and Human Services or Mental Health and Mental Retardation or the state developmental disabilities organization. In addition, local parent advocacy organizations, national autism and related developmental disability organizations, early intervention administrators, and school district special education coordinators often are knowledgeable about various programs and their respective eligibility requirements.

CONCLUSIONS

ASDs are chronic conditions that affect nearly 1 of every 150 children and require ongoing medical and nonmedical intervention. There is a growing body of evidence that supports the efficacy of certain interventions in ameliorating symptoms and enhancing functioning, but much remains to be learned. In addition to their important roles in identifying ASDs through screening and surveillance, establishing the diagnosis, conducting an etiologic evaluation, and providing genetic counseling after a diagnosis is made,[2] pediatricians and other primary health care professionals are in a position to provide important longitudinal medical care and to support and educate families and guide them to empirically supported interventions for their children.

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