

REVIEW ARTICLE

Advances in the Diagnosis and Treatment of Autism Spectrum Disorders in Children

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ABSTRACT

Objective • This study aims to review recent developments in the diagnosis and treatment of Autism Spectrum Disorder (ASD) and provide insights for its clinical management.

Methods • The literatures were researched from the pubmed, Wanfang and CNKI. We searched for research on the etiology, pathogenesis, diagnosis (screening and evaluation), and treatment of Autism spectrum disorder. When selecting papers to be included, priority should be given to randomized clinical trials, systematic evaluations, meta-analyses, clinical practice guidelines, and articles related to general medical readers.

Results • ASD is a widely present neurodevelopmental disorder characterized by social and communication difficulties, narrow interests, and repetitive behavior, accompanied by symptoms such as irritability, self-harm, attention deficit hyperactivity disorder (ADHD), and sleep problems. Irritability, self-harm, ADHD, and sleep problems are common accompanying symptoms that contribute to the challenges faced by individuals with ASD. At present, there is no fully effective treatment method for ASD, and key factors affecting the prognosis of

ASD include early diagnosis time, early language communication level, intelligence level, disease severity, comorbidities, family participation, appropriate intervention, and social support. Therefore, early individualized long-term comprehensive training and drug therapy, hyperbaric oxygen therapy, and combined family participation can improve the prognosis of pediatric patients. Before selecting treatment plans for children, collecting as much information as possible about various treatment methods and choosing personalized treatment plans based on the child's developmental assessment level is necessary. In addition, the treatment of ASD is also influenced by factors such as family economic status, parental mentality, and social environment. During the training process, it is important to be family-centered, tolerant, and understand children's behavior.

Conclusion • It is significant to take effective treatment measures to improve the quality of life and prognosis of children with autism spectrum disorders. (*Altern Ther Health Med*. [E-pub ahead of print.]

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INTRODUCTION

Autism spectrum disorder (ASD) is a widespread developmental disorder characterized by social and communication disorders, narrow interests, and stereotyped and repetitive behaviors. ASD, a neuropsychiatric disorder, exhibits significant deficiencies in synaptic connectivity. ASD's prevalence is not only rising in the United States but also globally, making it a significant public health concern across

different countries. ASD's etiology is complex and involves a combination of genetic, environmental, and neurological factors. This type of synaptic instability is not only present in developmental disorders of the nervous system but also in delayed neurodegenerative diseases. In 2013, the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), collectively referring to autism, Asperger's syndrome and unclassified pervasive developmental disorders in children as ASD.¹⁻² In the United States, one in 88 children has ASD, and few data are reported in developing countries, with one study from India reporting a prevalence of 0.8% to 1.3% in children aged 2-9.³ There is a clear trend of increasing incidence, possibly due to increased awareness of ASD and more testing.⁴ When children often exhibit social and language disorders, developmental delays, abnormal behavior, or poor academic performance, ASD should be highly suspected. A

comprehensive assessment of autism spectrum disorders should include a detailed medical history, thorough examination, and close observation of children's social and behavioral relationships. The heterogeneity of symptoms, variations in severity, and overlaps with other conditions can make diagnosis and subsequent treatment complex. In recent years, clinical research on the correlation between treatment measures for children with autism spectrum disorders has continued to deepen. Some of the other common approaches are used to ASD treatment including emerging or gaining attention, such as behavioral therapies, speech and language therapy, occupational therapy, and applied behavior analysis. Still, no good treatment methods have been found, resulting in poor prognosis for children.

Overview of ASD

“Autism” is a translation of the English letter autism, which means “self”. Although scholars described the characteristic behavior in 1943, it was not until 1980 that it was included as a separate disorder in the Diagnostic and Statistical Manual of Mental Disorders, III (DSM-III).³⁻⁴ Since then, its naming and diagnostic criteria have undergone many changes, most recently in 2013, when the DSM-V changed the existing term “spectrum developmental disorder” to ASD and proposed diagnostic criteria and etiological mechanisms.⁵ Although the pathogenesis of ASD is not yet clear, the most widely recognized interaction is between genetic and environmental factors, with 81% of ASD trait variations attributed to genetic factors. In the same study, 14% to 22% of environmental factors were associated with ASD risk, leading to neurotransmitter imbalance, neural pathway dysfunction, synaptogenesis, and neuronal connectivity abnormalities. Parental conditions and in utero and perinatal factors may contribute to ASD etiology. More recently, epigenetic changes, including DNA methylation and micro RNA alterations, have been associated with ASD and proposed as potential biomarkers. Many autism risk genes affect gene expression regulation, neurogenesis, chromatin modification, and synaptic function. Willsey et al. studied the 10 genes with the strongest statistical correlation with ASD, all of which are expressed in the telencephalon (the forebrain mainly composed of the cerebral hemisphere), corresponding to the development of the human prenatal frontal cortex. Estrogen alleviates the impact of gene disruption on ASD risk, which may help explain gender differences in prevalence.⁶

Clinical manifestations of ASD

Children with autism present on a continuum or spectrum, and there is considerable variation in the Severity and Severity of core symptoms (social disorders, verbal communication disorders, and stereotypical repetitive behaviors). ASD is characterized not only by persistent impairments in reciprocal social communication and social interactions, but is also manifested by restricted, repetitive patterns of behavior, interests, or activities. Children may begin to show symptoms as early as 18 to 24 months of age when life circumstances change and social interaction is needed.⁷ The main manifestations of ASD are (1) social: (a) Lack of social

gaze, smile, and attachment; (b) Attention deficit in social interaction; (c) can not play normal games; (d) Failure to follow social rules; (e) Unable to form partnerships, they often play alone and indulge themselves in things they are interested in. (2) Communication: (a) It is manifested as immediate imitation, he says what others say, or delayed imitation, a few days or dozens of days after hearing a word, he suddenly said it in an inappropriate occasion; (b) Language comprehension disorder, no response to adults calling his name, no response to other people's gestures, but the hearing organ is intact, hearing normal; (c) Lack of meaningful language communication; (d) self-talk gibberish; (e) Nonverbal communication. (3) stereotyped and repetitive behaviors: (a) stereotyped daily living habits. Children with autism often insist on the environment being unchanged. Once a certain rule is formed, it is not easy to change; (b) Focus too much on certain things. (4) Cognitive defects: some children can not successfully carry out intelligence tests due to communication barriers. Most children show varying degrees of intellectual defects in their intelligence and social interaction ability, intelligence between the internal abilities and the obvious imbalance. (5) sensory and perceptual disorders: The child does not respond to the sound or the call of his name. They are particularly sensitive to certain sounds, such as doors closing, dogs barking, or motorcycles. (6) Complications: (a) Epilepsy: the incidence of epilepsy is 25%-30%, showing the bimodal type (infancy and adolescence); (b) Mental illness: attention deficit, depression, anxiety, and obsessive-compulsive disorder; (c) Eating: including reduced chewing, poor food acceptance, extreme food choice, anorexia or misbehavior at meals; (d) Gastrointestinal diseases: vomiting, gastroesophageal reflux, recurrent diarrhea, chronic constipation, recurrent abdominal pain were the common complaints; (e) Sleep disorders: difficulty falling asleep, repeated waking at night, unusual bedtime habits leading to increased daytime behavior problems and increased parental pressure; (f) Deformity: syndrome or non-specific deformity can be seen in 18%-20% of children.⁸⁻⁹

Screening and diagnosis of ASD

Developmental screening is comprehensive developmental screening and monitoring using an effective, structured scale in all children who are “clearly developing normally,” and the American Academy of Pediatrics recommends ASD-specific screening at 3 to 36 months of age. Some of the early signs that parents and caregivers might observe, such as lack of response to their name, limited social interaction, etc. Therefore, it is hard to diagnose the ASD.

Autism screening and warning signs			
Age (months)	Warning signs	Age (months)	Warning signs
3	1. No response to loud sounds 2. Not looking at the face, not following moving people or objects 3. Not developing or unable to laugh when teasing	18	1. No conscious call of “dad” or “mom” 2. Not able to refer to people or objects as required 3. No eye contact with people
6	1. Pronunciation is poor, unable to laugh out loud	24	1. No meaningful language
8	1. No response when hearing sound 2. Unable to distinguish between strangers and acquaintances	30	1. Single and rigid interests 2. Unable to say 23-word phrases 3. Unable to signal urination or defecation
12	1. Unable to wave to say “goodbye” or clap 2. Calling names without response	36	1. Unable to communicate with other children or play games 2. Unable to say one's own name

However doctors in India do not follow these guidelines.⁹⁻¹⁰ They rely on a different method of looking for “visions” in young children. These measures are often ineffective for children with autism.¹⁰ The screening process for Chinese children can also use the Modified Chinese Children’s Autism Spectrum Assessment Scale. Use the revised Early Childhood Autism Checklist (M-CHAT-R/F) for autism-specific screening between the ages of 16 and 30 months.¹¹ The scores and instructions are easy to understand, and children are classified as low risk for autism (no further assessment required), moderate risk (reassessment required after 1 month, further assessment if still positive, or high risk (immediate assessment). Even if medical professionals cannot identify autism, they should know exactly how to screen the children they come into contact with for early detection and timely intervention.¹²⁻¹³

The purpose of diagnosis is to determine the presence of the disorder, assess the Severity, level of function, and confirm the presence of comorbidities, which can be accomplished in the following ways: (1) Medical history records, in which parents describe any obvious symptoms of discomfort during the prenatal, postpartum, neonatal period and other previous times. (2) To detect the signs of ASD and confirm the development status. (3) Measurement and examination, whether there are microcephaly, giant deformity, short stature, and other malformation characteristics. (4) Clinical and developmental assessment, looking at the play, behavior, interaction, speech, and gestures, and assessing developmental profiles for impairments in these areas, particularly interaction and language. (5) Make a clear diagnosis based on behavior, not etiology. All DSM-V diagnostic criteria for ASD should be met. The following conditions need to be defined: (i) Severity: according to the standards of DSM-V(DSM-V stipulates that the diagnosis of autism spectrum disorders must meet the following five criteria A to E: A. Continuously displaying deficiencies in social communication and interaction in various environments; B. Limited and repetitive behaviors, interests, or activities; C. These symptoms must have been manifested in the early stages of development; D. These symptoms bring clinically significant obstacles in social, occupational, or other important functions. E. Intellectual developmental deficits or global developmental delays cannot simply explain these symptoms.)¹⁴; (ii) mental retardation(There may include developmental delays in cognitive and learning abilities. They may exhibit difficulties in attention, memory, problem-solving, and flexibility, requiring special schools for learning.); (iii) Language barrier(Difficulties in language expression and understanding, including language delays, phonetic and intonation abnormalities, as well as difficulties in understanding non textual language.); (iv) Medical, genetic or environmental factors; (v) neurodevelopmental, mental or behavioral disorders; (vi) Evaluation of complications. Asds are usually associated with other diseases, which may cause children to lose some abilities like the primary disease and need to be actively identified and managed. (6) Diagnosis is made. Most children diagnosed at 24 months remain diagnosed for the rest of their lives, so an in-depth, comprehensive assessment is

recommended.¹³ Differential diagnosis: (1) Attention-deficit Hyperactivity Disorder (ADHD): This is the most common misdiagnosis. Inattention, hyperactivity, and impulsivity are manifestations of ADHD, but intelligence, communication, play, and social interaction are normal; (2) Social dysfunction: resulting in limited function but Lack of repetitive behavior or abnormal sensory response; (3) Unexplained hearing impairment: except for speech impairment compensated by gesture, other areas are normal.^{10,12-13} Other common findings include additional behavioral problems, sleep disturbance, brain abnormalities, seizures, feeding issues, gastrointestinal problems, visual dysfunction.

ASD is a clinical diagnosis that lacks any laboratory tests. Testing aims to look for related sensory problems that may remain unrecognized, such as hearing and vision impairment, to detect other causes that may affect developmental disabilities, such as hypothyroidism, and to identify comorbidities.¹⁵ Fragile X syndrome is a single-gene disease that causes the most cases of autism and intellectual disability. It is an X-linked incomplete exodominant genetic disease, named after the fragile site of the X chromosome end in cells that appears to be broken after being mutated in a special culture medium. Male patients exhibit intellectual disability, megarchidism, special facial features, language, and behavioral disorders, etc. Male patients are more common and have severe symptoms. About one-third of female carriers exhibit intellectual disability or other symptoms, but most of them are mild. All boys with ASDs need to be tested for Fragile X syndrome and targeted accordingly if the child is malformed or suspected of a genetic or metabolic disorder.

INTERVENTION AND TREATMENT OF ASD

Behavioral and developmental interventions

At present, behavioral and developmental interventions for ASD mainly include three types: (1) Interventions based on interpersonal relationship promotion, including relationship development intervention (RDI), floor time, and (2) Interventions based on skill development, including the picture change communication system (PECS), behavioral decomposition, social stories, peer intervention, etc. (3) A comprehensive intervention model is designed to address multiple deficiencies and development goals in multiple areas of ASD patients. Early initiation of the Denver Model (ESDM), a comprehensive developmental behavioral intervention, can improve the outcomes of young children diagnosed with autism spectrum disorder (ASD).¹⁴ And providing treatment and education for children with autism and communication-related disabilities (TEACCH), based on the Lovaas Applied Behavior Analysis (ABA) intervention model.¹⁵⁻¹⁷

An intervention based on promoting interpersonal relationships. RDI is a program aimed at empowering and guiding parents of children, adolescents, and young people with autism spectrum disorders (ASD) and similar developmental disorders as facilitators of their children’s intellectual development. RDI teaches parents to play an important role in improving critical emotional, social, and metacognitive abilities

through carefully graded guidance and interaction in daily activities. Deficiency of the theory of mind refers to the fact that children with ASD cannot speculate on the mental activities of others.¹⁸ Common attention deficit refers to that children with ASD, unlike normal children, cannot form the ability to jointly notice something with their caregivers since infancy. Therefore, children with ASD have poor social reference ability, cannot share emotions, feelings, and experiences with others, and cannot establish kinship and friendship with relatives and others.¹⁶ The purpose of RDI is to enhance children's ability to understand others' psychology by improving their ability to common attention and social communication and communication. The training step is to first assess the children's interpersonal relationship development level, and then according to the assessment results, according to the normal rules of children's interpersonal relationship development, eye contact - social reference - interaction - coordination - emotional experience sharing - enjoy family friendship and other training.¹⁶⁻¹⁹ By reviewing the theoretical basis of RDI, current methods, and preliminary research results, some scholars show that although no randomized, controlled, double-blind study on RDI has been completed, preliminary research shows that through RDI course training and treatment counseling for ASD parents, Parents will play a significant role in the improvement of experience sharing, communication, social interaction and adaptability of children with ASD.²⁰

American psychiatrist Stanley Greenspan created floor time as a play therapy method to improve social interaction and communication disorders in children with ASD through interactive play between adults and children.²¹ Based on the characteristics of children with ASD and their stages of development, floor time sets up six ability development stairs, which are the foundation for promoting children to learn advanced skills. The goal is to promote attention development, increase interest and intimacy in the environment, increase two-way and purposeful communication, help express and use feelings and concepts, and promote the development of logical thinking skills.²² The difference from RDI is that children dominate the training content of Floor Time. During the training process, parents and therapists cooperate with the interests and activities of children, and, at the same time, create new changes, surprises and appropriate difficulties in the process so as to guide children to solve problems in a happy time, to improve their social interaction and communication ability.²¹⁻²² Floor time training is not limited to rehabilitation institutions. It can be applied to daily life.

Skills-based intervention. PECS is primarily trained for children with communication difficulties due to limited or no language. Clinical observation shows that children with ASD are good at processing visual information, so visual tools effectively compensate for auditory processing, sequence, and organization difficulties in children with ASD.²³ It works by teaching children with ASD to use the imaging system to cope with simple problems. The American Academy of Pediatrics Guidelines for non-medical interventions for ASD shows that some observational and randomized controlled studies have

shown that PECS can effectively improve the ability of children with ASD to communicate with others. PECS should be tried in children with limited verbal communication or in children with ASD who have failed to respond to other communication enhancement interventions.²⁴

A social story is a social intervention technique mainly aimed at problems in the field of social interaction. It was proposed by Carol Gray in 1991. It is a cognitive-oriented intervention method based on Baron-Cohen's "Theory of mind" and Hobson's "Theory of affective cognitive impairment".²⁵ The goal is to explain specific target behaviors to the child and to explain the situation and appropriate behavior of the person interacting with the environment. Children are trained to develop new activities and show socially expectant behavior. The guidelines for non-medical interventions for ASD point to evidence that social stories can improve social interaction in children with ASD and are an effective intervention.²⁶

Comprehensive intervention model. It has been found that ESDM (Early Start Denver Model) and early intensive behavioral therapy based on Lovaas can improve speech, social adjustment, and cognitive ability in children. ESDM is a standardized training curriculum and assessment system for infants with ASD aged 12 to 48 months or children up to the age of 3 years.²⁵⁻²⁷ The therapeutic principle is based on the Denver model, applied behavior analysis, and core response training and integrates the educational practice of applied behavior analysis and the interpersonal relations-centered intervention model in the treatment process.²²⁻²³ The curriculum design is based on the development process of children, aiming at early childhood development skills such as language, play, social interaction, attention, imitation, motor skills, self-care, and adaptive behavior education training. ESDM advocates the participation and leadership of parents and supports parent-child interaction.²⁸ The study found that implementing professional training for parents and families of children with children and corresponding professional guidance in the treatment process is expected to open up a new intervention model combining family and rehabilitation institutions.²⁹

ABA refers to applying behaviorism principles, with positive reinforcement, punishment, regression, and other techniques, to correct various abnormal behaviors in children with ASD, while promoting the development of the overall ability of children with ASD.³⁰ ABA intervention modes mainly include round training (DTT) and critical response training (PRT). Both DTT and PRT are highly structured intervention models that emphasize empirical intervention strategies for autism.²⁶⁻²⁸ The training process should be individualized and systematic and ensure that the treatment has a certain intensity, 25~40 hours a week, 1~3 times a day, and 1~3 hours each time. The most direct reason for children's of active participation and interaction in life and collective activities is the lack of broad motivation.²⁹ Moreover, studies have shown that early intensive behavioral intervention with pivotal response treatment (PRT) as the main method can increase children's active language, IQ, and receptive language levels.²⁹⁻³⁰ A review of behavioral and

developmental intervention systems for ASD has shown that current studies have shown that discrete trial training (DTT) can improve adaptive and practical skills in children with ASD. Still, the improvement in communication skills is not significant, and there is no evidence to support the LoVAAs-based intervention model over other intervention models.³¹

The theories of treatment and education of autistic and related communication handicapped children (TEACCH) are based on social learning theory, development theory, and behavior theory. TEACCH makes full use of children's visual advantages, reasonably arranges the training environment and intervention procedures, and increases children's understanding and adaptability to the environment and training content to improve children's defects in social communication, perception, movement, language, and other aspects.^{15,22-26} First of all, arrange training venues according to different training contents. The placement of objects and toys should emphasize visual cues. The training process should be programmed, and a training program table should be set. The training content mainly includes children's imitation ability, gross motor, fine motor, cognitive ability, hand-eye coordination, language expression and understanding ability, self-care ability, social communication ability, and emotional processing.^{9,15-18,29-31} In the training process, children should make full use of body posture, labels, prompts, words, and charts to increase their understanding and mastery of the content, and at the same time, motor behavior reinforcement and correction techniques to improve abnormal behavior.³¹ TEACCH has been found to improve social interaction, communication, and cognition in children with ASD and the core symptoms of ASD. However, no evidence exists to confirm or evaluate that Teacch is superior to other behavioral interventions or complementary and alternative medicine treatments.³²

Drug therapy

Currently, there are no specific drugs for the treatment of ASD. The rational application of some drugs can improve the behavior and educational intervention effect of children with ASD for the accompanying symptoms of ASD, such as irritability, self-injurious behavior, attention deficit hyperactivity disorder (ADHD), sleep problems, etc.

Treatment for irritability, self-injury, and other behaviors. Risperidone is the first autism medication approved by the US Food and Drug Administration (FDA). It is mainly used in children with ASD with symptoms of excitement, hyperactivity, and irritability and has some effect on the core symptoms of children with ASD, such as social disturbance.³³ A meta-analysis showed that risperidone alleviated irritability, aggression, and repetitive stereotyping in children with ASD. Domestic research in 2011 showed that risperidone can significantly reduce the self-injurious behavior and aggressive behavior of children with ASD, improve their sleep disorders, and improve their cognitive and language abilities.³⁴ The common side effects include fatigue, drowsiness, enuresis, and tremors. Aripiprazole is the second drug approved by the US FDA for the treatment of irritable behavior in children with

ASD.³²⁻³³ Randomized controlled studies have shown that aripiprazole can improve irritable behavior in children with ASD, and the drug is safe and well tolerated. The main side effects include weight gain, drowsiness and extrapyramidal reactions, but the incidence of extrapyramidal reactions is lower than that of risperidone.³³⁻³⁴

Treatment for attention deficit and hyperactivity disorder. Current research shows that 41%~78% of children with ASD are complicated with hyperactivity, impulsivity, attention deficit, and other symptoms, which will seriously affect the quality of life of children[34]. According to the existing research on the treatment of ASDs combined with ADHD, in 2012, the psychopharmacology Committee of the Autism Treatment Network provided clinical medication references for children with ASDs accompanied with ADHD, and methylphenidate could be selected for treatment.³⁵ However, compared with children with ADHD alone, the therapeutic effect of ASDs combined with ADHD is not good. And side effects such as excitement and other emotional side effects increased. In addition, tomoxetine hydrochloride can be applied to children with tic and anxiety symptoms simultaneously; the effective rate is about 50%.^{16-18,35} Guanfacine and clonidine are also optional drugs, but atypical antipsychotic drugs should be considered when children with ASD and ADHD are accompanied by severe irritable, impulsive, and aggressive behaviors.³⁵ ω -3 fatty acids are a kind of polyunsaturated fatty acids that can regulate the transmission process of various neurotransmitters, inhibit oxidative stress, and reduce the level of apoptosis of brain neurons. Preliminary studies suggest that ω -3 fatty acids may reduce hyperactivity symptoms in children with hyperactivity disorder ASD.³⁶

Treatment for sleep disorders. Compared with normal children, sleep disorders are more common in children with ASD; about 44%-83% of children with ASD are accompanied by sleep disorders. Some scholars have found that some patients with ASD have decreased melatonin levels in their blood, disappeared circadian rhythm, and may have melatonin receptor dysfunction caused by genetic abnormalities.^{33-34,36} The results of a randomized controlled study suggest that melatonin effectively treats sleep disorders in children with ASD, and the usual dose is 1 to 3 mg.³⁵ Other drugs for which there is little evidence are risperidone, L-carnitine, mirtazapine, clonidine, etc. Current research does not support the effectiveness of vitamin supplements or other substances in improving sleep.³⁶⁻³⁷

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy refers to placing the child in an environment of higher than one atmosphere and inhaling 100% oxygen to treat the disease, which can increase the oxygen partial pressure and prevent oxidation reaction.^{31-32,34} It is well tolerated by most patients, with middle ear barotrauma being the most common adverse event reported.³⁸ Related studies have shown that most children with autism spectrum disorders are accompanied by monocytes, dendritic cells and other cell abnormalities, mitochondrial dysfunction,

and increased oxidative stress.³⁶⁻³⁷ Therefore, hyperbaric oxygen therapy can effectively reduce inflammatory and oxidative stress responses. Some scholars have analyzed the effects of hyperbaric oxygen on the behavior of rats with autism and the levels of IL-1 β , IL-6 and IL-10 in peripheral blood.³⁸⁻³⁹ The results showed that the occurrence and development of autism may be closely related to the abnormal expression of cytokines, and hyperbaric oxygen can significantly reduce the occurrence of the inflammatory response, thus promoting the growth and development of rats with autism and improving their behavioral ability.³⁹⁻⁴⁰ At the same time, hyperbaric oxygen can significantly increase cerebral blood perfusion, increase the antioxidant enzyme content, and improve the body's antioxidant capacity. In addition, the hyperbaric oxygen therapy environment is beautiful, has less pressure, high safe, and can significantly reduce the fear caused by the treatment of children, suitable for children with autism spectrum disorder treatment.⁴⁰

OUTLOOK

For most ASD patients, the situation has improved and will continue to improve. We hope that research can redirect attention to individuals who still face significant difficulties and provide more inclusive and independent pathways for more people. Both science and public policy have the potential to contribute to this change. In collaboration with family, school, and community providers, clinicians can change the lives of individual children and adults by providing accurate and realistic information, support, and hope. In terms of global health, focusing on the goals of children and adults with ASD and their families, rather than how to fill gaps in existing systems, may help determine appropriate priorities. Innovative solution include empowering frontline healthcare workers to adapt evidence-based interventions to resource scarce environments.⁴¹

DATA AVAILABILITY

The data could be obtained by contacting the corresponding author.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Xiaoyan Lin and Guo Wang contributed equally to this work.

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All authors contributed to the study and agreed to be listed as authors.

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