

# New Assessments and Treatments in ASD

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## Opinion statement

The assessment of autism spectrum disorder (ASD) is complex and remains clinical, despite advances in basic research. In this chapter, we review new and updated clinical tools, such as screening and diagnostic tests, and discuss the DSM-5 criteria introduced in 2013. We provide an algorithm to guide clinical evaluation and referrals. We also review non-behavioral treatments and summarize recent research. Current conventional treatment of ASD in children includes intensive behavioral interventions (known as applied behavioral analysis or ABA), rehabilitative services such as speech therapy, occupational therapy, physical therapy, social skills training, and counseling. We present new validated information and provide clinical guidance for the evaluation and treatment of young children and youth with ASD.

## Introduction

Autism spectrum disorder (ASD) is defined as delayed social communication skills and restricted, repetitive behaviors (RRB) [1]. The assessment of ASD is complex and remains clinical. In this chapter, we review new and updated tools and discuss DSM-5 criteria introduced in 2013 [1]. We also review non-behavioral treatments and summarize recent research.

The practice parameters introduced by Filipek et al. in 2001 [2••] and the recommendations

from the American Academy of Pediatrics (AAP) [3••] continue to provide the basis for the assessment of ASD. The diagnosis of ASD continues to be made close to 4 years of age on average [4]. There are even greater delays in the identification of children from different cultural and ethnic backgrounds and low socio-economic status (SES). Children with ASD whose care is compliant with AAP guidelines [5•] are diagnosed earlier than children who receive no well-child care.

**Table 1. Selected ASD Level 1 and Level 2 screening tools and other useful assessment tests**

Screening tool	Age	Format	Time to complete in min	Sensitivity/specificity	Availability
<b>Level 1</b>					
MCHAT-R [6]	16–36 months	Questionnaire: 20 items Follow-up questionnaire if score 3–7	5–10	at $\geq 2$ yrs 0.94/0.83, PPV at 98% DD, and 54% ASD	<a href="http://www.Mchatscreen.com">www.Mchatscreen.com</a>
CAST [7]	4–11 years	Questionnaire: 37 items	10	0.88/0.97	<a href="http://www.autismresearchcentre.com/arc_tests">www.autismresearchcentre.com/arc_tests</a>
<b>Level 2</b>					
SCQ [8]	4 years and up	Questionnaire: 40 items Lifetime and Current	10 each	0.85–0.96/0.67–0.80	Purchase: Western Psychological Services
CARS-2 [11]	2 years and up	Observation 15 items	15–20	Agreement with DSM-5, 84%	Purchase: Western Psychological Services
SRS-2 [10]	3 years and up	Questionnaire: 65 items	15–20	Agreement with ADI-R, 0.75–0.91	Purchase: PAR
GARS-3	3–22 years	Questionnaire: 56 items	10	0.65/0.81 GARS-2(12) GARS-3 0.97/0.97(ProEd)	Purchase: Pro Ed Inc
<b>Level 2 Interactive</b>					
STAT [13]	24–36 months	Interactive, training needed	20	0.92/0.85	Purchase: VU e-innovations
RITA-T [14]	18–39 months	Interactive, training needed	10	1/0.84	<a href="http://www.umassmed.edu/autismRITA-T">www.umassmed.edu/autismRITA-T</a>
<b>Other useful assessment Tools</b>					
Vineland Behavior Adaptive Scales [28]	Birth and up	Survey Interview or parent rating, teacher rating	25–60 or up to 90	A measure of adaptive behavior from birth to adulthood	Purchase: Pearson Clinical Services
Vanderbilt Questionnaires	School age	Parent and teacher questionnaires	5–10	Software for scoring A measure of ADHD, ODD	<a href="http://www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales">http://www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales</a>

## New assessments in ASD

### *Level-1 or universal ASD screening tests*

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The Modified Checklist for Autism in Toddlers (MCHAT) was updated in 2014 (MCHAT-R) [6] and now includes 20 questions. A score of 3–7 requires a follow-up interview to specify the risk category ([www.mchatscreen.com](http://www.mchatscreen.com)). The cutoff score of 2 provides good sensitivity and specificity (Table 1), and a positive predictive value (PPV) for developmental delays of 98% (but only 54% for ASD). The Childhood Autism Spectrum Test (CAST; previously Childhood Asperger's Syndrome Test) can be used for those older than 3 years [7].

### *Level 2 ASD screening measures*

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These can be helpful in informing clinicians. See table 1 for a list of measures and their properties, and note that it is not comprehensive. The Social Communication Questionnaire (SCQ) [8] includes questions based on the Autism Diagnostic Interview-Revised (ADI-R) [9], a 90-min structured interview for research about autism signs and symptoms that requires special training, has low psychometric strength for children younger than 55 months, and requires a mental age above 2 years, as does the SCQ. The Social Responsiveness Scale (SRS-2) [10] has been updated and seems to show better correlation with the ADI-R. The Childhood Autism Rating Scale (CARS-2) has been found to show good correlation with the DSM-5 [11]. The Gilliam Autism Rating Scale (GARS/GARS 2) has low sensitivity and specificity [12]. The GARS 3 is reported to have improved properties, though no studies are yet available on its performance in clinical settings.

### *Interactive level 2 ASD test*

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This is preferred to a questionnaire in younger children and provides a better observational context. In addition to the Screening Tool for Autism in Toddlers and Young Children (STAT) [13], the Rapid Interactive Screening Test for Autism in Toddlers (RITA-T) [14] is a new interactive level 2 screening test for 18–36-month-olds. The STAT requires training and 20 min for administration and scoring; it has good sensitivity and specificity for those 2–3-year-olds with autism. The RITA-T is administered and scored in less than 10 min, and its training is 3 h long. At a cutoff score of >14, it has good sensitivity (1), specificity (0, 84), and PPV (0, 88).

### *DSM-5*

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The DSM-5 groups ASD criteria into two domains (social communication and restricted, repetitive behaviors or RRB), compared to the three domains in the DSM-IV (social deficits, language deficits, repetitive stereotypic

behaviors) [15]. DSM-5 criteria eliminate diagnostic subtypes within ASD that were present under DSM IV (Pervasive Developmental Disorder, Not Otherwise Specified or PDD-NOS, Asperger's Syndrome, Childhood Disintegrative Disorder (CDD), and Autism). It also deletes age-of-onset criteria and adds specifiers (neurobiological disorders, risk factors, or genetic factors) and modifiers such as language, cognitive and learning levels, and ADHD.

Although the DSM-5 criteria provide structure and guidelines to inform diagnosis, they have limitations as well, especially for children younger than 5 years of age, in whom specificity appears low [16]. In addition, there are concerns about individuals with PDD-NOS meeting criteria on the DSM-IV who would not meet criteria on the DSM-5. Children younger than 5 years may have insufficient symptoms on the RRB category of the DSM-5: for example, the repetitive use of objects, hand-finger mannerisms, and unusual sensory interests occur commonly in younger children with autism or developmental delays, whereas compulsions, rituals, and resistance to change are less commonly endorsed in young children as these features tend to increase with age [17••]. Development is important in assessing social communication and RRB [18••].

The DSM-5 introduces a new category: Social Communication Disorder (SCD), for those who do not meet the criteria for RRB but have a significant social pragmatic impairment. It is unclear yet how school programs and services will be provided to this group of children.

In conclusion, the DSM-5 criteria can provide structure to inform assessment of ASD at all ages, though it is problematic in younger children. Further studies are needed to clarify the SCD diagnosis and impact of ASD as defined by DSM-5.

#### *Autism Diagnostic Observation Schedule*

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The Autism Diagnostic Observation Schedule (ADOS) is a semi-structured observational diagnostic interview that assesses the social communication skills and RRB of children suspected to have ASD [19]. It has been updated to be consistent with the DSM-5, and a new toddler module has been developed (ADOS-T) [20]. The ADOS requires extensive training, time to administer, and is costly. However, it provides a structured setting to inform diagnosis and continues to be the gold standard measure in clinics that evaluate children for autism [21].

#### *Evaluation of sensory processing difficulties*

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The evaluation and treatment of *sensory behaviors* have been foremost concerns since they were included in the DSM-5 criteria for ASD. It is important to assess the sensory difficulties that some children have (with sounds, touch, food) but recognize that these behaviors can be present in disorders other than ASD and to become familiar with measures to evaluate them [22], such as the Sensory Processing Measure (SPM) and the Sensory Profile

[23, 24]. Some interventions can be beneficial, and the AAP has developed recommendations to monitor treatment and discuss options with families [25••].

### *Regression of language and social skills*

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Regression of language and social skills in ASD is reported to occur in 32.1% [26, 27]; it is described as an abrupt or gradual loss of previously acquired skills in children with ASD after apparently normal development for the first 1–2 years of life [26]. No specific causes or underlying mechanisms have been found, and there have been mixed results regarding prognosis and long-term outcomes of children with regression. When evaluating a child with a history of regression, it is crucial to tease out the developmental trajectory, investigate underlying pathophysiology such as seizure disorders and metabolic and genetic causes, and complete a clinical workup.

### *ASD assessment*

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ASD assessment needs to include a medical and developmental history with developmental trajectory and history of regression, as well as direct observation of behaviors. One can use validated measures to gather information from parents, teachers, or early intervention providers (such as the Vineland Adaptive Behavior Scales [28], or the Vanderbilt Questionnaires; Table 1). The evaluation of developmental and cognitive levels, educational and language testing, and ADHD evaluation are important [29] as well as assessments of other co-morbid conditions such as anxiety and mood disorders. It is also very important to consider cultural factors when evaluating children for ASD or other developmental delays. Please refer to useful recommendations developed by the Massachusetts Act Early State team ([www.maactearly.org](http://www.maactearly.org)).

## New research updates in ASD

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Important recent studies on EEG, functional and structural MRI, eye tracking, autonomic functions, transcranial magnetic stimulation (TMS), noninvasive positron emission tomography (PET), and single photon emission computed tomography (SPECT) have investigated the underlying pathophysiology and identified potential biological markers for ASD [30]. These techniques are research tools at this point. Genetic research has greatly expanded our understanding of ASD (see below).

### **Eye tracking and pupillometry**

Aberrant eye gaze mechanisms have been implicated in ASD such as diminished eye gaze and eye movements and can be studied using eye tracking technology [31•]. Pupillary constriction is a reliable measure of autonomic

nervous system function, which is poorly modulated and correlates to sensory behaviors in ASD [31•]. Eye tracking and pupillometry have been combined in a novel study of social and emotional calibration in response to a standard stimulus. While eye tracking was similar to controls, children with ASD had less pupillary dilatation than controls, which correlated to the severity of ASD [32].

### Autonomic nervous system

Respiratory and autonomic nervous system dysfunction in ASD show atypical respiratory patterns (Biot's and Cheyne-Stokes) and cardiac vagal hypofunction using precise measures [33••]. Gastrointestinal dysfunction, anxiety, and history of developmental regression correlated to decreased cardiac vagal tone in ASD [34]. The findings implicate low parasympathetic activity in ASD and are consistent with chronic sensory hyperarousal.

### Transcranial magnetic stimulation

Noninvasive repetitive transcranial magnetic stimulation (TMS) is a promising approach to the diagnosis and treatment of ASD. When it was applied in 12 weekly sessions over the dorsolateral prefrontal cortex in children with ASD, autonomic functions improved, along with behavioral measures [35]. TMS lends itself to research for understanding, as well as potential treatment, of altered synaptic plasticity in ASD [36]. TMS appears to be safe, but further research and clinical trials are needed [37•].

### PET and SPECT

Several studies looking at different neurotransmitters, glucose metabolism, or cerebral blood flow in ASD are available; however, results are inconsistent. Anomalies have been reported in cerebral blood flow in the temporal lobes and speech areas and in glucose metabolism in the thalamus and putamen [38]. Serotonin is the most commonly investigated neurotransmitter in ASD [39] with reports of disruption of serotonergic innervation during development. PET and SPECT are research tools with no clinical indications at this point, and further studies are needed to identify biological mechanisms underlying ASD.

### MRI/fMRI

Abnormalities of early brain growth have been reported; however, no consistent pathology has been identified on MRI. The size of the brain stem, posterior fossa, and corpus callosum and the volumes of the amygdala and hippocampus have been studied; abnormalities of the white matter have been reported [40•]. With diffusion tensor imaging (DTI), reduced fractional anisotropy and axial diffusivity were reported in ASD in numerous white matter tracts, including the corpus callosum and thalamocortical fibers [41]. Children with ASD exhibited atypical asymmetry in language-related white matter structure [42].

At this time, this is an area of research that has limitations as patient groups need to be well characterized clinically, and most studies lack longitudinal follow-up. The clinical indications for brain imaging (MRI)

continue to be: focal neurological findings, epilepsy, or a focally abnormal EEG, and MRI is not recommended as a routine test.

### Electroencephalography and magnetoencephalography

Electroencephalography (EEG) and magnetoencephalography (MEG) offer novel insights to brain function in ASD through research, as well as practical approaches to clinical evaluation. Abnormal findings on traditional EEG, such as focal slowing and paroxysmal discharges (even in the absence of clinical seizures), have been associated with ASD, especially in patients with developmental regression, macrocephaly, and temporal lobe localization [43]. Resting state EEG in children with ASD compared to controls, with quantitative methods, demonstrates reduced power in the alpha frequency range (8–14 Hz), as well as reduced network connectivity, which may reflect abnormal patterns of maturation and provide quantitative diagnostic biomarkers [44]. Despite advances, there are many complex variables involved in quantitative EEG that require further research [45•].

MEG is superior to EEG with respect to spatial resolution and does not depend on the electrical conductivity of brain tissue. When combined with MRI, one can precisely localize sources and strength of electrical activity as well as network connectivity. Although not yet widely available, resting state MEG, by itself, has shown atypical reduced connectivity and coherence between areas that correlate to low sociality in young children with ASD. These are becoming useful biomarkers for diagnosis and follow-up in clinical treatment trials [46]. When combined with functional connectivity MRI, hypoconnectivity between many sources of low or high gamma activity (30–60 Hz) becomes evident in patterns that differ in ASD compared to controls [47]. Gamma activity, measured by MEG, combined with magnetic resonance spectroscopy (MRS) to measure gamma-amino butyric acid (GABA) concentrations, has shown decreased GABA (the major inhibitory neurotransmitter) and atypical development of gamma-band coherence in children and adolescents with ASD [48••]. This approach will lend itself to understanding delayed maturation of excitatory: inhibitory balance in ASD, and to potential treatments, such as bumetanide, which increases GABA and may restore the normal maturational trajectory [49•].

### Genetics

Genetic research has greatly expanded our understanding that the extreme clinical heterogeneity of ASD is connected to convergent biochemical pathways by identifying more than 100 specific genes and genomic regions and over 800 genes that are involved more generally [50]. In up to 40% of patients, ASD can now be associated with specific genetic abnormalities, up to 10% by copy number variations on chromosomal microarrays (most of which occur *de novo*), and 30% by whole exome or genome sequencing. Numerous genes and pathways have been identified in genome-wide association studies (GWAS) and gene sequencing technology that affect neurite outgrowth, synaptic functions, *wnt* signaling, and chromatin remodeling [51, 52]. Along with similar advances in related fields, it is now apparent that similar genetic findings blur the clinical boundaries between ASD and schizophrenia, ADHD, intellectual disability, and epilepsy, which suggests that common phenotypes are different, though



overlapping, forms of developmental brain dysfunction that share common disease mechanisms [53, 54•]. Analysis of transcriptomes of postmortem ASD brain confirms convergent molecular pathology and suggests that dysregulation of transcription and splicing may lead to neuronal and synaptic dysfunction in ASD [55].

Clinical genetics in the evaluation of ASD requires a tiered approach that should be tailored to the individual patient and family [56]. After the diagnosis of ASD, initial medical evaluation should be followed by a careful 3-generation family history. If a syndromic diagnosis is suspected, specific testing may be done (e.g., fragile X, Rett) [57]. A chromosomal microarray for de novo copy number variations (CNVs) will be appropriate for most patients, as well as fragile X testing for male patients. Metabolic testing may be indicated by developmental regression associated with illness or fever, cyclic vomiting, gastrointestinal dysfunction, microcephaly, and seizures. A second tier of evaluation may include whole exome or genome sequencing, MRI, and MR spectroscopy. At each step, genetic counseling is indicated, whether or not a genetic etiology is identified [53]. Given continued experience with common and rare genetic variants, along with delineation of phenotypic data, new genetic causes of ASD are accumulating at an increasing rate [58••, 59]. It is therefore important to periodically update genetic evaluation and testing for patients for whom the etiology of ASD remains unknown.

## New treatments in ASD

### Current conventional treatment

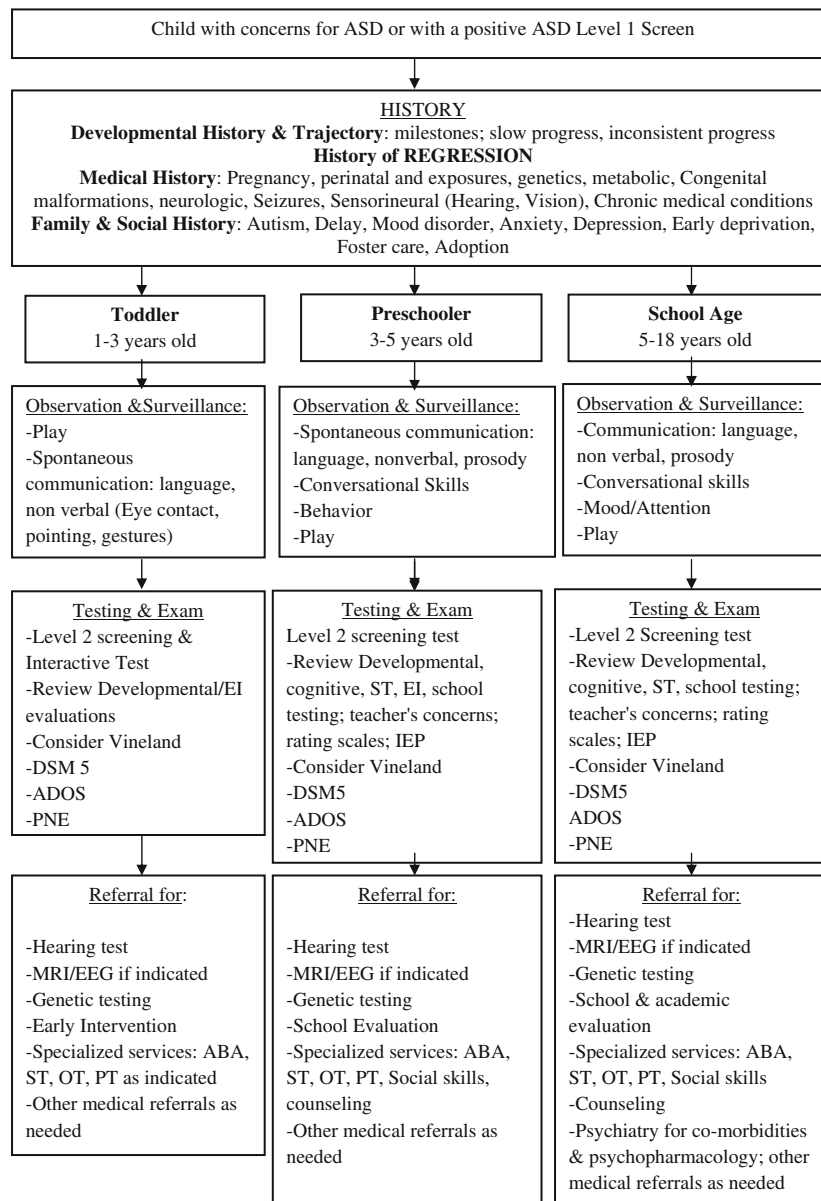
Current conventional treatment of ASD in children includes intensive behavioral interventions (known as applied behavioral analysis or ABA), rehabilitative services such as speech therapy, occupational therapy, physical therapy, social skills training, and counseling. Please refer to the flow chart (Fig. 1) for recommended treatments by age. Below, we do not review new behavioral or developmental approaches, but rather non-behavioral interventions.

Traditional pharmaceuticals are commonly used to treat autistic symptoms, but do not affect the core symptoms of ASD [60••]. Despite their limitations and narrow range of effects, a number of agents can alleviate features of ASD, in different degrees and with side effects that vary among individual patients. The selection of agents requires careful consideration of individual symptoms and needs, with regular follow-up and monitoring for efficacy and side effects.

Most agents are used off-label; two atypical antipsychotic medications (risperidone and aripiprazole) are currently the only FDA-approved medications for the treatment of aggression and irritability in ASD [61]. Both are dopamine D2 and serotonin 2A receptor antagonists, and their efficacy has been confirmed in clinical trials. Side effects include sedation, increased appetite and weight gain, and potential for extrapyramidal symptoms and paradoxical restlessness, among others. Other “atypicals” include quetiapine, ziprasidone, and olanzapine. Despite their side effects, they are preferable to the sedation and risk of extrapyramidal syndrome associated with the “typical” agents, including chlorpromazine and haloperidol.

Methylphenidate and other stimulant medications are dopamine reuptake inhibitors that are usually effective for treatment of ADHD. In patients with





**Fig. 1.** ASD Assessment. *ST* speech therapy, *OT* occupational therapy, *PT* physical therapy, *ABA* applied behavioral analysis, *ET* early intervention, *PNE* physical and neurological exam, *IEP* individualized educational plan.

autism, they may also be effective for symptoms of ADHD but may induce irritability, even if they improve attention and reduce hyperactivity [62•]. Guanfacine and clonidine are  $\alpha$ 2-adrenergic receptor agonists that provide alternative treatments for symptoms of ADHD, and clonidine is useful for sleep onset, though not maintenance [63]. Atomoxetine, a norepinephrine reuptake inhibitor, has demonstrated efficacy for ADHD symptoms in children with ASD, and its effects may be enhanced by parent training [64•].

Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, citalopram) have not shown consistent benefits for improving repetitive behaviors in children

and adolescents 5–17 years of age [65, 66]. A recent trial of buspirone (a 5HT<sub>1A</sub> partial agonist) in young children (2 to 6 years) with ASD demonstrated improvements in restricted and repetitive behaviors, consistent with the known trophic effects of serotonin in early brain development [67•]. Caution is advised because irritability, hyperactivity, and insomnia may result from stimulating serotonin in young children, and SSRIs can exacerbate mania in individuals with latent bipolar disorder (a frequent feature in the family histories of patients with ASD).

For sleep, a common problem in ASD, melatonin, and  $\alpha$ -agonists (e.g., clonidine) have been helpful for inducing sleep onset. The benefits of melatonin reflect atypical metabolism and low production of the hormone in ASD [68]. However, its short half life means that it often does not maintain sleep and may be combined with, or replaced by, a controlled release form of melatonin [69]. Other agents used for sleep (e.g., iron supplements, antihistamines, atypical antipsychotics, antidepressants, benzodiazepines, gabapentin, and anticonvulsants) have variable responses and side effects and have not been well studied in ASD [70•].

Gastrointestinal problems occur commonly in ASD and are evaluated following general pediatric guidelines [71]. Treatments for gastroesophageal reflux disease, chronic abdominal pain, constipation and diarrhea may ameliorate concurrent abnormal sleep and behavior. Differences in the microbiome in ASD compared to typically developing children raise the possibility that current research may lead to fecal transplants as well as new probiotics and medications [72•].

Mitochondrial dysfunction and oxidative stress are likely to occur in 20% or more of children with ASD and may be treatable but difficult to diagnose [73•]. Various deficits in electron transport or Krebs cycle intermediates during development may prevent optimal immune and metabolic responses under stress and may become less evident as development proceeds. Screening for mitochondrial functions may lead to trials of antioxidants or cofactors (e.g., coenzyme Q10, carnitine, vitamin B<sub>1</sub>), even though their efficacy has not been established in systematic studies [74].

## Novel compounds

Novel compounds (Table 2) for treatment of ASD are so designated because they have credible postulated mechanisms of action in ASD, but are not advocated by many practitioners because their safety or efficacy is based on limited evidence. For each compound listed, a reliable reference discusses the rationale for its use, safety, and suggested dosing regimen. The reader is encouraged to review the references cited as well as others from reliable sources in considering recommendations for treatment. Note that although many of these agents appear to be innocuous, they are largely untested and may have unforeseen interactions with other medications. Pending further research and clinical experience, the reader is cautioned that apparently benign “supplements” can act as “drugs,” even if they are not so classified. The following compounds are grouped according to their effects on neurotransmitter systems, as neurohormones, folate-dependent one-carbon metabolism, antioxidants and anti-inflammatories, and food-derived compounds that affect cellular metabolism.

Compounds that facilitate GABA activity take advantage of its deficiency in ASD. Failure of the normal conversion of GABA from being excitatory to inhibitory

**Table 2. Novel therapies and evidence: medication options for ASD**

Compound	Description	Effects and evidence	References
Arbaclofen	GABA(B) receptor agonist	Improved social behavior, reduced irritability; negative trial results	[75]
Buspirone	5HT <sub>1A</sub> serotonin receptor partial agonist	Clinical trial in children 2–6 with ASD: improved restrictive and repetitive behaviors. Reduced irritability in combination with risperidone	[67•, 81]
Bumetanide	Loop diuretic; inhibits sodium and chloride resorption. Increases GABA inhibition	Animal and human clinical trials in ASD	[49•]
Curcumin	Natural phenol derivative of turmeric; anti-inflammatory, antioxidant	Effective in propanoic acid animal model, on behavior and biochemical markers. Human trials needed	[93, 94]
Donepezil	Acetylcholinesterase inhibitor	Several human trials; most show improvements in ASD behaviors and REM sleep	[99]
Folinic acid	Folic acid supplementation for cerebral folate deficiency or autoantibodies to folate receptor alpha	Reports of improvements in symptoms of ASD	[87••]
Galantamine	Acetylcholinesterase inhibitor	Augmentation therapy with risperidone in 4–12-year-olds, reduced irritability and lethargy/social withdrawal	[78]
Insulin-like growth factor-1 (IGF-1)	Critical factor in normal CNS development	Several clinical studies show potential efficacy in ASD and NDD	[84]
Luteolin	Flavonoid; antioxidant, anti-inflammatory	Positive effects on adaptive functioning and behavior; reduced TNF and IL-6	[95•]
Memantine	NMDA glutamate receptor antagonist	Variable trial results in ASD symptoms	[76]
Methyl B12	Cellular methylation cofactor and antioxidant	Clinical trial showed improved CGI scores but no change in parent-rated ABC or SRS	[88]
N-acetylcysteine	Mucolytic, antioxidant, prevents apoptosis, and improves neuroinflammation	Apparent efficacy in ASD and other neuropsychiatric disorders	[90, 91]
Oxytocin	Neuropeptide	Several trials; improves social cognition and eye gaze and interacts with serotonin	[82•, 83]
Propranolol	Beta adrenergic receptor antagonist	Improve conversational reciprocity, possibly as anxiolytic	[80•]
Rivastigmine	Acetylcholinesterase inhibitor	Improve expressive speech and autism behaviors	[79]
Sulforaphane	Isothiocyanate, broccoli sprout extract	A single placebo-controlled trial demonstrated significant clinical benefits	[96•, 97]
Tetrahydrobiopterin (BH4)	Cofactor for production of monoamine neurotransmitters; low levels in ASD	Reduced core symptoms of ASD	[89]

early in development in ASD may account for an imbalance between inhibition and excitation and the frequently paradoxical effects of GABAergic compounds (e.g. benzodiazepines). Arbaclofen, a modified form of baclofen, is a GABA(B) receptor agonist that has shown promise for improved social behavior but overall negative early clinical trial results [75]. Bumetanide, a loop diuretic, chloride importer antagonist, and antihypertensive, increases GABA inhibition by reducing intracellular chloride in cortical neurons. Clinical trials of bumetanide have demonstrated relative safety and efficacy in ASD in global ratings as well as facial and emotional processing [49•]. Based on decreased GABA activity and therefore increased ratio of excitatory to inhibitory activity in ASD, memantine, a glutamate receptor antagonist used for treatment of Alzheimer disease, was reported to show improved social interaction and communication in open-label trials, but no

benefits in a large placebo-controlled trial [76].

Acetylcholine receptors, both muscarinic and nicotinic, are decreased, especially in the basal forebrain and cortex in ASD, which have provided the rationale for trials of acetylcholinesterase inhibitors. Seven trials of Donepezil have shown improvements in behavior and REM sleep in some, but not others, with mostly mild side effects [77]. Galantamine was effective in several trials and when used with risperidone, in reducing irritability and social withdrawal, and was well tolerated [78]. Rivastigmine improved expressive speech and autistic behaviors in a single open-label study [79].

Adrenergic receptors, both  $\beta_1$  and  $\beta_2$ , are nonselectively antagonized by propranolol, which readily crosses the blood–brain barrier. Single doses of propranolol have led to improved conversational reciprocity in a study in young adults with ASD, possibly acting as an anxiolytic and improving non-verbal communication [80•]. Side effects from its repeated or long term use (e.g., fatigue, depression, autonomic changes) may limit its usefulness.

Serotonergic compounds may have different effects in early, compared to later, brain development. As noted above, a recent trial of buspirone was effective in 2 to 6-year-old children with ASD [67•]. In children and adolescents with ASD, buspirone at low doses was superior to placebo when given with risperidone for treating irritability [81].

The neuropeptide oxytocin generates great interest due to its involvement in social cognition and eye gaze, both of which have improved in clinical trials and neuroimaging studies in ASD [82•]. However, its short duration of action (usually by intranasal administration) and uncertain effects of long-term use require larger and more extensive clinical trials. Recent evidence for important interaction between oxytocin and serotonin signaling may lead to simultaneous treatment of both systems [83]. Insulin-like growth factor-1 (IGF-1) is a commercially available polypeptide hormone with important roles during brain development and in synaptic connectivity. Positive effects in preclinical models of ASD and early results of a clinical trial in Phelan-McDermid syndrome (a genetically defined form of ASD) suggest that it may be beneficial for social impairment and repetitive behaviors [84].

We now recognize that folate-dependent one-carbon metabolism is central to several critical and interwoven pathways in which individuals with ASD differ from controls with respect to their cellular folate, methylation, glutathione, and tetrahydrobiopterin metabolism [85]. Genetic polymorphisms within these pathways, antibodies to folate receptors, nutritional deficiency, certain toxins, and environmental factors may lead to different effects on oxidation-reduction (redox) balance that damage cellular DNA, protein, and lipids through oxidative stress. Folinic acid, a reduced form of folic acid, crosses the blood–brain barrier and can treat symptoms of ASD in cerebral folate deficiency, as well as ASD with folate-receptor antibodies [86]. In a recent clinical trial, high-dose folinic acid improved verbal communication in children with ASD [87••]. Vitamin B<sub>12</sub> (Methyl B12), an important cofactor for methylation, improved clinician-rated symptoms of ASD as well as biochemical measures of methylation capacity [88].

Tetrahydrobiopterin (BH4) is essential for the production of monoamine neurotransmitters and nitric oxide, which are affected in ASD, and low levels have been reported in the CNS. Treatment with BH4 may reduce core

symptoms of ASD [89].

*N*-Acetylcysteine (NAC), an antioxidant and glutamate modulator, is in use as a mucolytic and to treat acetaminophen overdose. NAC increases intracellular glutathione by providing its cysteine precursor, and several neuropsychiatric disorders, including ASD, have responded to NAC in clinical trials [90]. There is evidence for its safety, as well as efficacy, for irritability in ASD; however, a recent study found no effects on social impairment [91].

Nutraceuticals (plant-derived compounds) hold promise as treatments for ASD, for both their safety and efficacy, although some research studies have been limited by small sample sizes and study designs [92]. Curcumin is a phenol derivative of turmeric (Asian spice and medicinal herb). It has anti-inflammatory and antioxidant properties and inhibits activation of microglia *in vitro* but has poor oral bioavailability [93]. Curcumin was effective orally, using both behavioral and biochemical measures, in a propanoic acid rodent model of ASD [94]. Despite its potential, curcumin has not been approved for therapeutic use in humans; clinical trials are needed to assess its safety and efficacy. Luteolin, a flavonoid plant pigment, is a multifunctional antioxidant and anti-inflammatory that inhibits mast cell degranulation and microglial activation. Combined with quercetin (another flavonoid), luteolin improved adaptive functioning and ASD symptoms in an open-label trial [95•]. Sulforaphane, an isothiocyanate derived from broccoli, has been studied widely in cancer and recently showed efficacy in improving sociability and aberrant behaviors in a placebo-controlled trial in young men with ASD [96•]. The rationale for its use in ASD is based on its effects on several cellular processes, such as redox metabolism, mitochondrial function, immune dysregulation, and synaptic function [97]. A similar clinical trial of sulforaphane is currently underway in children with ASD (NCT02561481).

No matter how safe some of these novel, as well as the traditional, compounds for the treatment of ASD may appear, most are not FDA-approved and any of them may have as yet unforeseen side effects or interactions with dietary factors, other essential medications, or environmental factors that cannot be predicted from the limited research and experience available. Only the continuing efforts of the families, researchers, and autism support organizations will provide the information necessary to assure their safety and efficacy for persons with ASD.

In conclusion, these assessments and treatments offer a new and expanded array of possible approaches to ASD. The lists are not exhaustive and do not include complementary and alternative medical assessments, assays and treatments, and diets [98•]. Not included is the emerging research on immunology, microbiome, metabolomics, and metabolic testing, as well as the assessment of ASD in adults. However, we have attempted to include new validated information and provide clinical guidance for the evaluation and treatment of young children and youth with ASD.

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## Compliance with Ethical Standards

### Conflict of Interest

Roula N. Choueiri reports that she is the principal author on a paper referenced in the review (A New Interactive Autism Screening test in Toddlers). It is a test she is currently developing; however, she receives no royalties and there are no financial benefits from it. It is copyrighted to Tufts Medical Center and University of Massachusetts Medical School both hold intellectual property. Andrew W. Zimmerman reports that he has a patent on the use of sulforaphane for treatment of autism spectrum disorder issued to Johns Hopkins University and is a co-author on reference #96 (Singh K et al., PNAS 2014), a clinical trial of sulforaphane in treatment of ASD.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
- 2.•• Filipek PA, Accardo PJ, Ashwal S, Baranek GT, Cook Jr EH, Dawson G, et al. Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. *Neurology*. 2000;55(4):468–79.
- This paper is important as clinical parameters to follow in the assessment of ASD.
- 3.•• Johnson CP, Myers SM. American Academy of Pediatrics Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1183–215. doi:10.1542/peds.2007-2361.
- This paper is important as clinical parameters to follow in the assessment of ASD.
4. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ*. 2014 Mar 28;63(2):1–21.
- 5.• Daniels AM, Mandell DS. Children's compliance with American Academy of Pediatrics' well-child care visit guidelines and the early detection of autism. *J Autism Dev Disord*. 2013;43(12):2844–54. doi:10.1007/s10803-013-1831-x.
- This paper emphasizes the importance of screening and compliance with AAP guidelines.
6. Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. Validation of the modified checklist for Autism in toddlers, revised with follow-up (M-CHAT-R/F). *Pediatrics*. 2014;133(1):37–45. doi:10.1542/peds.2013-1813.
7. Williams J, Allison C, Scott F, Stott C, Bolton P, Baron-Cohen S, et al. The Childhood Asperger Syndrome Test (CAST): test-retest reliability. *Autism*. 2006;10(4):415–27. doi:10.1177/1362361306066612.
8. Chandler S, Charman T, Baird G, Simonoff E, Loucas T, Meldrum D, et al. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(10):1324–32. doi:10.1097/chi.0b013e31812f7d8d.
9. Rutter ML, Le Couteur A, Lord C. *Autism diagnostic interview—revised*. Los Angeles: Western Psychological Services; 2003.
10. Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, et al. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *J Autism Dev Disord*. 2003;33(4):427–33.
11. Moulton E, Bradbury K, Barton M, Fein D. Factor analysis of the childhood autism rating scale in a sample of two year olds with an autism spectrum disorder. *J Autism Dev Disord*. 2016. doi:10.1007/s10803-016-2936-9.
12. Volker MA, Dua EH, Lopata C, Thomeer ML, Toomey JA, Smerbeck AM, et al. Factor structure, internal



- consistency, and screening sensitivity of the GARS-2 in a developmental disabilities sample. *Autism Res Treat*. 2016;2016:8243079. doi:[10.1155/2016/8243079](https://doi.org/10.1155/2016/8243079).
13. Stone WL, Coonrod EE, Turner LM, Pozdol SL. Psychometric properties of the STAT for early autism screening. *J Autism Dev Disord*. 2004;34(6):691–701.
  14. Choueiri R, Wagner S. A New interactive screening test for autism spectrum disorders in toddlers. *J Pediatr*. 2015;167(2):460–6. doi:[10.1016/j.jpeds.2015.05.029](https://doi.org/10.1016/j.jpeds.2015.05.029).
  15. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (4th ed., text rev.)*. Washington, DC: American Psychiatric Publishing; 2000.
  16. Christiansz JA, Gray KM, Taffe J, Tonge BJ. Autism spectrum disorder in the DSM-5: diagnostic sensitivity and specificity in early childhood. *J Autism Dev Disord*. 2016;46(6):2054–63. doi:[10.1007/s10803-016-2734-4](https://doi.org/10.1007/s10803-016-2734-4).
  - 17.●● Kulage KM, Smaldone AM, Cohn EG. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *J Autism Dev Disord*. 2014;44(8):1918–32. doi:[10.1007/s10803-014-2065-2](https://doi.org/10.1007/s10803-014-2065-2).  
An important review of DSM 5 changes and practice.
  - 18.●● Lord C, Bishop SL. Recent advances in autism research as reflected in DSM-5 criteria for autism spectrum disorder. *Annu Rev Clin Psychol*. 2015;11:53–70. doi:[10.1146/annurev-clinpsy-032814-112745](https://doi.org/10.1146/annurev-clinpsy-032814-112745).  
An important review of DSM 5 changes and research.
  19. Lord C, Rutter ML, DiLavore P, Risi S. *Autism Diagnostic Observation Schedule (ADOS) manual*. Los Angeles: Western Psychological Services; 2001.
  20. Luyster R, Gotham K, Guthrie W, Coffing M, Petrak R, Pierce K, et al. The Autism Diagnostic Observation Schedule-toddler module: a new module of a standardized diagnostic measure for autism spectrum disorders. *J Autism Dev Disord*. 2009;39(9):1305–20. doi:[10.1007/s10803-009-0746-z](https://doi.org/10.1007/s10803-009-0746-z).
  21. Guthrie W, Swineford LB, Wetherby AM, Lord C. Comparison of DSM-IV and DSM-5 factor structure models for toddlers with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2013;52(8):797–805 e2. doi:[10.1016/j.jaac.2013.05.004](https://doi.org/10.1016/j.jaac.2013.05.004).
  22. Schaaf RC, Lane AE. Toward a best-practice protocol for assessment of sensory features in ASD. *J Autism Dev Disord*. 2015;45(5):1380–95. doi:[10.1007/s10803-014-2299-z](https://doi.org/10.1007/s10803-014-2299-z).
  23. Miller-Kuhaneck H, Henry D, Glennon T. *Sensory Processing Measure (SPM)—Home Form*. Torrance: Western Psychological Services; 2010.
  24. Dunn W. *Sensory profile: adolescent/adult sensory profile*. San Antonio: Pearson Assessments; 2002.
  - 25.●● Section On C, Integrative M. Council on Children with D, American Academy of P, Zimmer M, Desch L. Sensory integration therapies for children with developmental and behavioral disorders. *Pediatrics*. 2012;129(6):1186–9. doi:[10.1542/peds.2012-0876](https://doi.org/10.1542/peds.2012-0876).  
Recommendations from the AAP on sensory based therapies.
  26. Barger BD, Campbell JM, McDonough JD. Prevalence and onset of regression within autism spectrum disorders: a meta-analytic review. *J Autism Dev Disord*. 2013;43(4):817–28. doi:[10.1007/s10803-012-1621-x](https://doi.org/10.1007/s10803-012-1621-x).
  27. Williams K, Brignell A, Prior M, Bartak L, Roberts J. Regression in autism spectrum disorders. *J Paediatr Child Health*. 2015;51(1):61–4. doi:[10.1111/jpc.12805](https://doi.org/10.1111/jpc.12805).
  28. Sparrow SS, Balla DA, Cicchetti DV. *Vineland Adaptive Behavior Scales Second Edition Survey Forms Manual*. AGS Publishing; 2005.
  29. Ozonoff S, Goodlin-Jones BL, Solomon M. Evidence-based assessment of autism spectrum disorders in children and adolescents. *J Clin Child Adolesc Psychol*. 2005;34(3):523–40. doi:[10.1207/s15374424jccp3403\\_8](https://doi.org/10.1207/s15374424jccp3403_8).
  30. Bolte S, Bartl-Pokorny KD, Jonsson U, Berggren S, Zhang D, Kostrzewa E, et al. How can clinicians detect and treat autism early? Methodological trends of technology use in research. *Acta Paediatr*. 2016;105(2):137–44. doi:[10.1111/apa.13243](https://doi.org/10.1111/apa.13243).
  - 31.● Daluwatte C, Miles JH, Sun J, Yao G. Association between pupillary light reflex and sensory behaviors in children with autism spectrum disorders. *Res Dev Disabil*. 2015;37:209–15. doi:[10.1016/j.ridd.2014.11.019](https://doi.org/10.1016/j.ridd.2014.11.019).  
This paper outlines the basis for differences in the pupillary light reflex in ASD.
  32. Nuske HJ, Vivanti G, Dissanayake C. Others' emotions teach, but not in autism: an eye-tracking pupillometry study. *Mol Autism*. 2016;7(1):36. doi:[10.1186/s13229-016-0098-4](https://doi.org/10.1186/s13229-016-0098-4).
  - 33.●● Ming X, Patel R, Kang V, Chokroverty S, Julu PO. Respiratory and autonomic dysfunction in children with autism spectrum disorders. *Brain Dev*. 2016;38(2):225–32. doi:[10.1016/j.braindev.2015.07.003](https://doi.org/10.1016/j.braindev.2015.07.003).  
This is a useful review of autonomic testing and dysfunction in ASD.
  34. Ferguson BJ, Marler S, Altstein LL, Lee EB, Akers J, Sohl K, et al. Psychophysiological associations with gastrointestinal symptomatology in autism spectrum disorder. *Autism Res*. 2016. doi:[10.1002/aur.1646](https://doi.org/10.1002/aur.1646).
  35. Wang Y, Hensley MK, Tasman A, Sears L, Casanova MF, Sokhadze EM. Heart rate variability and skin conductance during repetitive TMS course in children with autism. *Appl Psychophysiol Biofeedback*. 2016;41(1):47–60. doi:[10.1007/s10484-015-9311-z](https://doi.org/10.1007/s10484-015-9311-z).
  36. Oberman LM, Ifert-Miller F, Najib U, Bashir S, Heydrich JG, Picker J, et al. Abnormal mechanisms of plasticity and metaplasticity in autism spectrum disorders and fragile X syndrome. *J Child Adolesc Psychopharmacol*. 2016;26(7):617–24. doi:[10.1089/cap.2015.0166](https://doi.org/10.1089/cap.2015.0166).
  - 37.● Oberman LM, Enticott PG, Casanova MF, Rotenberg A, Pascual-Leone A, McCracken JT, et al. Transcranial magnetic stimulation in autism spectrum disorder: challenges, promise, and roadmap for future research. *Autism Res*. 2016;9(2):184–203. doi:[10.1002/aur.1567](https://doi.org/10.1002/aur.1567).  
This paper is a helpful review of TMS in ASD.



38. Zurcher NR, Bhanot A, McDougle CJ, Hooker JM. A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neurosci Biobehav Rev.* 2015;52:56–73. doi:10.1016/j.neubiorev.2015.02.002.
39. Chugani DC. Neuroimaging and neurochemistry of autism. *Pediatr Clin North Am.* 2012;59(1):63–73. doi:10.1016/j.pcl.2011.10.002.
- 40.● Ismail MM, Keynton RS, Mostapha MM, ElTanboly AH, Casanova MF, Gimelfarb GL, et al. Studying autism spectrum disorder with structural and diffusion magnetic resonance imaging: a survey. *Front Hum Neurosci.* 2016;10:211. doi:10.3389/fnhum.2016.00211.
- This is a good review of recent techniques using MRI for research in ASD.
41. Vogan VM, Morgan BR, Leung RC, Anagnostou E, Doyle-Thomas K, Taylor MJ. Widespread white matter differences in children and adolescents with autism spectrum disorder. *J Autism Dev Disord.* 2016;46(6):2138–47. doi:10.1007/s10803-016-2744-2.
42. Joseph RM, Fricker Z, Fenoglio A, Lindgren KA, Knaus TA, Tager-Flusberg H. Structural asymmetries of language-related gray and white matter and their relationship to language function in young children with ASD. *Brain Imaging Behav.* 2014;8(1):60–72. doi:10.1007/s11682-013-9245-0.
43. Valvo G, Baldini S, Retico A, Rossi G, Tancredi R, Ferrari AR, et al. Temporal lobe connects regression and macrocephaly to autism spectrum disorders. *Eur Child Adolesc Psychiatry.* 2016;25(4):421–9. doi:10.1007/s00787-015-0746-9.
44. Matlis S, Boric K, Chu CJ, Kramer MA. Robust disruptions in electroencephalogram cortical oscillations and large-scale functional networks in autism. *BMC Neurol.* 2015;15:97. doi:10.1186/s12883-015-0355-8.
- 45.● Heunis TM, Aldrich C, de Vries PJ. Recent advances in resting-state electroencephalography biomarkers for autism spectrum disorder—a review of methodological and clinical challenges. *Pediatr Neurol.* 2016;61:28–37. doi:10.1016/j.pediatrneurol.2016.03.010.
- This review covers advances in EEG in the field of ASD.
46. Kikuchi M, Yoshimura Y, Mutou K, Minabe Y. Magnetoencephalography in the study of children with autism spectrum disorder. *Psychiatry Clin Neurosci.* 2016;70(2):74–88. doi:10.1111/pcn.12338.
47. Datko M, Gougelet R, Huang MX, Pineda JA. Resting state functional connectivity MRI among spectral MEG current sources in children on the autism spectrum. *Front Neurosci.* 2016;10:258. doi:10.3389/fnins.2016.00258.
- 48.●● Port RG, Gaetz W, Bloy L, Wang DJ, Blaskey L, Kuschner ES, et al. Exploring the relationship between cortical GABA concentrations, auditory gamma-band responses and development in ASD: Evidence for an altered maturational trajectory in ASD. *Autism Res.* 2016. doi:10.1002/aur.1686.
- This unique study explores excitatory/inhibitory imbalance in ASD using both MEG and MRS.
- 49.● Lemonnier E, Degrez C, Phelep M, Tyzio R, Josse F, Grandgeorge M, et al. A randomised controlled trial of bumetanide in the treatment of autism in children. *Transl Psychiatry.* 2012;2, e202. doi:10.1038/tp.2012.124.
- In this paper, the basis for the use of bumetanide is outlined in a well controlled clinical trial.
50. O’Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, et al. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature.* 2012;485(7397):246–50. doi:10.1038/nature10989.
51. Hussman JP, Chung RH, Griswold AJ, Jaworski JM, Salyakina D, Ma D, et al. A noise-reduction GWAS analysis implicates altered regulation of neurite outgrowth and guidance in autism. *Mol Autism.* 2011;2(1):1. doi:10.1186/2040-2392-2-1.
52. Krumm N, O’Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. *Trends Neurosci.* 2014;37(2):95–105. doi:10.1016/j.tins.2013.11.005.
53. Finucane B, Myers SM. Genetic counseling for autism spectrum disorder in an evolving theoretical landscape. *Curr Genet Med Rep.* 2016;4:147–53. doi:10.1007/s40142-016-0099-9.
- 54.● de la Torre-Ubieta L, Won H, Stein JL, Geschwind DH. Advancing the understanding of autism disease mechanisms through genetics. *Nat Med.* 2016;22(4):345–61. doi:10.1038/nm.4071.
- A comprehensive and thoughtful paper, the authors outline current advances in genetics of ASD.
55. Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature.* 2011;474(7351):380–4. doi:10.1038/nature10110.
56. Schaefer GB, Mendelsohn NJ, Professional P, Guidelines C. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* 2013;15(5):399–407. doi:10.1038/gim.2013.32.
57. Rosti RO, Sadek AA, Vaux KK, Gleeson JG. The genetic landscape of autism spectrum disorders. *Dev Med Child Neurol.* 2014;56(1):12–8. doi:10.1111/dmcn.12278.
- 58.●● An JY, Claudianos C. Genetic heterogeneity in autism: from single gene to a pathway perspective. *Neurosci Biobehav Rev.* 2016;68:442–53. doi:10.1016/j.neubiorev.2016.06.013.
- This important paper advances conceptual thinking about a “pathway perspective” in ASD.
59. Bourgeron T. Current knowledge on the genetics of autism and propositions for future research. *C R Biol.* 2016;339(7–8):300–7. doi:10.1016/j.crv.2016.05.004.
- 60.●● Penagarikano O. New therapeutic options for autism spectrum disorder: experimental evidences. *Exp Neurobiol.* 2015;24(4):301–11. doi:10.5607/en.2015.24.4.301.

Useful approach to exploration of therapeutic options for ASD is outlined in this paper.

61. Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic treatment of severe irritability and problem behaviors in autism: a systematic review and meta-analysis. *Pediatrics*. 2016;137 Suppl 2:S124–35. doi:10.1542/peds.2015-2851K.
62. Ji N, Findling RL. An update on pharmacotherapy for autism spectrum disorder in children and adolescents. *Curr Opin Psychiatry*. 2015;28(2):91–101. doi:10.1097/YCO.000000000000132.

This is a well written paper by knowledgeable authors on use of medications for ASD.

63. Scahill L, McCracken JT, King BH, Rockhill C, Shah B, Politte L, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *Am J Psychiatry*. 2015;172(12):1197–206. doi:10.1176/appi.ajp.2015.15010055.
64. Handen BL, Aman MG, Arnold LE, Hyman SL, Tumuluru RV, Lecavalier L, et al. Atomoxetine, parent training, and their combination in children with autism spectrum disorder and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(11):905–15. doi:10.1016/j.jaac.2015.08.013.

A unique approach is offered in this paper: combining parent training with a medication.

65. Hollander E, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology*. 2005;30(3):582–9. doi:10.1038/sj.npp.1300627.
66. King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry*. 2009;66(6):583–90. doi:10.1001/archgenpsychiatry.2009.30.
67. Chugani DC, Chugani HT, Wiznitzer M, Parikh S, Evans PA, Hansen RL, et al. Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: a randomized trial. *J Pediatr*. 2016;170:45–53.e1-4. doi:10.1016/j.jpeds.2015.11.033.

This is a landmark study of serotonergic therapy in young children with ASD.

68. Veatch OJ, Goldman SE, Adkins KW, Malow BA. Melatonin in children with autism spectrum disorders: how does the evidence fit together? *J Nat Sci*. 2015;1(7):e125.
69. Cortese S, Brown TE, Corkum P, Gruber R, O'Brien LM, Stein M, et al. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2013;52(8):784–96. doi:10.1016/j.jaac.2013.06.001.
70. Malow BA, Katz T, Reynolds AM, Shui A, Carno M, Connolly HV, et al. Sleep difficulties and medications in children with autism spectrum disorders: a registry study. *Pediatrics*. 2016;137 Suppl 2:S98–S104. doi:10.

1542/peds.2015-2851H.

Sleep difficulties in ASD are well-addressed in this study.

71. Buie T, Fuchs GJ, III Furuta GT, Kooros K, Levy J, Lewis JD, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. *Pediatrics*. 2010;125 Suppl 1:S19–29. doi:10.1542/peds.2009-1878D.
72. Buie T. Potential etiologic factors of microbiome disruption in autism. *Clin Ther*. 2015;37(5):976–83. doi:10.1016/j.clinthera.2015.04.001.

This is an excellent review of the microbiome in ASD by an expert in the field.

73. Legido A, Jethva R, Goldenthal MJ. Mitochondrial dysfunction in autism. *Semin Pediatr Neurol*. 2013;20(3):163–75. doi:10.1016/j.spen.2013.10.008.
- Mitochondrial dysfunction is nicely reviewed in this paper.
74. Haas RH, Parikh S, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics*. 2007;120(6):1326–33. doi:10.1542/peds.2007-0391.
  75. Brondino N, Fusar-Poli L, Panisi C, Damiani S, Barale F, Politi P. Pharmacological modulation of GABA function in autism spectrum disorders: a systematic review of human studies. *J Autism Dev Disord*. 2016;46(3):825–39. doi:10.1007/s10803-015-2619-y.
  76. Aman MG, Findling RL, Hardan AY, Hendren RL, Melmed RD, Kehinde-Nelson O, et al. Safety and efficacy of memantine in children with autism: randomized, placebo-controlled study and open-label extension. *J Child Adolesc Psychopharmacol*. 2016. doi:10.1089/cap.2015.0146.
  77. Buckley AW, Sassower K, Rodriguez AJ, Jennison K, Wingert K, Buckley J, et al. An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders. *J Child Adolesc Psychopharmacol*. 2011;21(4):353–7. doi:10.1089/cap.2010.0121.
  78. Ghaleiha A, Ghyasvand M, Mohammadi MR, Farokhnia M, Yadegari N, Tabrizi M, et al. Galantamine efficacy and tolerability as an augmentative therapy in autistic children: a randomized, double-blind, placebo-controlled trial. *J Psychopharmacol*. 2014;28(7):677–85. doi:10.1177/0269881113508830.
  79. Chez MG, Aimonovitch M, Buchanan T, Mrazek S, Tremb RJ. Treating autistic spectrum disorders in children: utility of the cholinesterase inhibitor rivastigmine tartrate. *J Child Neurol*. 2004;19(3):165–9.
  80. Zamzow RM, Ferguson BJ, Stichter JP, Porges EC, Ragsdale AS, Lewis ML, et al. Effects of propranolol on conversational reciprocity in autism spectrum disorder: a pilot, double-blind, single-dose psychopharmacological challenge study. *Psychopharmacology (Berl)*. 2016;233(7):1171–8. doi:10.1007/s00213-015-4199-0.

In this study, the authors offer an unusual approach to cognition and treatment in ASD using propranolol.

81. Ghanizadeh A, Ayoobzadehshirazi A. A randomized double-blind placebo-controlled clinical trial of adjunct buspirone for irritability in autism. *Pediatr Neurol*. 2015;52(1):77–81. doi:10.1016/j.pediatrneurol.2014.09.017.
82. • Preti A, Melis M, Siddi S, Vellante M, Doneddu G, Fadda R. Oxytocin and autism: a systematic review of randomized controlled trials. *J Child Adolesc Psychopharmacol*. 2014;24(2):54–68. doi:10.1089/cap.2013.0040.
- Many questions regarding oxytocin in ASD are addressed in this paper.
83. Mottotese R, Redoute J, Costes N, Le Bars D, Sirigu A. Switching brain serotonin with oxytocin. *Proc Natl Acad Sci U S A*. 2014;111(23):8637–42. doi:10.1073/pnas.1319810111.
84. Costales J, Kolevzon A. The therapeutic potential of insulin-like growth factor-1 in central nervous system disorders. *Neurosci Biobehav Rev*. 2016;63:207–22. doi:10.1016/j.neubiorev.2016.01.001.
85. Frye RE, James SJ. Metabolic pathology of autism in relation to redox metabolism. *Biomark Med*. 2014;8(3):321–30. doi:10.2217/bmm.13.158.
86. Desai A, Sequeira JM, Quadros EV. The metabolic basis for developmental disorders due to defective folate transport. *Biochimie*. 2016;126:31–42. doi:10.1016/j.biochi.2016.02.012.
87. •• Frye RE, Slattery J, Delhey L, Furgerson B, Strickland T, Tippett M, et al. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Mol Psychiatry*. 2016. doi:10.1038/mp.2016.168.
- This important recent clinical trial of folinic acid shows promise for treatment of ASD.
88. Hendren RL, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. Randomized, placebo-controlled trial of methyl B12 for children with autism. *J Child Adolesc Psychopharmacol*. 2016;26(9):774–83. doi:10.1089/cap.2015.0159.
89. Klaiman C, Huffman L, Masaki L, Elliott GR. Tetrahydrobiopterin as a treatment for autism spectrum disorders: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2013;23(5):320–8. doi:10.1089/cap.2012.0127.
90. Deepmala, Slattery J, Kumar N, Delhey L, Berk M, Dean O, et al. Clinical trials of N-acetylcysteine in psychiatry and neurology: a systematic review. *Neurosci Biobehav Rev*. 2015;55:294–321. doi:10.1016/j.neubiorev.2015.04.015.
91. Wink LK, Adams R, Wang Z, Klaunig JE, Plawewski MH, Posey DJ, et al. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. *Mol Autism*. 2016;7:26. doi:10.1186/s13229-016-0088-6.
92. Alanazi AS. The role of nutraceuticals in the management of autism. *Saudi Pharm J*. 2013;21(3):233–43. doi:10.1016/j.jsps.2012.10.001.
93. Rangarajan P, Karthikeyan A, Dheen ST. Role of dietary phenols in mitigating microglia-mediated neuroinflammation. *Neuromolecular Med*. 2016;18(3):453–64. doi:10.1007/s12017-016-8430-x.
94. Bhandari R, Kuhad A. Neuropsychopharmacotherapeutic efficacy of curcumin in experimental paradigm of autism spectrum disorders. *Life Sci*. 2015;141:156–69. doi:10.1016/j.lfs.2015.09.012.
95. • Taliou A, Zintzaras E, Lykouras L, Francis K. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. *Clin Ther*. 2013;35(5):592–602. doi:10.1016/j.clinthera.2013.04.006.
- Luteolin offers a potential treatment for ASD that appears to be nontoxic.
96. • Singh K, Connors SL, Macklin EA, Smith KD, Fahey JW, Talalay P, et al. Sulforaphane treatment of autism spectrum disorder (ASD). *Proc Natl Acad Sci U S A*. 2014;111(43):15550–5. doi:10.1073/pnas.1416940111.
- Sulforaphane shows benefit for ASD in this clinical trial, and may provide clues to underlying cellular mechanisms.
97. Liu H, Talalay P, Fahey JW. Biomarker-guided strategy for treatment of autism spectrum disorder (ASD). *CNS Neurol Disord Drug Targets*. 2016;15(5):602–13.
98. • Levy SE, Hyman SL. Complementary and alternative medicine treatments for children with autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2015;24(1):117–43. doi:10.1016/j.chc.2014.09.004.
- This paper is important for its coverage of nontraditional approaches to ASD.
99. Rossignol DA, Frye RE. The use of medications approved for Alzheimer's disease in autism spectrum disorder: a systematic review. *Front Pediatr*. 2014;2:87. doi:10.3389/fped.2014.00087.