Introduction: prevalence of autism increasing; undetermined whether incidence increasing; autism affects 1 in 58 boys and 1 in 79 children; these numbers may include patients previously considered odd or mentally retarded; reasons for diagnostic expansion and substitution include improved reporting, increased recognition, increasing acceptability, and increased availability of services

Risk factors: include exposure to mercury, coal dust, pollutants, and heavy metals, maternal infections such as rubella, and medications such as valproic acid and thalidomide; environmental factors may alter epigenetic process (modification of histones and methylation of DNA); first hit — genetic neurodevelopmental vulnerability; basis of autism; however, genetics explains only 50% of autism; second hit — environmental stressors and their interaction with genetic factors; third hit — lack of effective interventions; association between environmental factors and autism — many reported (some anecdotal and others supported by evidence); mercury reported as influential, but incidence of autism not increased in individuals with diets rich in fish containing mercury; increased incidence of autism found in populations exposed to airborne pesticides and burning coal; no evidence that vaccines associated with autism; no study has shown that vaccination followed by fever or ingestion of acetaminophen leads to autism; lack of vitamin D also implicated

Interventional targets: include behavioral programs (supported by level 4 evidence), speech and language, occupational therapy, and cognitive behavioral therapy (level 3 and 4 evidence), pharmacotherapy (level 2 and 3 evidence), biomedical and epigenetic approaches, and modification of genes

Behavioral treatments: cornerstone of treatment; ideally begun as early as possible; discrete trials training — adult gives reward if child demonstrates desired behavior; critics state this approach too adult centered and does not allow child to progress to other reinforcers; however, discrete trial training rarely used as sole approach; Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) — program used in schools and residential facilities; pivotal response training — centered on creating interest; object of interest used to engage child in relationship or reciprocal interaction that becomes self-reinforcing; Early Start Denver Model — begun in children 18 mo of age; uses behavioral or discrete trial techniques; parents trained to deliver interventions and interact with child; benefits of method confirmed by changes in brain electroencephalography and magnetic resonance imaging (MRI); reaching children with behavioral interventions sufficiently early allows for resculping of neurons and change in endophenotype

Adolescents and adults: evidence of benefit in adolescents and adults sparse; behavioral interventions have produced modest benefits in some studies, but data insufficient to draw definitive conclusions; educational interventions including language and communication strategies beneficial, but few studies have been performed; adaptive and life skills interventions available; TEACCH methods successful; vocational interventions may be successful but may not apply to every patient; important to treat ongoing medical and psychiatric problems; allied health interventions can be beneficial; MRI studies show that brain continues to grow and develop, so adults may respond to treatment

Comorbidities: regressive autism — 20% to 40% of young children experience regressive phase at 1.5 to 2 yr of age (ie, child develops normally but then regresses); second regression during adolescence or young adulthood also possible; children who regress become withdrawn; second wave of regression offers additional opportunity for intervention; medical comorbidities — gastrointestinal abnormalities present in 30% to 70% of patients with autism (particularly young patients); seizure disorder present in ≈30% of patients and tends to develop in late adolescence or young adulthood; mental retardation — reported in 70% of children in Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition–Revised); however, recent studies indicate rate ≈40%; neuromodulators — serotonin levels usually high, but sometimes low; mitochondrial disorders — 30% of children with autism have abnormalities in lactate, pyruvate, and other measures of mitochondrial function; other conditions — children with autism have higher than expected rates of eczema, allergies, asthma, infections, and headache

Genetic studies: genetic syndromes associated with autism include Prader-Willi, Angelman, fragile X, Williams, Rett, and DiGeorge; tuberous sclerosis complex and PTEN mutations also occur; children who may have autism should be evaluated with comparative genomic hybridization array, but reimbursement may be unavailable

Laboratory testing to evaluate epigenetic process: includes glucose, liver function, complete blood count, ferritin, magnesium, vitamin D₃, and receptor for methylenetetrahydrofolate reductase; less commonly ordered tests include vitamin C, C-reactive protein, fat soluble vitamins, lead, serum amino and urine organic acids, cholesterol, red blood cell folate, and

Educational Objectives
The goal of this program is to improve diagnosis and treatment of autism. After hearing and assimilating this program, the clinician will be better able to:
1. List established behavioral interventions for autism.
2. Recommend effective treatment for a child with autism and attention-deficit/hyperactivity disorder.
3. Choose the appropriate medication for treating irritability in autism.
5. Consider biomedical therapeutic strategies for autism.

Faculty Disclosure
In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Hendren presents information related to the off-label or investigational use of a therapy, product, or device.
Differential diagnosis vs comorbidity: physician sometimes must determine whether to make separate (additional) diagnosis of attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), tics, Tourette syndrome, or overanxious disorder; Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) supports separate diagnosis; children with autism can also have bipolar disorder, depression, or psychotic disorder; aggression observed in 53% of young children and may persist into adulthood

Attention-deficit/hyperactivity disorder: affects 16% to 66% of children with autism; adaptive functioning more impaired in children with autism and ADHD; in large study, 20% of children with autism initially diagnosed with ADHD

Stimulants: children with autism may do poorly on stimulants; Research Unit on Pediatric Psychopharmacology study found that children with autism and ADHD did well on stimulants but showed less improvement compared with children with ADHD alone; children with ADHD and autism may be treated with stimulants by starting with low dose and titrating slowly

Atomoxetine: can help child who does not respond to other treatments; may lessen anxiety; atomoxetine plus parent training associated with fewer side effects and greater efficacy compared with atomoxetine alone or no treatment; randomized controlled trial (RCT) compared with placebo group, patients on atomoxetine for 8 wk had significantly greater declines in hyperactivity scores on Aberrant Behavior Checklist and on Clinical Global Impression scale

Selective serotonin reuptake inhibitors (SSRIs): in uncontrolled studies, SSRIs associated with improvement; in RCT conducted in adults, SSRIs associated with significant improvement in repetitive behaviors; in another study, citalopram no better than placebo for treating repetitive behaviors; however, some practitioners still treat children with SSRIs based on supposition that citalopram not best SSRI, dose used in study too low, or measurement of anxiety employed in study not optimal

Antipsychotics: risperidone (Risperdal) and aripiprazole (Abilify) approved for treating irritability in autism; each has side effects

Summary of conventional medications: stimulants help some children but should be titrated slowly; antidepressants may be more effective for anxiety than for OCD (however, study suggests that antidepressants may help adults with OCD); α agonists including guanfacine may be used for anxiety; anti-convulsants (such as divalproex [Depakote]) may be used in patients with both mood dysregulation and neurologic abnormalities; lithium useful in children with bipolar disorder and autism spectrum disorder; antipsychotics — adverse effects often problematic; although some patients do well on lurasidone, multisite trial showed that it is no better than placebo for children with autism; some patients develop akathisia on lurasisdone; no good studies to suggest that asenapine or quetiapine (Seroquel) are treatments of choice

Pharmacologic challenges: sleep — first-line treatment is melatonin; other useful agents include γ-amino- butyric acid (GABA) acid plus L-theanine and valerian root; melatonin helps patients fall asleep but does not help them stay asleep; next choice hydroxyzine; if these do not help, consider clonidines; next, trazodone or mirtazapine may be used but are associated with weight gain; use olanzapine if child cannot sleep with any other treatment; skin picking — first-line treatment is N-acetylcysteine (NAC); other effective treatments include SSRIs, duloxetine, and buspirone; screeching — some children respond to divalproex, but problem difficult to treat; treatment-resistant OCD may be treated with NAC, L-methionine, or clomipramine plus SSRIs

Gene-environment interactions and endophenotype: patients with autism may have immune system abnormalities or inflammation, oxidative stress, disturbed methylation, mitochondrial dysfunction, free fatty acid metabolism abnormalities, excitatory and inhibitory imbalance, hormonal effects, and microglia and microbiome abnormalities; however, difficult to determine whether these processes are active; challenges for clinical trials — difficult to target populations for clinical studies due to lack of knowledge; for example, in study evaluating excitatory and inhibitory processes, glutamate levels may be relevant; studies may show negative findings if proper population not selected; for example, study that evaluated memantine for autism in children had negative results, but subjects in study not selected for factors associated with response to N-methyl-D-aspartate agonists; increased knowledge about biomarkers could advance study of targeted treatments; nutritional recommendations, prescription medications, and biomedical treatments may be useful; autism whole-body disorder

Biomedical therapies: recent studies have evaluated methyl B12 and hyperbaric O2; ω-3 fatty acids produce small improvement; no definitive evidence available on vitamin D; study of memantine negative; pancreatic digestive enzymes promising; strategies to treat immune system and inflammation could include melatonin (intravenous immunoglobulin usually not beneficial); little evidence for other treatments including methylation with folic acid or methyl B12 or treatment of mitochondrial dysfunction with carnitine or coenzyme Q10; many new agents being introduced for treatment of mitochondrial dysfunction; most robust evidence available for melatonin (drug clearly beneficial for sleep); ongoing study evaluating high-dose vitamin D (6000 IU/day may be given without serious side effects, even in young children; vitamin offers modest benefits and may be recommended to families); study showed that subcutaneous injections of methyl B12 superior to placebo and associated with clear changes in oxidative stress; study showed clear benefit of NAC as glutamate modulator and antioxidant (especially helpful in children with irritability, self-picking, and behaviors associated with OCD); findings on effect of diet inconsistent; altering microbiome with probiotics of interest

Pancreatic digestive enzymes: associated with positive findings in multicenter trial; however, trial not yet reported because Food and Drug Administration requested larger study; in patients with low levels of fecal chymotrypsin who received treatment with pancreatic enzymes, changes observed in gastrointestinal function as well as core symptoms of autism

Sulforaphane: administered as concentrated extract of broccoli sprouts; superior to placebo; changes in biomarkers of oxidative stress observed; ongoing study using urinary metabolomics as biomarker to identify children who may respond to sulforaphane

Marijuana: may be considered if other treatments ineffective, but benefits modest

Conclusion: autism treated with integrated approach; important components of management speech therapy, occupational therapy, behavioral treatments, and pharmacologic management of associated symptoms; biomedical treatments may include melatonin, ω-3 fatty acids, vitamin D, probiotics, and digestive enzymes

Questions and Answers

Testing mitochondrial function: lactate and pyruvate may be checked before vaccinating; family should be asked about weakness; muscle biopsy provides definitive diagnosis

Geographic patterns: none established, but statistics difficult to collect in some communities; although polluted areas may have increased prevalence of autism, incidence of autism similar worldwide

Prolactin levels: for children on risperidone, prolactin levels need not be checked unless lactation or other abnormal signs observed; level >100 ng/mL abnormal

Role of primary care practitioner: Modified Checklist for Autism in Toddlers useful screening tool; Social
Communication Questionnaire screening instrument to help establish diagnosis; online evaluations available for parents in rural areas; important to initiate treatment early; parent who perceives abnormality should be taken seriously; no harm in interventions such as speech and language therapy even if child not ultimately diagnosed with autism; such interventions should be considered in families waiting for evaluation

Antidepressants: autism reported in offspring of women who take SSRIs during pregnancy; however, recent consensus conference concluded that outcomes worse in children of women who do not receive adequate treatment for depression; difficult to determine whether autism associated with antidepressants, depression itself, or other factors

Eccentricity vs autism: adults often present with questions about diagnosis of autism; some have personality disorders; Autism Diagnostic Interview or Autism Diagnostic Observation Schedule used to make retrospective diagnosis

Managing referrals: child psychiatrist can refer child with presumed autism to other specialists and services; in some communities, referrals may be made by development pediatrician or neurologist well versed in autism

Suggested Reading


Acknowledgments

Dr. Hendren was recorded at the 21st National Psychopharmacology Update, held February 10-13, 2016, in Las Vegas, NV, and presented by the Nevada Psychiatric Association. For information about upcoming CME activities from the Nevada Psychiatric Association, please visit nvpshelfry.org. The Audio Digest Foundation thanks Dr. Hendren and the Nevada Psychiatric Association for their cooperation in the production of this program.

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NEURODEVELOPMENTAL TREATMENT TARGETS IN AUTISM

To test online, go to www.audiodigest.org and sign in to online services.
To submit a test form by mail or fax, complete Pretest section before listening and Posttest section after listening.

1. The increased prevalence of autism can be attributed to:
   (A) Increased recognition of autism
   (B) Improved reporting of autism
   (C) Increased availability of services for autism
   (D) All the above **

2. The cornerstone of treatment for autism is:
   (A) Pharmacotherapy
   (B) Behavioral treatment **
   (C) Epigenetic modification
   (D) Management of medical comorbidities

3. Which of the following therapeutic interventions uses an object of interest to engage the child with autism in a relationship?
   (A) Early Start Denver Model
   (B) Discrete trials training
   (C) Pivotal response training **
   (D) Treatment and Education of Autistic and Related Communication Handicapped Children

4. Of children with autism, _______ have abnormalities in lactate, pyruvate, and other measures of mitochondrial function.
   (A) 10%  (B) 30%  (C) 50%  (D) 70% **

5. The Research Unit on Pediatric Psychopharmacology study found that improvement on stimulants was _______ in children with autism and attention-deficit/hyperactivity disorder (ADHD) than in children with ADHD alone.
   (A) Less **
   (B) Greater

6. Which of the following antipsychotics has been approved for treating irritability in autism?
   (A) Lurasidone
   (B) Quetiapine
   (C) Asenapine
   (D) Risperidone **

7. Which of the following is considered first-line treatment in children with autism who have difficulty sleeping?
   (A) Melatonin **
   (B) Valerian root
   (C) Clonidine
   (D) Trazodone

8. Which of the following is considered first-line treatment in children with autism who are affected by skin picking?
   (A) Clomipramine
   (B) Duloxetine
   (C) N-acetylcysteine **
   (D) Buspirone

9. Which of the following biomedical therapies for children with autism showed promise in a multicenter trial?
   (A) Memantine
   (B) Intravenous immunoglobulin
   (C) Pancreatic digestive enzymes
   (D) Methylation with folinic acid

10. A study of children with autism found that treatment with sulforaphane was:
    (A) Poorly tolerated
    (B) Associated with changes in biomarkers of oxidative stress
    (C) Not superior to placebo
    (D) A and C

Answers to Audio Digest Psychiatry Volume 45, Issue 08: 1-D, 2-D, 3-C, 4-C, 5-C, 6-B, 7-D, 8-A, 9-C, 10-B