Integrating Treatment for Autism Spectrum Disorders Through the Life Cycle

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Faculty Disclosure

• Grants — Curemark, Roche, Otsuka
• Advisory Board — Curemark, BioMarin, Janssen, Axial Biotherapeutics
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• Dr. Hendren does intend to discuss the use of off-label/unapproved use of drugs
Learning Objectives

• Identify successes and challenges in the developmental progression through the life cycle for people with developmental disabilities and their families

• Identify and effectively treat comorbid medical, emotional and behavioral symptoms associated with autism spectrum disorders (ASD)

• Consider integrating biomedical treatments for ASD including conventional psychotropic medication and what has been referred to as CAM/CIM into a comprehensive program.
Autism Prevalence On The Rise*
There has been a 600% increase in prevalence over the last two decades.

2010 1 in 68;
2014 1 in 59 CDC

*Recent research has indicated that changes in diagnostic practices may account for at least 25% of the increase in prevalence over time, however much of the increase is still unaccounted for and may be influenced by environmental factors.
Prevalence of Autism

• Possible explanations include
  – Diagnostic expansion and substitution
  – Better reporting
  – Increased recognition
  – Increasing acceptability
  – Immigration for services
  – Environmental toxins
  – Infectious and immune vulnerability
  – Epigenetic processes

ASD Genetic Etiology (Levels 1 & 2)

- Multiple genes: NRXN12q, 7q11.23, 15q11-13, 16p11.2, SHANK 3, 2, NLGN4, MTHFR 677>T, SEMA5A, 2Q22.1, GRIN2B, 5P14.1, CDH9, 10, FRX, PTEN

- Identical twins: 60% to 90%
  - Fraternal twins: 0% to 36%
  - Siblings: 4% to 19%

- Clear genetic etiology accounts for 25% of autism cases

- Hundreds of genetic mutations, some de novo, lead to many ways to develop and treat autism

- Is Precision Medicine Possible? Weiss KM, Issues Science and Technology in 2017

ASD and Environmental Risk

• Documented: prenatal or early postnatal exposure to viral infections (rubella), valproic acid, thalidomide (Level 1)

• Proposed: influence of mercury, lead, environmental toxins, vaccines, lack of vitamin D (Levels 3 & 4)

• Parental age (older paternal and maternal; differences) (Level 1)

• Maternal metabolic conditions (Level 2)

• Influenza or fever during pregnancy (Level 2)

• Environmental pollution (Level 2)

Model for Autism Etiology

• First hit – Genetic neurodevelopmental vulnerability

• Second hit – Environmental “stressor” and interaction between the two

• Third hit – Restricted development
Translating from “Terroir”: Model
Epigenetic Layer to Targeted Treatment

Gene-Environment Interactions and Epigenetic Processes

(Level 2)

- Immune abnormalities/inflammation
- Oxidative stress
- Disturbed methylation
- Mitochondrial dysfunction
- Free fatty acid metabolism
- Excitatory/inhibitory imbalance
- Hormonal effects
- Microglia/Astrocytes
- Microbiome

Autism Through the Life Cycle
Brain Growth and Development

- Parental history and early developmental experiences also exert effects through epigenetic information not contained in the DNA sequence, which cause changes in gene expression
  - methylation and chromatin patterning
  - Histone acetylation
  - noncoding RNAs and mitochondria

- Transgenerational epigenetic effects interact with conditions at conception to program the developmental trajectory of the embryo and fetus, ultimately affecting the lifetime health of the child

Brain Growth and Development

• We searched the MEDLINE database for studies published between January 1, 2005 and July 1, 2018 for perinatal risk factors and autism, risk factors such as infections, medications, and environmental factors including non-chemical stressors, chemical and nutritional factors. Then, we searched for interventions that may improve neurodevelopmental outcome including nutritional supplements during pregnancy, breastfeeding, and postpartum stress reduction.

• Our review, in agreement with other reviews, supports the possibility that interventions to normalize or mitigate these processes, particularly in the preconception or perinatal period, could lead to resilience and health in the developing and newborn child.

Cheng…Hendren, Medical Hypothesis, 127 (2019) 26-33
Hertz-Picciotto et al, 2018, Wang et al, 2017, Getahun et al., 2017, Hisle-Gorman et al., 2018
Pregnancy Autism Risk (Grade B Mod)

- Maternal Infection and Inflammation (congenital rubella)
- Environmental Toxicants (methylmercury, PCBs, Toluene, Arsenic)
- Air Pollution
- Pesticides
- Bisphenols and Phthalates
- Valproic Acid
- Thalidomide
- SSRIs
- Acetaminophen
- Heavy Metals

Can Autism be Prevented? (Grade C Mod)

- Folic Acid and multivitamin Supplements before and during pregnancy associated with reduced risk of ASD (45,300 children; P<.001)
- Omega-3 Polyunsaturated Fatty Acid
- Vitamin D
- Antioxidants
- Iron
- Choline/phosphatidylcholine
- One practice minimized toxicant exposure; maximized breastfeeding; probiotics, nutritional counseling; limited antibiotics; minimized acetaminophen
  - Out of 294 general pediatric patients followed since 2005 there were 0 new cases of autism

Levine SZ et al., 2018; Suren et al., 2013; Morgese & Trabace, 2016; Stubbs et al., 2016; Zhang et al, 2015; Schmidt et al., 2014; Ross et al, 2016; Mumper E. *North American Journal of Medicine and Science*. 2013;6(3):134-144
P2i – Preconception to Infancy

- Goal is to establish a program that reduces miscarriages and helps ensure infants a healthy start in life

- [www.ForumP2i.com](http://www.ForumP2i.com)

- University of Georgia Center for Excellence

Early Intervention

The majority of research and clinical programs are targeted at younger children where neurodevelopmental processes are more plastic.
• Compared with children with ID/DD, children with ASD were younger when parents first had concerns and first discussed those concerns with a provider
• Compared with parents of children with ID/DD, parents of children with ASD were less likely to receive proactive responses to their concerns and more likely to receive reassuring/passive responses
• Among children with ASD, those with more proactive provider responses to concerns had shorter delays in ASD diagnosis compared with those with passive/reassuring provider responses
• Although parents of children with ASD have early concerns, delays in diagnosis are common, particularly when providers’ responses are reassuring or passive, highlighting the need for targeted improvements in primary care
Later Intervention

Is late adolescence and young adulthood too late to intervene?
Development in ASD in Adolescence (Levels 2 & 3)

- Microstructure of the thalamus, a key sensory and motor brain area, appears to develop differently in individuals with autism spectrum disorder with differences narrowing with age.

- PEERS social skills treatment improves particular aspects of emotional, behavioral, and social functioning that may be necessary for developing and maintaining quality peer relationships and remediating social isolation in adolescents with ASD.

• Approximately **one-half (53.4%) of young adults with ASD** had ever worked for pay outside the home since leaving high school, the lowest rate among disability groups.

• Young adults with an ASD **earned an average of $8.10/hour**, significantly lower than average wages for young adults in the comparison groups, and held jobs that clustered within fewer occupational types. Odds of ever having had a paid job were higher for those who were older, from higher-income households, and with better conversational abilities or functional skills.
Primary Care for Adults with ASD

- Individuals’ challenges fall along spectra on multiple axes (spoken language, written communication, performance on daily living activities, need for consistency, sensory sensitivity, emotional regulation)
- Adults with ASD have increased rates of chronic medical illness, including epilepsy, GI disorders, feeding and nutritional problems, metabolic syndrome, anxiety, depression, and sleep disturbances
- Youth age 11 to 22 years with ASD and ID were reported to thrive less than peers with ID only
- Group differences in sociocommunicative ability and school participation mediated the relationship between ASD and less thriving

Autism Comorbidity & Interventions
Translating from “Terroir”: Model
Epigenetic Layer to Targeted Treatment

Level-Based Interventions

Level 4 – Behavioral interventions, family support, structure

Level 3-4 – Speech and language, OT, therapy, CBT

Level 2-3 – Pharmacotherapy

Level 2 – Biomedical/epigenetic

Level 1 – Gene modification

CBT = cognitive-behavioral therapy; OT = occupational therapy.
Behavioral Treatments for ASD (Level 4)

- ABA – Discrete Trials Training (Level 1)
- TEACCH (Level 3)
- Pivotal Response Training (Level 1)
- Incidental Teaching Approach (Level 2)
- Floor time & Developmental, Individual-Difference Relationship-Based model (Level 3)
- Early Start Denver Model (Level 1)
- Naturalistic Developmental Behavioral Interventions (NDBI) for ASD (Level 2)

ASD Medical Comorbidities

- **Sleep Disorders** (50% - 80%)
  - symptom severity,
  - comorbidity

- **GI abnormalities** (30%–70%)
  - Correlation with symptom severity
  - 85-95% of 5-HT receptors in gut

- **Epilepsy** (30%)
  - two waves;
  - 2 x higher mortality;
  - Likely worsens prognosis

ASD Medical Comorbidities

• Immune Disorders
  – Food allergies, allergic rhinitis, atopic dermatitis, autoimmune disorders, asthma
  – Increased proinflammatory cytokines
  – Corticosteroids, celecoxib, IVIG

• Higher than expected rates of other medical conditions – eczema, allergies, asthma, ear and respiratory infections, headache

ASD Medical Comorbidities

- Mental retardation (70% of full syndrome)
- Regressive autism (20%–47%)
- Mitochondrial disorders
ASD Differential Diagnosis or Comorbidity

- ADHD
- OCD
- Tics and Tourette’s
- Overanxious Disorder
- Bipolar Disorder
- Depressive Disorder
- Learning Disorder
- Psychotic Disorder
- Catatonic Autism
- Aggression – 53% – younger; associated with medical comorbidities

Summary of Conventional Medications for Autism  (Level 2)

- Stimulants: works for some; start low and go slow
- Antidepressants: maybe for anxiety; OCD and ASD mixed
- Alpha-adrenergic agonists: worth a try for anxiety but limited studies
- Anticonvulsants: ? mood dysregulation + neurologic abnormalities; limited studies
- Antipsychotics: indication for risperidone and aripiprazole (Level 1), but adverse effects. ? asenapine, negative lurasidone study in children

Risperidone and aripiprazole (irritability) are the only FDA-approved medications or biomedical agents for treating autism.
Medications to Consider (Level 3 & 4)

- Propranolol
- Naltrexone
- Buspirone
- Memantine
- Amitriptyline

Autism Pharmacologic Challenges
(Levels 2, 3, & 4)

- Sleep – melatonin, GABA/L-theanine, hydroxyzine, clonidine, trazodone, mirtazapine, olanzapine
- Skin picking – NAC, SSRIs, duloxetine, buspirone
- Screeching, yelping – divalproex
- Tx-resistant OCD – NAC, L-methylfolate, clomipramine + SSRI
- Anxiety – GABA-A, pregabalin

www.ClinicalTrials.gov
Based on my experience, other practitioners’ experience, and reports from family members.
CAM/CIM/Biomedical and Autism

- National Center for Complementary and Alternative Medicine defines CAM as “a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine”
- Up to 70% of people with ASD are reported to be using some form of biological treatment
- Up to 28% to 82% of children recently diagnosed with autism use CAM
- The main reasons for choosing CAM were related to concerns with the safety and adverse effects of prescribed medications
- Physicians not perceived as a knowledgeable resource
Gene-Environment Interactions and Endophenotype  (Terroir Level 2; Evidence Levels 2 & 3)

- Immune abnormalities/inflammation
- Oxidative stress
- Disturbed methylation
- Mitochondrial dysfunction
- Free fatty acid metabolism
- Excitatory/inhibitory imbalance
- Hormonal effects
- Microglia

• Significant subsets of people with autism have intestinal inflammation, digestive enzyme abnormalities, metabolic impairments, oxidative stress, mitochondrial dysfunction, and immune problems that range from immune deficiency to hypersensitivity to autoimmunity

• In many cases, improvement of autistic symptoms is achieved by a combination of nutritional recommendations, prescription medications, and addressing the underlying medical conditions seen in these individuals
BioMedical/CIM Treatments

- Melatonin
- Omega-3
- Vitamin D3
- Methyl B12
- NAC
- Vitamin/Mineral Supplements
- Diet
- Microbiome
- Pancreatic Digestive Enzymes
- Balovaptin
- CBD/THC
PRONTO Lab

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Oak Hill serves a heterogeneous population of children, adolescents, and young adults, all of whom have autism spectrum disorder (ASD) or other neurologically-based disorders of relating and communicating. Students receive special education instruction and customized on-site clinical programs which may include speech/language pathology, occupational therapy, and group and individual psychotherapy. A portion of students have received recent functional behavior analyses (FBAs), with school staff implementing positive behavior intervention programs. The school also offers arts-based therapies and adaptive arts instruction.

Optimize children's internal environment to best utilize educational, social, and life skills interventions by:

- Identifying educational and treatment targets
- Measuring effects of interventions
  - behavioral, academic, social, physiological
- Creating a Medical Home
- Enhancing biomedical resilience
- Developing new effective treatments

Supported by J. S. Foundation
ASD is associated with many cellular and biochemical abnormalities:

- Increased oxidative stress
- Lower capacity for cells to deal with oxidative stress (including decreased antioxidant glutathione)
- Mitochondrial dysfunction
- Neuroinflammation

Sulforaphane has been shown to positively assist with all of these
Sulforaphane Trial at Oak Hill School

**Methods**
- 15 subjects, ages 5-22 (mean age 14.7), with ASD diagnoses, attending Oak Hill School (San Anselmo, CA)
- Open-label, 12-week study
- Daily, weight-based dose of sulforaphane
- Baseline and final ABC, SRS, and urine sample

**Results**
- ABC improved -7.1 points (95% CI: -17.4 to 3.2).
- SRS improved significantly -9.7 points (95% CI: -18.7 to -0.8).
- 77 urinary metabolites were correlated with changes in symptoms, clustered into the following pathways:
  - Oxidative stress
  - Amino acid/gut microbiome
  - Neurotransmitters
  - Hormones
  - Sphingomyelini metabolism

Bent …Hendren, Molecular Autism, 2018
Other trials at OHS and Goals

Recently Completed/Upcoming clinical trials

• Folinic acid
  • Decreased folate levels implicated in autism and other developmental differences
  • Planned 3-month trial at Oak Hill with urinary metabolomics
  • Small trial and trend toward improvement

• CM-AT
  • Pancreatic digestive enzyme to increase levels of chymotrypsin in the body, donated by Curemark, LLC.
  • Decreased chymotrypsin levels implicated in autism
  • Planned 3-month trial at Oak Hill with urinary metabolomics
  • Pending IND approval from FDA

Other directions

• PEERS
• UCSF Clinic at OHS
• OMT study

Eventual goals

• Develop metabolomic methods to identify and create individualized, targeted, biomedical treatment plans
• Develop integrated care program between parents, teachers, and clinicians
  • Dang et al. (2017)
Lifting the Veil of Autism
Integrated Approach to Autism Treatment

• Medical – genetic, neurology, GI, other medical symptoms
• Ancillary – speech, OT
• Behavioral
• Treat associated symptoms – pharmacology
• Biomedical assessment and treatments – melatonin, omega-3, vitamin D3, probiotics, digestive enzymes
• Building personal relationships and resilience are all encompassing
Practical Take-Aways

1. New research in classification and gene by environment interaction are changing the way we conceptualize ASDs

2. Biomedical assessment and treatments are changing our practices to a more “whole body” “integrated” treatment focused on treatment targets and building resilience

3. Several biomedical treatments have adequate evidence to use for many patients including melatonin, probiotics, omega-3s, and possibly vitamin D3, sulforaphane, folinic acid, methyl B12, restrictive diets, vitamins and digestive enzymes.

4. In my practice, I suggest Omega-3, vitamin D, multiple vitamin and if indicated melatonin and NAC to all patients. I discuss trying sulforaphane, folinic acid, probiotics, digestive enzymes, and CoQ10.
ADHD and ASD

- Clinically significant symptoms of ADHD have been reported in 16% to 66% of children with ASD.

- Greater impairment in adaptive functioning and poorer health-related quality of life in children with ASD and ADHD than when there are fewer ADHD symptoms.

- Allowed as a comorbidity in DSM-5.

ASD and ADHD cont

- ASD and ADHD have shared genetic heritability and are both associated with shared impairments in social functioning and executive functioning.

- For children diagnosed with ADHD (n=48) or ASD (n=164), of the ADHD sample, 21% met the ASD cut-offs on the ADOS and 30% met ASD cut-offs on all domains of the ADI-R. Four social communication ADOS items (Quality of Social Overtures, Unusual Eye Contact, Facial Expressions Directed to Examiner, and Amount of Reciprocal Social Communication) adequately differentiated the groups.
Stimulants and ASD

- Evidence for effectiveness mixed with less information for amphetamines
- Early studies suggest ineffectiveness and poor tolerability
- RUPP – RCT of 72 youth using methylphenidate suggest improvement in some, but with lower rates of improvement and more adverse events than in children with ADHD without ASD
- Atomoxetine – small studies suggest improvement, but less than children with ADHD without ASD
  - ATX + Parent Training for ASD + ADHD – better side effect profile

RUPP = Research Units on Pediatric Psychopharmacology
Alpha-2 Adrenergic Agonists

- Clonidine – 2 DBPC trials
  - Modest benefit for overactivity, sensory responses, decreased irritability, stereotypy, and oppositional behavior
  - Sedation, fatigue, decreased activity

- Guanfacine
  - Retrospective (N = 80), prospective (N = 11)
    - Decreased hyperactivity
    - Sedation, constipation, sleep disruption, irritability
  - Multisite RCT (N=62) ER for 8 weeks; modal dose 3mg
    - 43.6% decline in ABC- Hyperactivity active vs 13.2% placebo
    - CGI-I 50% vs 9.4%

ASD and ADHD cont

• Cochrane review of methylphenidate for ASD found short term use of methylphenidate might improve symptoms of hyperactivity and possibly inattention with no evidence of negative impact on core symptoms of ASD or that it improves social interaction, stereotypical behaviors or overall ASD.

• Case control study of 347 children found ADHD symptoms predict poorer adaptive behavior for autistic children across settings, even for children with subclinical co-occurring ADHD symptoms.
Having a comorbid diagnosis of ID was also associated with repetitive behaviors, with individuals diagnosed with ID exhibiting more repetitive behaviors than individuals with ASD only.

Age-related pattern of symptom abatement in Restricted Repetitive Behavior is not dependent upon gender, a comorbid diagnosis of ID, or taking psychotropic medication.

However, brain processes underlying inhibitory control appear to be underdeveloped in ASD and develop differently from adolescence to adulthood in ASD.

Depressive Symptom Trajectories in ASD

- Prevalence of comorbid depression seems to correlate with higher functioning forms of ASD and increasing age.

- Internalizing symptoms were associated with poorer emotional regulation in school age, and with lower life satisfaction and greater social difficulties in early adulthood.

- Although symptom levels in females increase at a faster rate throughout adolescence, males with ASD appear to have elevated levels of depressive symptoms in school age that are maintained into young adulthood.

Suicide and ASD

• National survey of 185 people with ASD aged 14 to 80 found 49% in the clinical range for depression and 36% reporting recent suicidal ideation. Females reported higher depression rates than males. Loneliness and social support operate respectively as protective and risk factors for depression and suicidal ideation.

• Nationwide survey in Taiwan found patients with ASD had increased risk of suicide attempts compared to those without ASD especially in adolescents and young adults.
SSRIs and Autism

- Serotonin consistently shown to be dysregulated in ASD
- Fluvoxamine and sertraline demonstrate improvement in aggression and social relations
- Perhaps improved language and correlation with family history of affective disorder
- DBPC trial of fluoxetine in adults found significant improvement in repetitive behaviors
- “Lack of Efficacy of Citalopram for Repetitive Behaviors in ASD” DBPC trial with 149 children (5 to 17 years) with ASD, mean dose 16.5 mg/day. No significant difference on CGI-I or CYBOCS

Psychotic Disorder and Bipolar Disorder in ASD

- 9062 people with ASD in Sweden followed from age 17 to 27 years

- AORs for nonaffective psychotic disorder and bipolar disorder in people with non-ID ASD were 12.3 (95% CI, 9.5-15.9) and 8.5 (95% CI, 6.5-11.2), respectively, which was greater than ID ASD

- This rate is higher than in age and sex matched individuals without ASD in the general population

- May have to do with common underlying genetic risk factors or to exposure sensitivity

AOR = adjusted odds ratio.
Disruptive Mood Dysregulation Syndrome (DMDD)

- Severe temper outbursts at least three times a week
- Sad, irritable or angry mood almost every day
- Reaction is bigger than expected
- Child must be at least six years old
- Symptoms begin before age ten
- Symptoms are present for at least a year
- Child has trouble functioning in more than one place (e.g., home, school and/or with friends)
- Stimulants, antipsychotics, mood stabilizers
Antipsychotics and ASD

• A Double-Blind Placebo Controlled Trial of Risperidone in Autistic Disorder
  – 8 weeks of treatment associated with statistically significant decrease in self-injury, aggression, agitation, stereotypy and hyperactivity

• Aripiprazole in the Treatment of Irritability in Youth with Autism
  • 8 week DBPC fixed and flexible dose study of over 300 children & adolescents 6 to 17 yrs
  • 85% completion; Average dose 8.1mg; 50 – 52% responders based on ABC-I and CGI-I of much or very much improve

Autism Biomedical CIM Interventions
Melatonin

- Endogenous neurohormone causes drowsiness, establishes circadian rhythms and synchronization of peripheral oscillators, and is produced from serotonin

- Review and meta-analysis of 35 studies reported that of 18 treatment studies, there were 5 RCTs (N = 61, 2 to 10 mg/day) where sleep duration (44 min, ES = .93) was increased, sleep onset latency was decreased (39 min, ES = 1.28), but nighttime awakenings were unchanged

- Adverse effects were minimal to none

- May also benefit social communication impairments and stereotyped behaviors or interests

Vitamin D
Vitamin D Council

- “Ecological Evidence” – Northern latitudes, rainfall, skin pigment. Low levels of vitamin D reported
- Vitamin D activates serotonin-synthesizing gene
- Vitamin D is a “potent neurosteroid”
- UCSF study
  - 25(OH)D at or below 30 ng/mL
  - Initial loading dose of 10,000 IU of D3, then 300/IU/kg of vitamin D3
  - Target level 90 ng/mL
  - Safety measured by 25(OH)D and calcium level, tremor, weakness, fatigue, diarrhea, anorexia, headache confusion, psychosis

Methyl B12 Study
UCSF (Autism Speaks)

- 53 children between the ages of 3 and 7 years enrolled in study at UCSF funded by Autism Speaks
- Eligible children randomly assigned to 8 weeks of treatment with methyl B12 at 75 ug/kg given SubQ every 3 days
- Primary outcome measure CGI-I and the mean at 8 weeks was significantly better (lower) in the methyl B12 group (2.4) compared to the placebo group (3.1) (95% CI 1.2 to 0.2, \( P = .005 \))
- Clinical improvement in CGI-I was significantly correlated with methionine \( (P = .05) \), decreases in SAH \( (P = .007) \), and improvements in SAM/SAH \( (P = .007) \)

NAC in Children with Autism

- NAC is an glutamatergic modulator and an antioxidant
- 12-week, double-blind, randomized, placebo-controlled study of NAC in children with autistic disorder
- NAC was initiated at 900 mg daily for 4 weeks, then 900 mg twice daily for 4 weeks, and 900 mg 3 times daily for 4 weeks
- 33 patients (31 male, 2 female; aged 3.2 to 10.7 years) were randomized
- Oral NAC was well tolerated with limited adverse effects
- Compared with placebo, NAC resulted in significant improvements on ABC-I (F = 6.80; P < .001; d = .96)

UCSF-IAN Omega-3 Results

- 863 e-mail invitations
- 118 responded
- 57 met eligibility criteria from 28 states
- Recruitment completed in 6 weeks
- 57 teachers contacted and agreed to participate
- 100% completion rate, study finished in 12 weeks
- Results
  - Omega-3: ABC-H: -5.3 points
  - Placebo: ABC-H: -3.4 points $P = .38$, ES = .26
- Implications
  - Internet is a powerful tool for clinical trials
  - Sample size insufficient to judge efficacy of omega-3

IAN = Interactive Autism Network.
Vitamin/Mineral Supplement and ASD

• RCT of oral vitamin/mineral supplement for 3 months with 141 children and adults with ASD

• Improved the nutritional and metabolic status of children with autism, including improvements in methylation, GSH, oxidative stress, sulfation, ATP, NADH, and NADPH

• The supplement group had significantly greater improvements than did the placebo group on the Parental Global Impression-Revised Average Change ($P = .008$), Hyperactivity ($P = .003$), and Tantrumming ($P = .009$)

Diet

- Inconsistencies between parent reports and the results of clinical trials for a gluten-free casein-free diet in children with autism with no RCT showing benefit

- Several studies suggest a relationship between non-celiac gluten sensitivity and autism

- Detailed metabolic screening in a Greek cohort of ASD patients revealed biomarkers (urine 3-hydroxyisovaleric acid and serum b-OH-b) in 7% (13/187) of patients for whom biotin supplementation or institution of a ketogenic diet resulted in mild to significant clinical improvement in autistic feature

- Specific carbohydrate diet

Microbiota Modulate Behavioral and Physiological Abnormalities Associated With Neurodevelopmental Disorders (Grade C Mod)

- Demonstrate GI barrier defects and microbiota alterations in the MIA mouse model that is known to display features of ASD

- Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like, and sensorimotor behaviors

- Maternal high fat diet in mice results in social and synaptic defects corrected by probiotic treatment

MIA = maternal immune activation. 

Pancreatic Digestive Enzymes

- Enzyme deficiencies in children with autism result in an inability to digest protein
- The inability to digest protein affects the production of amino acids essential for brain function
- RCT completed but not published
- Biomarker – fecal chymotrypsin

ClinicalTrials.gov Identifier: NCT00881452, NCT00912691.
Balovaptin Autism Tx Study
(Grade I Medium; insuff)

• Works by blocking a brain receptor of the vasopressin receptor that is associated with control of stress, anxiety, affection, and aggression

• 213 high functioning ASD males ages 18 to 45 years. Participants take either 1.5 mg or 4 mg or 10 mg or placebo daily for 12 weeks

• Results are showing improvements on Vineland II composite score, but not on SRS-2 for subjects treated in 4 mg or 10 mg Balovaptan.

• Balovaptan was well tolerated across all doses & no drug-related safety concerns were identified.

• Currently finished Phase II Pediatrics AVIATION study for ages 5-17 for 24 weeks DBPC followed by 52 weeks of open label extension phase.

• Phase III Adult study is also ongoing currently (VIADUCT study)
Other Considerations

• Medical marijuana/THC/CBD and the endocannabinoid systems (Level 4)
• GABA-A (Level 3)
• Vitamins and Mineral Supplements (Level 2)
  – Relatively high doses of Vitamins B1, B2, B3, B5, B6, B12, biotin, folate, C, D, and K
  – Folate instead of folic acid
  – MSM (a good source of sulfate which is low in many ASD)
  – Low-dose lithium (more than 100× below the levels when it is used as a psychiatric medication

THC = tetrahydrocannabinol; CBD = cannabidiol.