Evidence for New and Emerging Biomedical Treatments for Autism

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Faculty Disclosure

- Research Grants — Curemark, Roche, Sunovion, Vitamin D Council
- Advisory Board — Forest, Curemark, BioMarin, Neuren, Janssen
- Reviewer—Autism Speaks, Simons Foundation, Brain Canada, DOD

- Dr. Hendren does intend to discuss the use of off-label/unapproved use of drugs
Learning Objectives

• Discuss models for understanding CAM/CIM interventions potential mechanisms of action

• Review several promising Biomedical/CAM treatments relevant to ASD

• Informed integration of biomedical treatments for ASD including conventional psychotropic medication and what has been referred to as CAM/CIM
Key Points

- Families commonly seek alternative and complementary biomedical treatments for their children with NDDs
- A potential rationale for biomedical treatments for NDDs is their potentially beneficial effect on epigenetic processes, which are increasingly demonstrated to have a role in the gene x environment interactions that underlie the development of NDD
- Three agents with a rationale for use with NDDs, at least 1 RCT showing efficacy and safety data include melatonin, omega-3, folate and micronutrients
- Additional agents with promise include NAC, methylcobalamin (methyl B12), and digestive enzymes

Autism Prevalence On The Rise*
There has been a 600% increase in prevalence over the last two decades.

AUTISM SPEAKS™
It's time to listen.
www.AutismSpeaks.org

*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

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

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.
Gene-Environment Interactions and Endophenotype

Level 2

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

Challenges of CAM/Biomedical Research

- Sample size for effect size
- Heterogeneity of ASD
- Duration of trial
- Biomarker for inclusion
- Holding other treatments constant
- Blinding
- Formulation variability
- IRB issues
- Ethical issues

Autism Biomedical Interventions
"I'm afraid you've had a paradigm shift."
CAM/CIM 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

Can Autism be Prevented? (Levels 3 & 4)

- Autism Research Institute
  www.autism.com/prevention

- Prevention magazine
  www.prevention.com/health/health-concerns/10-chemicals-linked-autism

- Generation Rescue – Jenny McCarthy’s organization with recommendations before, during, and after pregnancy
  www.generationrescue.org/prevention/

- Maureen McDonnell’s recommendations
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

Prenatal Autism Risk (Levels 1 & 2)

- Maternal Diabetes (Ornoy et al., 2016)
- Maternal Autoimmune Disorders
- Advanced Maternal and Paternal Age
- Older women deficient in iron have a 5 times greater risk of having a baby with autism
- Prenatal steroid perturbations
- Preterm birth, small for gestational age, and Cesarean delivery

Pregnancy Autism Risk (Levels 1 & 2)

- 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

Few Doctors Warn Expectant Mothers about Environmental Hazards

- 2514 responses, for a response rate of 14%
- 78% of obstetricians agreed that they can reduce patient exposures to environmental health hazards by counseling patients; but 50% reported that they rarely take an environmental health history; >20% reported routinely asking about environmental exposures commonly found in pregnant; and only 1 in 15 reported any training on the topic
- Barriers included: a lack of knowledge of and uncertainty about the evidence; concerns that patients lack the capacity to reduce harmful exposures; and fear of causing anxiety among patients

Can Autism be Prevented? (Levels 3 & 4)

- Folate and Folinic Acid Supplementation
- Omega-3 Polyunsaturated Fatty Acid
- Vitamin D
- Antioxidants
- Iron
- Choline/phosphatidylcholine
- Minimize toxicant exposure; max breastfeeding; probiotics, nutritional counseling; limit antibiotics; minimize acetaminophen
- Out of 294 general pediatric patients followed since 2005 there were 0 new cases of autism

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

- University of Georgia Center for Excellence

- Preconception Health and Health Care
  - Reconvened Select Panel
• 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
• Consider intestinal inflammation in the DDx of people with autism who present with diarrhea, constipation, alternating diarrhea and constipation, sleep disturbances, behavioral outbursts, or unusual posturing
• Consider self-abusive behavior as a possible indicator of pain, difficulty toilet training as potential gut pathology, and trouble sleeping as a sign of GI reflux or abdominal pain
• Diarrhea – associated with malabsorption related to digestive enzyme deficiencies or inflammation
• Probiotics may be used to produce antimicrobial substances, enhance phagocytic and natural killer cell activity, stimulate secretory IgA, and block adhesion of pathogens and toxins
Mitochondrial Dysfunction (Levels 3 & 4)

- Subset of people with autism have mitochondrial dysfunction, which can be inherited or acquired
- Evidence links oxidative stress, mitochondrial dysfunction, and immune dysregulation/inflammation in brain regions involved in speech and auditory processing, and social behavior
- Treatments used for mitochondrial disease (L-carnitine, multivitamin w/ B vitamins, antioxidants, vitamin E, CoQ10, vitamin C, methyl B12, NAC, ubiquinol, and carnosine) have demonstrated significant improvements in ASD

CoQ10 = coenzyme Q10; NAC = N-acetylcysteine.
Immune Dysregulation (Levels 2, 3, & 4)

- Inflammation seems to be associated with a number of neuropsychiatric disorders
- Physical symptoms include allergic shiners, atopic dermatitis, fungal skin infections, oral thrush, and warts
- Evidence of immune dysregulation includes increased IgE, IgA deficiency, lymphopenia, evidence of autoimmunity, and abnormal natural killer cell function
- Behavioral symptoms of autism and impairments in focus and concentration in individuals with ADHD may correlate with pollen counts and therefore be amenable to classic interventions with allergy medications and environmental controls

Potential Biomedical/CAM Treatments

- Actos
- Acupuncture
- Animal Assisted Therapy
- Antibiotics
- Antifungals (Diflucan, Nystatin)
- Antiviral (Valtrex)
- Amino Acids
- Auditory Integration Therapy (Music Therapy)
- Chelation

Potential Biomedical/CAM Treatments (cont)

- Craniosacral Therapy
- Curcumin
- Cyproheptadine
- DHEA
- Digestive Enzymes
- Dimethylglycine (DMG, TMG)
- Fatty Acids (Omega 3)
- 5 HTP
- Folic/folinic Acid
- Glutathione
- Gluten/Casein Free Diet
- Food Allergy Treatment
Potential Biomedical/CAM Treatments (cont)

- Hyperbaric Oxygen (HBOT)
- Iron Supplement
- Inflixmab (Remicade)
- Immune Therapies
- IVIG
- L-Carnosine
- Magnesium
- Melatonin
- Methyl B12
- NAC
- Naltrexone
- Neurofeedback
Potential Biomedical/CAM Treatments
(cont)

- Oxalate (low) Diet
- Oxytocin
- P5P
- Probiotics
- Ribose and NADH
- SAMe
- Secretin
- Sensory Integration Therapy
- Specific Carbohydrate Diet
- St. John’s Wort
- Steroids
- Transfer Factor
Potential Biomedical/CAM Treatments (cont)

- Vitamin A
- Vitamin B3
- Vitamin B6/Mag
- Vitamin C
- Zinc
Biomedical Treatment Studies
UCSF and MIND Institute (Levels 2 & 3)

- Methyl B12 – oxidative stress
- HBOT – inflammation
- Omega-3 free fatty acids
- Vitamin D – immune system
- DBPC study of memantine – excitotoxicity and stimulation of synapse formation
- Pancreatic digestive enzymes

Biomedical Therapeutic Strategies

**Immune/Inflammation**
- Melatonin (Level 2)
- IV/IG (Level 4)
- Corticosteroids (Level 4)
- Celecoxib plus risperidone: RCT for irritability, withdrawal, and stereotypy (Level 3)

**Mitochondrial Function**
- Carnitine (Level 3)
- CoQ10 (Level 4)
- L-carnosine (Level 3)

**Methylation**
- Folic/folinic acid (Level 3)

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

HBOT in ASDs

- Two negative studies and 1 positive RCT study
- Recruited 10 children with ASD for open-label study of 80 sessions at 1.5 ATA and 100% oxygen
- 9 out of 10 parents reported much or very much improved and ABC improvements in irritability, lethargy, hyperactivity, aggressiveness, and learning and memory
- Enrolled children did not exhibit abnormal cytokine levels at baseline and no significant changes in mean cytokine levels were observed

ABC = Aberrant Behavior Checklist; ATA = atmospheres absolute.
Mitochondrial Function Interventions

- Scavenging ROS:
  - Vitamin C
  - Vitamin E
  - Selenium
  - Taurine, hypotaurine
  - α-lipoic acid
  - N-acetylcysteine
  - Mitoquinone
  - Szeto–Schiller peptides
  - Coenzyme Q10
  - Idebenone
  - Minocycline
  - Diaminophenothiazines
  - Polyphenols
  - Despramipexole

- Stimulating cellular antioxidant pathways (e.g. NRF2):
  - Triterpenoids
  - Fumarates
  - Polyphenols
  - N-acetylcysteine
  - α-lipoic acid

- Modulating calcium flux:
  - Xestospongii C (IP3R antagonist)
  - Dihydropyridines (L-type calcium channel blockers)

- Other mechanisms:
  - Uridine

- Targeting electron transport chain:
  - Coenzyme Q10
  - Idebenone
  - Diaminophenothiazines
  - Vitamin E quinones

- Targeting anti-apoptotic mechanisms:
  - Raspagline
  - Thiazolidinediones
  - BI-11A7

- Targeting mPTP:
  - Olesoxime
  - Minocycline
  - Latrerpirdine
  - Rasagiline
  - Cyclosporine
  - NiM811

Biomedical Therapeutic Strategies

**Oxidative Stress**
- Glutathione
- Methyl B12
- Curcumin – anti-inflammatory and antioxidant activity

**Neurotransmitter Production**
- Tetrahydrobiopterin
- Rivastigmine – parasympathomimetic or cholinergic agent
- Galantamine – acetylcholinesterase inhibitor

**GABA**
- Arbaclofen (STX209)
- Bumetanide – diuretic

**Glutamate**
- Riluzole – used to treat amyotrophic lateral sclerosis
- D-cycloserine – partial agonist of the neuronal NMDA receptor

NMDA = N-methyl-D-aspartate.
Metabolic Biomarkers of Increased Oxidative Stress and Impaired Methylation Capacity in Children with Autism

Comparison of methionine cycle and transsulfuration metabolites between autistic children and control children.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Control children $(n = 33)$</th>
<th>Autistic children $(n = 20)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine $(\mu mol/L)$</td>
<td>$31.5 \pm 5.7$ (23–48)</td>
<td>$19.3 \pm 9.7$ (15–25)$^2$</td>
</tr>
<tr>
<td>SAM $(nmol/L)$</td>
<td>$96.9 \pm 12$ (77–127)</td>
<td>$75.8 \pm 16.2$ (68–100)$^2$</td>
</tr>
<tr>
<td>SAH $(nmol/L)$</td>
<td>$19.4 \pm 3.4$ (16–27)</td>
<td>$28.9 \pm 7.2$ (14–41)$^2$</td>
</tr>
<tr>
<td>SAM:SAH</td>
<td>$5.2 \pm 1.3$ (4–8)</td>
<td>$2.9 \pm 0.8$ (2–4)$^2$</td>
</tr>
<tr>
<td>Adenosine $(\mu mol/L)$</td>
<td>$0.27 \pm 0.1$ (0.1–0.4)</td>
<td>$0.39 \pm 0.2$ (0.17–0.83)$^4$</td>
</tr>
<tr>
<td>Homocysteine $(\mu mol/L)$</td>
<td>$6.4 \pm 1.3$ (4.3–9.0)</td>
<td>$5.8 \pm 1.0$ (4.0–5.8)$^3$</td>
</tr>
<tr>
<td>Cystathionine $(\mu mol/L)$</td>
<td>$0.17 \pm 0.05$ (0.1–0.27)</td>
<td>$0.14 \pm 0.06$ (0.04–0.2)$^5$</td>
</tr>
<tr>
<td>Cysteine $(\mu mol/L)$</td>
<td>$202 \pm 17$ (172–252)</td>
<td>$163 \pm 15$ (133–189)$^2$</td>
</tr>
<tr>
<td>tGSH $(\mu mol/L)$</td>
<td>$7.6 \pm 1.4$ (3.8–9.2)</td>
<td>$4.1 \pm 0.5$ (3.3–5.2)$^2$</td>
</tr>
<tr>
<td>Oxidized glutathione $(nmol/L)$</td>
<td>$0.32 \pm 0.1$ (0.1–0.43)</td>
<td>$0.55 \pm 0.2$ (0.29–0.97)$^2$</td>
</tr>
<tr>
<td>tGSH:GSSG</td>
<td>$25.5 \pm 8.9$ (13–49)</td>
<td>$8.6 \pm 3.5$ (4–11)$^2$</td>
</tr>
</tbody>
</table>

$^7$ All values are $\bar{x} \pm SD$; range in parentheses. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; tGSH, total glutathione; GSSG, oxidized glutathione.

$^{2-5}$ Significantly different from control children: $^2 P < 0.001$, $^3 P < 0.01$, $^4 P < 0.05$, $^5 P < 0.002$. 

Methyl B12 Study
MIND Institute

• 30 patients completed the 12-week, double-blind cross-over study of methyl B12 administered subcutaneously in the buttocks at a dosage of 67.5 mcg/kg to 75 mcg/kg every 3 days for 6 weeks

• Minor trauma from subcutaneous injections and increased hyperactivity

• No statistically significant mean differences in behavior tests or in GSH status between active and placebo groups

• 9 patients (30%) demonstrated clinically significant improvement on the CGI and at least 2 additional behavioral measures

• Responders exhibited significantly increased plasma concentrations of GSH and GSH/GSSG

CGI = Clinical Global Impression scale; GSH = glutathione; GSSG = glutathione disulfide.
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)

Memantine

- Aberrant functioning of NMDA receptor and/or altered glutamate may play a role in autism
- Reports of case series demonstrating significant improvement in language and socialization in children with autism
- Well tolerated in children. Some experience fatigue, modest increase in LFTs
- Multisite RCT completed – active did not separate from placebo

Metabolic/Amino Acids/Nutrient

- B6/Magnesium
- Folic acid
- Iron
- L-carnosine
- Ascorbic acid
- Zinc and copper
- Inositol

**Microbiome**
- Probiotics

Fatty Acid Supplementation in Autism
UC Davis MIND Institute; NIMH

• Children ages 3 to 8 years with an established diagnosis of ASD were randomly assigned to 12 weeks of omega-3 fatty acids (1.3 g/day) or an identical placebo

• Hyperactivity improved 2.7 (±4.8) points in the omega-3 group compared to 0.3 (±7.2) points in the placebo group ($P = .40$)

• Correlations were found between decreases in 5 fatty acid levels and decreases in hyperactivity

(Bent et al, JADD, 2011; 41:545-54)

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 \( P = .38, \text{ ES} = .26 \)
- Implications
  - Internet is a powerful tool for clinical trials
  - Sample size insufficient to judge efficacy of omega-3

IAN = Interactive Autism Network.
Folinic acid improves verbal communication in children with autism and language impairment

- Forty-eight children (mean age 7 years 4 months; 82% male) with ASD and language impairment were randomized to receive 12 weeks of high-dose folinic acid (2 mg kg$^{-1}$ per day, maximum 50 mg per day; n = 23) or placebo (n= 25).

- Improvement in verbal communication, as measured by a ability-appropriate standardized instrument, was significantly greater in participants receiving folinic acid as compared with those receiving placebo, resulting in an effect of 5.7 (1.0,10.4) standardized points with a medium-to-large effect size (Cohen’s d = 0.70).

- Folate receptor-α autoantibody (FRAA) status was predictive of response to treatment.

Frye RE et al., Molecular Psychiatry, 2016
Cerebral Folate Deficiency

• High prevalence (75%) of FRAs—an autoantibody that prevents folic acid from entering the brain—in children with ASD

• Improvement in ASD symptoms with high-dose folinic acid (2mg/kg/day; max 50 mg; in 2 divided doses)

• 12-week treatment with high-dose folinic acid in children with ASD improves mitochondrial function, specifically the ability of the mitochondrial to be resilient against oxidative stress

FRAs = folate receptor-α autoantibodies.

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 \((P = .009)\)

ATP = adenosine-5'-triphosphate; NADH = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate.
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 β-OH-β) 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

- 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
- Support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms

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.
Hormones

- Oxytocin – Genetic studies of patients with autism show decreased expression of the oxytocin receptor
- RCT crossover study of intranasal oxytocin (12 IU BID) in 31 children with autism found improvement in caregiver-rated social responsiveness and behavioral and emotional difficulties
- Oxytocin significantly increased the correct rate in inferring others’ social emotions. At the neural level, the peptide significantly enhanced the originally-diminished brain activity in the right anterior insula during inferring others’ social emotions ($P = .004$).

Biomedical Therapeutic Strategies (continued)

**Oxidative Stress**
- NAC (Level 2)
- Glutathione (Level 3)
- Methyl B12 (Level 3)
- Curcumin (Level 4)

**Neurotransmitter Production**
- Tetrahydrobiopterin (Level 3)

**GABA**
- Arbaclofen (STX209) (Level 2)
- Bumetanide – diuretic (Level 3)

**Glutamate**
- Riluzole – used to treat amyotrophic lateral sclerosis (Level 3)
- D-cycloserine – partial agonist of the neuronal NMDA receptor (Level 3)

GABA = gamma-aminobutyric acid; NMDA = N-methyl-D-aspartate.

Other Considerations for Adults with Autism

• 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
  – 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.
Ongoing Adult Autism Tx Study

- **VANILLA** (*Vasopressin Antagonist to Improve Social Communication in Autism*) study (Level 3)
- Works by blocking a brain receptor of the vasopressin receptor that is associated with control of stress, anxiety, affection, and aggression
- Finished 3 stages with 154 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
- Currently doing stage 4 with 87 participants across 30 sites in the United States

Other Treatments for ASD (Levels 2 & 3)

- **Sulforaphane:** After 18 weeks, participants receiving placebo experienced minimal change (<3.3%), compared to those receiving sulforaphane showed improvement of behavior: 34% for ABC \((P < .001)\); 17% for SRS \((P = .017)\); CGI-I \((P = .015 - .007)\). Upon discontinuation, total scores on all scales rose toward pretreatment levels.

- **Oak Hill School Study - Responders** (n=10) exhibited a 26.7-point decrease in total ABC \((p<0.001)\) and an 18.6-point decrease in SRS \((p=0.001)\), compared to non-significant increases of 2.9 points in ABC and 0.9 points in SRS for non-responders. Metabolomics showed that responders had higher levels of oxidative stress biomarkers in their urine after supplementing than did non-responders.
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
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 folinic acid, vitamin D3, methyl B12, oxytocin, restrictive diets, digestive enzymes, and choline.