Achieving optimal outcomes in autism

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While Dr. Rossignol has attempted to make the information in this presentation as accurate as possible, the information is provided without any expressed or implied warranty. The purpose of this lecture is to provide information about different conditions or treatments that may affect individuals with autism and other conditions. Please be advised that Dr. Rossignol is not giving medical advice and that circumstances may dictate different treatments. All of the reviewed treatments in this lecture are considered off-label and not FDA-approved. Before beginning any treatment, please consult with your or your child’s physician. The use of every treatment in autism is “off-label” except for Risperidone and Aripiprazole for the treatment of Irritability.

What is Autism?

- Is diagnosed solely based on behavioral observations (which are subjective)
- Is a spectrum disorder – some children are mild, some are severe
- There are no blood or other biological tests for identifying autism
- Therefore, a diagnosis of autism tells us nothing about the potential contributors or causes of the disorder
- Testing and treatments can potentially start before a diagnosis of autism is made

“Autistic Behaviors”

- Autistic behaviors may have a medical cause or contributor (which are objective), e.g.:
  - Seizures or seizure-like (epileptiform) activity may contribute to hyperactivity, aggressive behaviors, irritability, speech delay, self-stimulatory behaviors and sleep problems [Malow, 2004; Mulligan, 2014; Viscidi, 2013]
  - Gastrointestinal problems may lead to aggressive behaviors or self-injurious behaviors [Buie, 2005; Buie, 2010]
- Key Concept: Treatment of these medical problems may lead to behavioral improvements

Aims: To evaluate autistic children with GI complaints and aggression or self-injurious behavior in order to determine if these behaviors may be symptoms of GER (reflux). Methods: Six consecutive autistic children (ages 8–19 years) undergoing endoscopy and scheduled for BRAVO (wireless) pH probe were evaluated for histology and pH meter results. Findings: GER was identified in 5 of 5 patients tested by BRAVO pH testing. Esophagitis was seen in 3 of 6 patients biopsied. Conclusions: Aggressive or self-injurious behavior may be a manifestation of pain from GER and should prompt consideration of further investigation.

Krigsman, 2007  Medical Veritas 4:1528-36
**Important Concept**

- Several **metabolic abnormalities** have been reported to contribute to or cause a **potentially reversible** form of autism—e.g., Cerebral Folate Deficiency (CFD)
- The goal, from day one of evaluation, is to rapidly screen for these abnormalities, identify them, and start treating them
- Testing can be done by measuring certain **biomarkers** (laboratory tests that may identify abnormalities)

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**Approved medications: ASD**

- Risperidone (Risperdal®)
- Aripiprazole (Abilify®)
- Both are **antipsychotic** medications approved for treating irritability associated with ASD and thus do not treat core autistic symptoms or behaviors
- There are currently **no FDA approved** medications for the **core symptoms** of ASD

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**Choosing a treatment**

- We treat **metabolic or biochemical** abnormalities that may be **contributing to behavior**: in that sense, we are not treating “autism” or “ADHD”—e.g., Autism is treated with ABA therapy
- Use **proven treatments based on biomarkers** (laboratory tests or other tests like EEGs) and/or **evidence-based medicine** (choosing the best treatments based on the published medical literature)

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**Types of treatments**

- **A. Laboratory testing**
  - Non-proven treatments that are most likely harmless or low risk
  - Non-proven treatments that have high risk or high degree of side effects

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Krigsman, 2007
Medical Veritas
4:1528-35
Biomarkers

- **Biomarkers** help subgroup children and identify metabolic abnormalities that may be treatable
- Can include blood, urine, and stool testing but also testing such as MRI, EEG and X-rays
- Help to individualize treatments

Why are biomarkers important?

- Some children with ASD cannot communicate their needs or problems
- Some abnormalities might not be identified without a lab test (e.g., hypothyroidism)
- Biomarkers can be measured at baseline and followed over time to help gauge effectiveness of treatments

This article reviews the medical literature and discusses the authors' clinical experience using various biomarkers for measuring oxidative stress, methylation capacity and transsulfuration, immune function, gastrointestinal problems, and toxic metal burden. These biomarkers provide useful guides for selection, efficacy, and sufficiency of biomedical interventions. The use of these biomarkers is of great importance in young children with ADHD or individuals of any age with ASD, because typically they cannot adequately communicate regarding their symptoms.

Biomarker-Guided Interventions of Clinically Relevant Conditions Associated with Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder

James Jeffrey Bradstreet, MD, MD(FE), FAAFP; Scott Smith, PA; Matthew Barad, ND; Daniel A. Rossignol, MD, FAAFP

<table>
<thead>
<tr>
<th>BIOMEDICAL PROBLEM</th>
<th>ASD</th>
<th>ADHD</th>
</tr>
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<tbody>
<tr>
<td>Oxidative stress</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Decreased methylation and transsulfuration</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metal toxicity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intestinal dysbiosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Immune dysregulation / inflammation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cerebral hypoperfusion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Basic biomarkers

- Complete blood count (CBC): anemia, abnormal white count (low suggests viral infections), platelet count (high suggests inflammation), eosinophil count (high seen with allergies and parasites)
- Comprehensive metabolic (CMP): electrolytes, liver, kidney tests; low CO\textsubscript{2} suggests mitochondrial dysfunction or acidosis
Basic biomarkers

- Magnesium: deficiency may be associated with hyperactivity
- Zinc: deficiency may be associated with inattention
- Other minerals: low chromium may be associated with pica, low lithium may be associated with irritability
- Iron (ferritin): deficiency can be associated with insomnia, restless legs syndrome, lower IQ, and attention problems

- Cholesterol: deficiency may be associated with irritability, hyperactivity, self-stimulatory behaviors
- Testosterone: increase may be associated with aggression
- TSH: test for hypothyroidism which can be associated with developmental delay and inattention
- Vitamin A

Endocrine

- Cortisol (8 am): low levels can be associated with adrenal insufficiency
- TSH
- Anti-thyroid antibodies: seen in Hashimoto’s thyroiditis
- Thyroid hormones (free T3 and free T4)
- 7-dehydrocholesterol level (if cholesterol extremely low): screens for Smith-Lemli-Opitz Syndrome

Oxidative stress biomarkers

- Glutathione: low levels may be associated with impaired detoxification and increased oxidative stress
- Cysteine: precursor to glutathione
- Antioxidant proteins: transferrin and ceruloplasmin: low levels have been associated with regression in children with ASD
- Carnitine: low levels may be associated with mitochondrial dysfunction and oxidative stress
- Urinary 8-OHdG and 8-OHG: oxidized DNA and RNA

Methylation and Transsulfuration

- Cysteine or cystine: low levels may be associated with impaired glutathione production
- Methionine: low levels may be associated with impaired glutathione production
- Sulfate: low levels may be associated with impaired detoxification of pesticides, chemicals, and epinephrine (adrenaline)
- Taurine (on amino acid test)
Biomarkers of Immune Dysregulation

- Serum autoantibodies to brain endovasculature: may be associated with speech delay and speech regression
- Folate receptor autoantibodies
- Neopterin and Biopterin: measures of cell-mediated immune activation
- IgG with subclasses, IgM, IgA: markers of immunodeficiency, low levels also correlated with core autistic behaviors
- IgE: high levels associated with allergies

- Vaccine titers: lack of antibody production after immunization can be a marker of immunodeficiency
- Antinuclear antibodies (ANA): reflect autoimmunity
- Urinary N-methylhistamine: high levels consistent with inflammatory bowel disease
- Tumor necrosis factor-alpha: generalized marker of inflammation
- C-reactive protein and sed rate: inflammation

Biomarkers of GI dysfunction

- Stool calprotectin: Marker of inflammatory bowel disease
- Stool eosinophil-X: marker of food allergy related bowel inflammation or eosinophilic esophagitis
- Intestinal permeability: increased in bowel inflammation
- Organic acid test: can indicate functional vitamin B12 and folate deficiency as well as intestinal dysbiosis
- Stool culture and microscopic examination
- Prometheus IBD blood test

Mitochondrial Dysfunction

- Elevated ammonia
- Elevated lactic acid
- Elevated creatine kinase
- Quantitative plasma amino acids: Alanine to lysine > 2.5, high glycine, proline, sarcosine, tyrosine
- Low carnitine levels
- Elevated acylcarnitines
- Low CoEnzyme Q10
- Elevated pyruvate
- AST/ALT > 2.0
- Organic acid test, metabolic (urine)
- Low CO₂, increased anion gap
Morava Criteria: MD

- Clinical signs and symptoms (max 4 points)
  - Muscle weakness (1 point)
  - Developmental delay (1 point)
  - Loss of skills (1 point)
  - Seizures (1 point)
- Multisystem involvement (1 point): GI, endocrine
- Metabolic/imaging studies (max 4 points)
  - Elevated lactate (2 points)
  - Elevated alanine (2 points)
- Mitochondrial morphology (max 4 points)
- Score: 2-4 possible MD; 5-7 probable MD; 8-12 definite MD

Morava et al., 2006 Neurology 67(10):1823-6

Initial Lab Testing

**Mitochondrial dysfunction**
- Ammonia
- Lactic acid
- Creatine kinase
- Quantitative plasma amino acids
- Carnitine levels
- Acylcarnitine profile
- Organic acid test, metabolic (urine)

**Immune studies**
- ASO
- AntiDNAse B
- ANA
- Antigliadin antibodies
- Food allergy panel

Don’t forget about considering a 24 hour EEG!

**Initial Lab Testing**

- CBC
- CMP
- Ferritin
- Cholesterol
- Magnesium
- Testosterone
- TSH
- Vitamin D
- Micro OAT
- Stool testing

**Toxicity / Detoxification**
- Lead
- Mercury
- Cysteine
- Sulfate
- Packed red blood cell elements
- Hair metal testing
- Urinary porphyrins

B. Evidence-based
Symptoms-based
Treatments
Evidence Based Medicine (EBM)

- Using the best available evidence to aid clinical decision making
- Uses strength or level of evidence (LOE)
  - Benefit(s) of treatment
  - Risk(s) of treatment
- Basis is often randomized controlled trials (RCT), systematic reviews and meta-analysis

General lack of evidence in medicine

Over 50% of what is done in medicine is “Unknown Effectiveness”

Search parameters for supplements and medications in ASD

- Date of most recent search: 7/23/15
- Sources: PubMed, Scopus, Google Scholar, references from review and other articles, database
- Excluded: review articles, letters to editor (unless new data presented)
- Number of studies identified and reviewed: 368
- Number of studies on nutritional supplements: 112 (20 supplements)
- Number of studies on medications: 256 (45 medications)
- Did not look at Risperidone or Aripiprazole (both approved to treat irritability in autism)

Scoring

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one level 1a study or two level 1b studies</td>
</tr>
<tr>
<td>B</td>
<td>At least one level 1b, 2a, or 3a study, or two level 2b or 3b studies</td>
</tr>
<tr>
<td>C</td>
<td>At least one level 2b or 3b study, or two level 4 studies</td>
</tr>
<tr>
<td>D</td>
<td>Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level, or studies reporting no improvements</td>
</tr>
<tr>
<td>N</td>
<td>No studies identified</td>
</tr>
</tbody>
</table>


Scoring

- Randomized, double-blind, placebo-controlled study = 10 points
- Prospective, placebo-controlled study (but lower quality) = 5 points
- Open-label, prospective, non-controlled study = 3 points
- Retrospective case-control study = 3 points
- Case series (retrospective, 2 or more patients) = 2 points
- Case report (retrospective, 1 patient) = 1 point
- Negative studies = 0 points
Nutritional Supplements

Melatonin [Score: 92; Grade: A]
• The good: Improvements in sleep onset latency (time to fall asleep), nighttime awakenings, length of sleep, social interaction, irritability, alertness
• The bad: Morning drowsiness (<3%), Enuresis (bed wetting, <3%)
• The dose / length: 1-6 mg at bedtime; up to 4 years
• References [22 studies]: (points per study = 4.2)
  • 1b: 6 studies; 60 points
  • 2b: 3 studies; 9 points
  • 3b: none
  • 4 CS: 10 studies; 20 points
  • 4 CR: 3 studies; 3 points

Carnitine [Score: 44; Grade: A]
• The good: Improvements in sleep efficiency, energy level, apraxia, communication skills, expressive speech, autism behaviors, muscle strength
• The bad: Hyperactivity, loose stools
• The dose / length: 50-100 mg/kg/day; up to 6 months
• References [12 studies]: (points per study = 3.7)
  • 1b: 3 studies; 30 points
  • 2b: 1 study; 3 points
  • 3b: none
  • 4 CS: 3 studies; 6 points
  • 4 CR: 5 studies; 5 points

N-Acetylcysteine (NAC) [Score: 32; Grade: A]
• The good: Improvements in social interaction, aggressiveness, irritability
• The bad: Constipation (16%), increased appetite (16%), fatigue (13%), nervousness (13%), daytime drowsiness (13%)
• The dose / length: 600-2700 mg/day; 8-12 weeks
• References [5 studies]: (points per study = 6.4)
  • 1b: 3 studies; 30 points
  • 2b: none
  • 4 CS: 3 studies; 6 points
  • 4 CR: 2 studies; 2 points

Folinic acid [Score: 27; Grade: B]
• The good: Improvements in expressive speech, play skills, social skills, receptive language, attention, stereotypy
• The bad: Hyperactivity, self-stimulatory behaviors, aggression
• The dose / length: 400 mcg/day to 2-3 mg/kg/day; 2-4 months
• References [11 studies]: (points per study = 2.5)
  • 1b: none
  • 2b: 9 studies; 24 points (two studies had same population)
  • 3b: none
  • 4 CS: 1 study; 2 points
  • 4 CR: 1 study; 1 point

Supplement rankings by total points
1. Melatonin...................92
2. B6/Mag......................66
3. Carnitine...................44
4. NAC..........................32
5. Folinic acid.............27
6. Omega 3...................26
7. Multivitamin.............21
8. Probiotics................20
9. Vitamin C................14
10. B vitamins...............10
11. Carnosine................10
12. MB12.......................10
13. Piracetam...............10
14. Sulfaphane...............10
15. Coenzyme Q10..........9
16. Vitamin D...............5
17. Digestive enzymes.....3
18. Gingko....................3
19. Iron......................3
20. Pregnenolone..........3
Grade A Rankings: Supplements

1. Melatonin (92 points)  
2. Carnitine (44 points)  
3. NAC (32 points)  
4. Multivitamin (21 points)  

Mean Score = 47.3

Grade B Rankings: Supplements

1. Folinic acid (27 points)  
2. Probiotics (20 points)  
3. Vitamin C (14 points)  
4. Carnosine (10 points)  
5. Piracetam (10 points)  
6. Sulforaphane (10 points)

Mean Score = 15.2

Grade C Rankings: Supplements

1. B6/Mag (66 points)  
2. B vitamins (10 points)  
3. MB12 (10 points)  
4. Coenzyme Q10 (9 points)  
5. Vitamin D (5 points)  
6. Iron (3 points)  
7. Pregnenolone (3 points)

Mean Score = 15.1

Number of double-blind, placebo-controlled, positive studies: supplements

1. Melatonin 6  
2. Carnitine 3  
3. NAC 3  
4. Multivitamin 2  
5. B6/Mag 1  
6. Probiotics 1  
7. Vitamin C 1  
8. Carnosine 1  
9. Piracetam 1  
10. Sulforaphane 1

Medications

Oxytocin [Score: 137; Grade: A]

• The good: Improvements in eye contact, social interaction, emotional behavior, quality of life  
• The bad: Emotional problems, irritability, headache, migraine  
• The dose / length: 8-24 IU; 8-16 weeks  
• References [18 studies]: (points per study = 7.6)  
  1b: 15 studies; 130 points (+130 points, 2 x 0 points)  
  2b: 2 studies; 6 points  
  3b: none  
  4 CS: none  
  4 CR: 1 study; 1 point
Naltrexone [Score: 120; Grade: A]

- The good: Improvements in self-injurious behaviors, hyperactivity, agitation, irritability, temper tantrums, social interaction, stereotypy, attention, eye contact
- The bad: Transient sedation, nausea
- The dose / length: 0.5-2 mg/kg/day; 7 days to 6 months
- References [24 studies]: (points per study = 5.0)
  * 1b: 10 studies; 90 points (+90 points; 1 x 0 points)
  * 2b: 6 studies; 18 points
  * 3b: none
  * 4 CS: 4 studies; 8 points
  * 4 CR: 4 studies; 4 points

Propranolol [Score: 56; Grade: A]

- The good: Improvements in speech, cognition, memory, hypersexual behaviors, aggression, social interaction, eye contact
- The bad: Decreased heart rate and blood pressure, fatigue
- The dose / length: 10-40 mg/day; up to 1 year
- References [9 studies]: (points per study = 6.2)
  * 1b: 5 studies; 50 points
  * 2b: 1 study; 3 points
  * 3b: none
  * 4 CS: none
  * 4 CR: 3 studies; 3 points

Memantine [Score: 29; Grade: B]

- The good: Improvements in speech, social interaction, attention, self-stimulatory behaviors, irritability, hyperactivity
- The bad: Stuttering, irritability, dizziness (15%), nausea (10%), rash (10%), sedation (15%)
- The dose / length: up to 20 mg/day; up to 21 months
- References [10 studies]: (points per study = 2.9)
  * 1b: 1 study; 10 points
  * 2b: 5 studies; 15 points
  * 3b: none
  * 4 CS: 2 studies; 2 points (+2 points; 1 x 0 points)
  * 4 CR: 2 studies; 2 points

Galantamine [Score: 26; Grade: A]

- The good: Improvements in irritability, social interaction, expressive speech, hyperactivity, eye contact, attention
- The bad: Rash, headache, nervousness, increased appetite, weight gain
- The dose / length: 8-24 mg/day; 10-12 weeks
- References [4 studies]: (points per study = 6.5)
  * 1b: 2 studies; 20 points
  * 2b: 2 studies; 6 points
  * 3b: none
  * 4 CS: none
  * 4 CR: none

Pentoxifylline [Score: 25; Grade: B]

- The good: Improvements in receptive understanding, hyperactivity, social interaction, seizures (EEG), autism behaviors, attention, speech
- The bad: Nausea, vomiting, low blood pressure, headache, sleep problems, hyperactivity
- The dose / length: 200-600 mg/day; 3 months
- References [6 studies]: (points per study = 4.2)
  * 1b: 1 study; 10 points
  * 2b: 5 studies; 15 points
  * 3b: none
  * 4 CS: none
  * 4 CR: none

Medication rankings by total points

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total Points</th>
</tr>
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<tbody>
<tr>
<td>Oxytocin</td>
<td>137</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>120</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>77</td>
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<tr>
<td>Fenfluramine</td>
<td>69</td>
</tr>
<tr>
<td>Propranolol</td>
<td>56</td>
</tr>
<tr>
<td>BH4</td>
<td>51</td>
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<tr>
<td>Fluoxetine</td>
<td>50</td>
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<tr>
<td>Atomoxetine</td>
<td>47</td>
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<tr>
<td>Valproate</td>
<td>37</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>33</td>
</tr>
</tbody>
</table>
Medication rankings by total points

Grade A Rankings: Medications  Mean Score = 58.4
1. Oxytocin (137 points) 11. Amantadine (20 points)
2. Naltrexone (120 points) 12. Haloperidol (77 points)
3. Valproate (100 points) 13. Propranolol (56 points)
4. BH4 (51 points) 14. Chlorpromazine (12 points)
5. Atomoxetine (50 points) 15. Methylphenidate (11 points)
6. Fluoxetine (47 points) 16. Arbaclofen (10 points)
7. Atomoxetine (47 points) 17. Mirtazapine (8 points)
8. Buspirone (45 points) 18. Sertraline (9 points)
9. Amitriptyline (42 points) 19. Acamprosate (8 points)
10. Clonidine (25 points)

Grade B Rankings: Medications  Mean Score = 16.7
1. Valproate (37 points) 11. Celecoxib (10 points)
2. Memantine (29 points) 12. Riluzole (10 points)
3. Pentoxifylline (25 points) 13. Sertraline (9 points)
4. Fluvoxamine (23 points) 14. Acamprosate (8 points)
5. Buspirone (20 points) 15. Ralineptadine (8 points)
7. D-Cycloserine (25 points) 17. Fluoxetine (5 points)
8. Guanfacine (15 points) 18. Ramelteon (8 points)
9. Cyproheptadine (12 points) 19. Dextromethorphan (7 points)
10. Topiramate (12 points) 20. Fluoxetine (5 points)

Grade C Rankings: Medications  Mean Score = 9.8
1. Clomipramine (28 points) 11. Celecoxib (10 points)
2. Olanzapine (22 points) 12. Riluzole (10 points)
3. Donepezil (18 points) 13. Sertraline (9 points)
4. Mirtazapine (8 points) 14. Acamprosate (8 points)
5. Steroids (8 points) 15. Ramelteon (8 points)
6. Dextromethorphan (7 points) 16. Fluoxetine (5 points)
7. Famotidine (5 points) 17. Arbaclofen (3 points)
8. Escitalopram (3 points) 18. Ralineptadine (8 points)
9. Pioglitazone (3 points) 19. Vancomycin (3 points)
10. Vancomycin (3 points)

Number of double-blind, placebo-controlled, positive studies: medications

1. Oxytocin ……………… 13
2. Naltrexone…………… 9
3. Haloperidol…………… 7
4. Propranolol…………… 5
5. BH4………………….. 3
6. Atomoxetine………… 3
7. Methylphenidate…… 3
8. Valproate…………… 3

Two studies:
- Amantadine, Clomipramine, Clonidine, Fenfluramine, Fluoxetine, Galantamine
- Bumetanide, Buspirone, Celecoxib, Cyproheptadine, Dextromethorphan, Donepezil, Fluvoxamine, Guanfacine, Memantine, Olanzapine, Pentoxifylline, Riluzole, Topiramate

Symptom based listings
### Speech / Verbal Communication
- Carnitine [A, 44]
- Folinic acid [B, 27]
- Carnosine [B, 10]
- Sulforaphane [B, 10]
- B6/Mag [C, 66]
- MB12 [C, 10]
- Coenzyme Q10 [C, 9]
- Omega 3 fatty acids [D, 26]
- Propranolol [A, 56]
- BH4 [A, 51]
- Fluoxetine [A, 50]
- Atorvastatin [A, 47]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Valproate [B, 37]
- Memantine [B, 29]
- Flavonoids [B, 25]
- Sulfuraphane [B, 10]
- B6/Mag [C, 66]
- MB12 [C, 10]
- Omega 3 fatty acids [D, 26]
- Propranolol [A, 56]
- BH4 [A, 51]

### Receptive Language / Understanding
- Multivitamin [A, 21]
- Folinic acid [B, 27]
- Propranolol [A, 56]
- Pentoxifylline [B, 25]
- Donepezil [C, 18]
- Steroids [C, 8]
- Spironolactone [D, 1]

### Social Interaction
- Melatonin [A, 92]
- NAC [A, 32]
- Folinic acid [B, 27]
- Carnosine [B, 10]
- Sulforaphane [B, 10]
- B6/Mag [C, 66]
- MB12 [C, 10]
- Omega 3 fatty oil [D, 26]
- Oxytocin [A, 137]
- Naltrexone [A, 120]
- Propranolol [A, 56]
- BH4 [A, 51]
- Fluoxetine [A, 50]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Valproate [B, 37]
- Memantine [B, 29]
- Flavonoids [B, 25]
- Sulfuraphane [B, 10]
- B6/Mag [C, 66]
- MB12 [C, 10]
- Omega 3 fatty acids [D, 26]
- Propranolol [A, 56]
- BH4 [A, 51]

### Stereotypy / Repetitive Behaviors
- Folinic acid [B, 27]
- Vitamin C [B, 14]
- B6 / Mag [C, 66]
- Omega 3 fatty acids [D, 26]
- Naltrexone [A, 120]
- Fluoxetine [A, 50]
- Atorvastatin [A, 47]
- Clonidine [A, 25]
- Memantine [B, 29]
- Oxytocin [A, 137]
- Naltrexone [A, 120]
- Propranolol [A, 56]
- BH4 [A, 51]
- Fluoxetine [A, 50]
- Atorvastatin [A, 47]
- Clonidine [A, 25]
- Memantine [B, 29]
- Oxytocin [A, 137]
- Naltrexone [A, 120]
- Propranolol [A, 56]
- BH4 [A, 51]

### Attention
- Folinic acid [B, 27]
- Probiotics [B, 20]
- Iron [C, 5]
- Omega 3 fish oil [D, 26]
- Naltrexone [A, 120]
- Atomoxetine [A, 47]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Memantine [B, 29]
- Pentoxifylline [B, 25]
- Guanfacine [B, 15]
- Topiramate [B, 12]
- Riluzole [B, 10]
- Acamprosate [B, 8]
- Donepezil [C, 18]
- Reboxetine [D, 60]
- Levetiracetam [D, 6]

### Hyperactivity
- Multivitamin [A, 21]
- Omega 3 fish oil [D, 26]
- Naltrexone [A, 120]
- Haloperidol [A, 77]
- B6 / Mag [C, 66]
- Atomoxetine [A, 27]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Amantadine [A, 20]
- Memantine [B, 29]
- Fluoxetine [A, 50]
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- Clonidine [A, 25]
- Memantine [B, 29]
- Fluoxetine [A, 50]
- Atorvastatin [A, 47]
- Clonidine [A, 25]
- Memantine [B, 29]
**Irritability**

- Melatonin [A, 92]
- NAC [A, 32]
- Pregnenolone [C, 3]
- Naltrexone [A, 120]
- Haloperidol [A, 77]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Amantadine [A, 20]
- Valproate [B, 37]
- Memantine [B, 29]

- Buspiron [B, 20]
- Topiramate [B, 12]
- Celecoxib [B, 10]
- Riluzole [B, 10]
- Olanzapine [C, 22]
- Mirtazapine [C, 8]
- Famotidine [C, 5]
- Escitalopram [C, 3]
- Pioglitazone [C, 3]
- Spironolactone [D, 1]
- Mecamylamine [D, 0]

**Sleep**

- Melatonin [A, 92]
- Carnitine [A, 44]
- Multivitamin [A, 21]
- Coenzyme Q10 [C, 9]
- Iron [C, 3]

- Clonidine [A, 25]
- Guanfacine [B, 15]
- Ramelteon [B, 8]
- Donepezil [C, 18]
- Mirtazapine [C, 8]

**Eye contact**

- Omega 3 fatty acids [D, 26]
- Oxytocin [A, 137]
- Naltrexone [A, 120]
- Propranolol [A, 56]
- BH4 [A, 51]
- Galantamine [A, 26]
- Famotidine [C, 5]

**Overall Autism Behaviors**

- Carnitine [A, 44]
- Probiotics [B, 20]
- Camosine [B, 10]
- Sulforaphane [B, 10]
- B6 / Mag [C, 66]
- M812 [C, 10]
- Vitamin D [C, 5]
- Digestive enzymes [D, 3]
- Gingko biloba [D, 3]

- Naltrexone [A, 120]
- Haloperidol [A, 77]
- BH4 [A, 51]
- Pentoxifylline [B, 25]
- Bumetanide [B, 17]
- D-Cycloserine [B, 15]
- Cyproheptadine [B, 12]
- Ramelteon [B, 8]
- Donepezil [C, 18]
- Vancomycin [C, 3]
- Citalopram [D, 5]

**MAPS Curriculum**

**Focused on 6 major areas:**

1. Neurology
2. Metabolic
3. Immunology
4. GI / nutrition
5. Toxicology
6. Integration into clinical care / cases

**Partnering with Parent Groups**