Achieving optimal outcomes in autism

Dan Rossignol MD FAAFP

Rossignol Medical Center

California Office (Irvine, CA): 949.428.8878
Florida Office (Melbourne, FL): 321.259.7111

www.rossignolmedicalcenter.com

rossignolmd@gmail.com

Twitter: @danrossignol

NAA Conference
November 6, 2015

Disclaimer

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 <u>subjective</u>)
- 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 <u>objective</u>), 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]
- <u>Key Concept: Treatment of these medical problems may lead to behavioral improvements</u>

GASTROESOPHAGEAL REFLUX IN CHILDREN WITH AUTISM: HOW DO CHILDREN PRESENT AND CAN ONE TEST THESE CHILDREN?
Timothy M. Buie. Pediatric GI, MGH, Boston, MA.

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.

Buie, 2005 J Pediatr Gastroenterol Nutr 41(4):505

Krigsman, 2007 Medical Veritas 4:1528-36

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)

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 <u>no FDA approved</u> medications for the **core symptoms** of ASD

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 upon **biomarkers** (laboratory tests or other tests like EEGs) and/or **evidence-based medicine** (choosing the best treatments based on the published medical literature)

Types of treatments

- A. Treatments based on **lab results** (ideally these are also proven treatments)
  - e.g., Iron treatment for low ferritin
- B. **Proven** treatments based on **evidence-based**, symptoms-based ranking
  - e.g., Double-blind, placebo-controlled studies

- Non-proven treatments that are most likely harmless or low risk
- Non-proven treatments that have high risk or high degree of side effects

A. Laboratory testing

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

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

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

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.**

Bradstreet et al., 2010 Altern Med Rev 15(1):15-32

Table 1. Biomedical Problems Described in ASD and ADHD

BIOMEDICAL PROBLEM	ASD	ADHD
Oxidative stress	Yes	Yes
Decreased methylation and transsulfuration	Yes	Yes
Mitochondrial dysfunction	Yes	Yes
Metal toxicity	Yes	Yes
Intestinal dysbiosis	Yes	No
Immune dysregulation / inflammation	Yes	No
Cerebral hypoperfusion	Yes	Yes

Bradstreet et al., 2010 Altern Med Rev 15(1):15-32

Biomarkers

- Basic biomarkers
- Endocrine
- Oxidative stress
- Methylation and transsulfuration
- Immune dysregulation
- Gastrointestinal (GI) dysfunction
- Mitochondrial dysfunction

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_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**
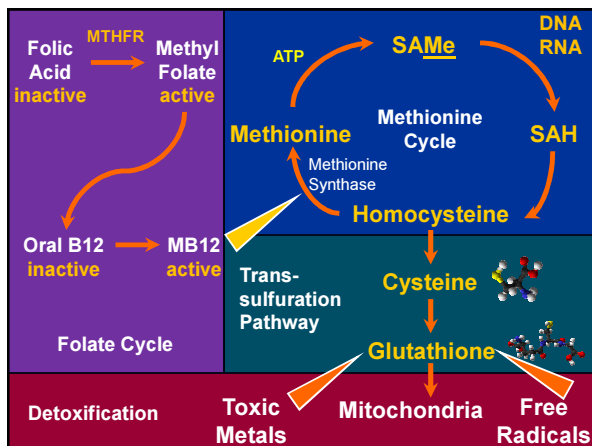
Basic biomarkers

- **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**

Folic Acid inactive → (MTHFR) → Methyl Folate active
Oral B12 inactive → MB12 active
Folate Cycle
ATP → SAMe → DNA RNA
Methionine ← Methionine Cycle → SAH
Methionine Synthase
Homocysteine
Trans-sulfuration Pathway
Cysteine
Glutathione
Detoxification
Toxic Metals — Mitochondria — Free Radicals

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

Biomarkers of Immune Dysregulation

- 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 Immune Dysregulation

- ASO / AntiDNAse B: confirm previous exposure to GABHS (group A beta-hemolytic streptococcus) in children without obvious strep exposure history
- Beta Hemolytic Strep Culture (Throat or rectal)
- Antigliadin antibodies: elevated in some people with celiac disease; appear to cross-react with Purkinje cells in cerebellum
- Urinary cryptopyrroles: Responds to high doses of B6 and zinc
- Food allergy panel

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

Rossignol and Frye, 2011 Mol Psychiatry, doi:10.1038/mp.2010.136
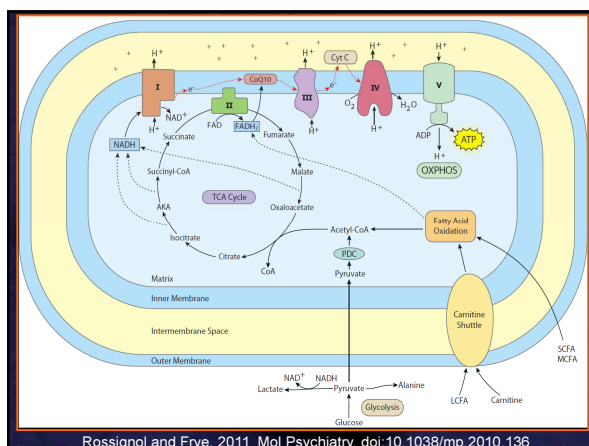
Mitochondrial Dysfunction

- 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 CO_2, 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

Section I: Clinical signs and symptoms *(1-2 points per sign/symptom as indicated. 4 points max this section)*

(a) Muscular presentation *(2 points max this category)* Points   I(a)
- Ophthalmoplegia *(2 points)*
- Facies myopathica
- Exercise intolerance
- Muscle weakness
- Rhabdomyolysis
- Abnormal EMG

(b) CNS presentation *(2 points max this category)* Points   I(b)
- Developmental delay
- Loss of skills
- Stroke-like episodes
- Migraine
- Seizures
- Myoclonus
- Cortical blindness
- Pyramidal signs
- Extrapyramidal signs
- Brain stem involvement

(c) Multisystem disease *(3 points max this category)* Points   I(c)
- Hematology
- GI tract
- Endocrine/growth
- Heart
- Kidney
- Vision
- Hearing
- Neuropathy
- Recurrent/familial   I(a) + I(b) + I(c)   I

(4 points max this section) **Total Points Section I:**

Rossignol and Frye, 2011 Autism Sci Digest (2):20-27

Section II: Metabolic/imaging studies *(1-2 points per sign/symptom as indicated. 4 points max this section)*
- Elevated lactate *(2 points)*
- Elevated lactate/pyruvate ratio
- Elevated alanine *(2 points)*
- Elevated CSF lactate *(2 points)*
- Elevated CSF protein
- Elevated CSF alanine *(2 points)*
- Urinary tricarbon acid excretion *(2 points)*
- Ethylmalonic aciduria
- Stroke-like picture MRI
- Leigh syndrome/MRI *(2 points)*
- Elevated lactate/MRS

II

(4 points max this section) **Total Points Section II:**

Section III: Morphology (muscle biopsy) *(1-4 points per sign/symptom as indicated. 4 points max this section)*
- Ragged red/blue fibers *(4 points)*
- Cox-negative fibers *(4 points)*
- Reduced COX staining *(4 points)*
- Reduced SDH staining
- SDH positive blood vessels *(2 points)*
- Abnormal mitochondria/EM *(2 points)*

III

(4 points max this section) **Total Points Section III:**

SCORE: Please consult your physician for help with interpretation   I + II + III
- 1   Mitochondrial disorder unlikely
- 2-4   Possible mitochondrial disorder
- 5-7   Probable mitochondrial disorder
- 8-12   Definite mitochondrial disorder

Total Score

†**Reference:**
Morava, E., L. van den Heuvel, F. Hol, M.C. de Vries, M. Hogeveen, R.J. Rodenburg, et al. (2006). Mitochondrial disease criteria: diagnostic applications in children. *Neurology*, 67, 1823-6.

Rossignol and Frye, 2011 Autism Sci Digest (2):20-27

Initial Lab Testing

Basic
- **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**

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!

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

http://clinicalevidence.bmj.com/ceweb/about/knowledge.jsp
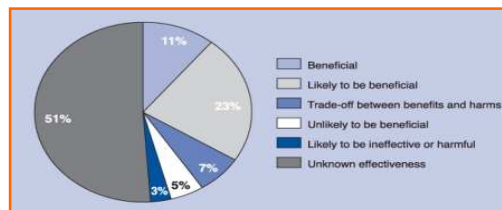
Over 50% of what is done in medicine is "Unknown Effectiveness"

Scoring

TABLE 2

Levels of evidence

Level	Description
1a	SR or meta-analysis of RCTs with homogeneity or Cochrane review with favorable findings
1b	Prospective high-quality RCT
2a	SR of cohort (prospective, nonrandomized) studies with homogeneity
2b	Individual cohort (prospective, nonrandomized) study or low-quality RCT
3a	SR of case-control (retrospective) studies with homogeneity
3b	Individual case-control (retrospective) study
4	Case series or reports
5	Expert opinion without critical appraisal or based on physiology or bench research

RCT: randomized controlled trial; SR: systematic review.
Source: Adapted from reference 16.

Rossignol, 2009 Ann Clin Psychiatry 21(4):213-236

Grade

TABLE 3

Grade of recommendation

Grade	Description
A	At least one level 1a study *or* two level 1b studies
B	At least one level 1b, 2a, or 3a study, *or* two level 2b or 3b studies
C	At least one level 2b or 3b study, *or* two level 4 studies
D	Level 5 evidence, *or* troublingly inconsistent or inconclusive studies of any level, *or* studies reporting no improvements
N	No studies identified

Source: Adapted from reference 16.

Rossignol, 2009 Ann Clin Psychiatry 21(4):213-236

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

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
  - 3b: none
  - 4 CS: none
  - 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	10. Carnosine.............................. 10
2. B6/Mag.............................66	10. MB12...................................... 10
3. Carnitine..........................44	10. Piracetam.............................. 10
4. NAC.................................. 32	10. Sulforaphane......................... 10
5. Folinic acid.....................27	15. Coenzyme Q10...................... 9
6. Omega 3...........................26	16. Vitamin D.............................. 5
7. Multivitamin.....................21	17. Digestive enzymes............... 3
8. Probiotics.........................20	17. Gingko.................................... 3
9. Vitamin C..........................14	17. Iron... 3
10. B vitamins.......................10	17. Pregnenolone........................ 3

Grade A Rankings: Supplements

Mean Score = 47.3

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

Grade B Rankings: Supplements

Mean Score = 15.2

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

Grade C Rankings: Supplements

Mean Score = 15.1

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

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

1. Melatonin	6
2. Carnitine	3
2. NAC	3
4. Multivitamin	2
5. B6/Mag	1
5. Probiotics	1
5. Vitamin C	1
5. Carnosine	1
5. Piracetam	1
5. 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

1. Oxytocin	137	11. Memantine	29
2. Naltrexone	120	12. Clomipramine	28
3. Haloperidol	77	13. Galantamine	26
4. Fenfluramine	69	14. Clonidine	25
5. Propranolol	56	14. Pentoxifylline	25
6. BH4	51	16. Fluvoxamine	23
7. Fluoxetine	50	17. Olanzapine	22
8. Atomoxetine	47	18. Amantadine	20
9. Valproate	37	18. Buspirone	20
10. Methylphenidate	33	20. Donepezil	18

Medication rankings by total points

21. Bumetanide	17	29. Steroids	8
22. D-cycloserine	15	33. Dextromethorphan	7
22. Guanfacine	15	34. Levetiracetam	6
24. Cyproheptadine	12	35. Citalopram	5
24. Topiramate	12	35. Famotidine	5
26. Celecoxib	10	37. Arbaclofen	3
26. Riluzole	10	37. Escitalopram	3
28. Sertraline	9	37. Pioglitazone	3
29. Acamprosate	8	37. Vancomycin	3
29. Mirtazapine	8	41. Amitriptyline	2
29. Ramelteon	8	42. Spironolactone	1

Grade A Rankings: Medications   Mean Score = 58.4

1. Oxytocin (137 points)
2. Naltrexone (120 points)
3. Haloperidol (77 points)
4. Propranolol (56 points)
5. BH4 (51 points)
6. Fluoxetine (50 points)
7. Atomoxetine (47 points)
8. Methylphenidate (33 points)
9. Galantamine (26 points)
10. Clonidine (25 points)
11. Amantadine (20 points)

Grade B Rankings: Medications   Mean Score = 16.7

1. Valproate (37 points)
2. Memantine (29 points)
3. Pentoxifylline (25 points)
4. Fluvoxamine (23 points)
5. Buspirone (20 points)
6. Bumetanide (17 points)
7. D-Cycloserine (15 points)
7. Guanfacine (15 points)
9. Cyproheptadine (12 points)
9. Topiramate (12 points)
11. Celecoxib (10 points)
11. Riluzole (10 points)
13. Sertraline (9 points)
14. Acamprosate (8 points)
14. Ramelteon (8 points)

Grade C Rankings: Medications   Mean Score = 9.8

1. Clomipramine (28 points)
2. Olanzapine (22 points)
3. Donepezil (18 points)
4. Mirtazapine (8 points)
4. Steroids (8 points)
6. Dextromethorphan (7 points)
7. Famotidine (5 points)
8. Arbaclofen (3 points)
8. Escitalopram (3 points)
8. Pioglitazone (3 points)
8. Vancomycin (3 points)

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

1. Oxytoxin	13
2. Naltrexone	9
3. Haloperidol	7
4. Propranolol	5
5. BH4	3
5. Atomoxetine	3
5. Methylphenidate	3
5. Valproate	3

<u>Two studies:</u>
Amantadine, Clomipramine, Clonidine, Fenfluramine, Fluoxetine, Galantamine
<u>One study:</u>
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]
- Atomoxetine [A, 47]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Amantadine [A, 20]
- Valproate [B, 37]
- Memantine [B, 29]
- Pentoxifylline [B, 25]
- Cyproheptadine [B, 12]
- Olanzapine [C, 22]
- Donepezil [C, 18]
- Steroids [C, 8]

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 fish 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]
- Pentoxifylline [B, 25]
- Fluvoxamine [B, 23]
- Bumetanide [B, 17]
- D-Cycloserine [B, 15]
- Celecoxib [B, 10]
- Riluzole [B, 10]
- Acamprosate [B, 8]
- Olanzapine [C, 22]

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]
- Atomoxetine [A, 47]
- Clonidine [A, 25]
- Memantine [B, 29]

- Fluvoxamine [B, 23]
- Cyproheptadine [B, 12]
- Topiramate [B, 12]
- Celecoxib [B, 10]
- Riluzole [B, 10]
- Sertraline [B, 9]
- Olanzapine [C, 22]
- Escitalopram [C, 3]
- Pioglitazone [C, 3]
- Spironolactone [D, 1]

Attention

- Folinic acid [B, 27]
- Probiotics [B, 20]
- Iron [C, 3]
- 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]
- Acamprosate [B, 8]
- Donepezil [C, 18]
- Fenfluramine [D, 60]
- Levetiracetam [D, 6]

Hyperactivity

- Multivitamin [A, 21]
- Omega 3 fish oil [D, 26]

- Naltrexone [A, 120]
- Haloperidol [A, 77]
- BH4 [A, 51]
- Methylphenidate [A, 33]
- Atomoxetine [A, 27]
- Galantamine [A, 26]
- Clonidine [A, 25]
- Amantadine [A, 20]
- Memantine [B, 29]

- Pentoxifylline [B, 25]
- Buspirone [B, 20]
- Guanfacine [B, 15]
- Topiramate [B, 12]
- Riluzole [B, 10]
- Acamprosate [B, 8]
- Clomipramine [C, 28]
- Olanzapine [C, 22]
- Mirtazapine [C, 8]
- Dextromethorphan [C, 7]
- Famotidine [C, 5]
- Escitalopram [C, 3]

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]

- Buspirone [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]
- Carnosine [B, 10]
- Sulforaphane [B, 10]
- B6 / Mag [C, 66]
- MB12 [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]

Training Physicians

MAPS

Medical Academy
of Pediatric Special Needs

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