THE ENDOCRINOLOGY OF AUTISM

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February 23, 2021

Objectives

1. What is Autism?
2. A Brief Review "Conventional" Therapies"
3. *Autism as an Offset of TBI*
4. The Growth Hormone/IGF Disconnect
5. Extreme Testosterone in the Autistic Child
6. What I've Learned from the Autistic Spectrum What You Can Use Everyday from ASD Children

Financial Disclosures-None

What is Autism?

- Pervasive developmental disorder:
  - Impaired social interactions
  - Deficits in verbal and nonverbal communication
  - Abnormal repetitive behaviors.
    - Hand or finger flapping,
    - Parts of objects

Etiology of autism?

Maternal Activation, Microglial Activation, Inflammation, Cytokine Storm

What is Autism?

Delayed language skills.

- Inability to initiate or sustain a conversation
- Repeated use of idiosyncratic language
- Lack of age-appropriate imaginative play
- Failure to develop peer relationships
- Lack of joyful experiences
- Preference for solitary activities

Wyatt-1st Day of Kindergarten

29 Week Gestation-3 # 1 oz.

Placental Separation

Premature Rupture of Membranes

Respiratory DIstress-Home O2 x 10 months

Inadequate calorie intake-G tube x 12 mo.

Immune deficiencies

Father-took Valproic Acid for Seizure Dx.

Mother-Hx of Thyroid Cancer

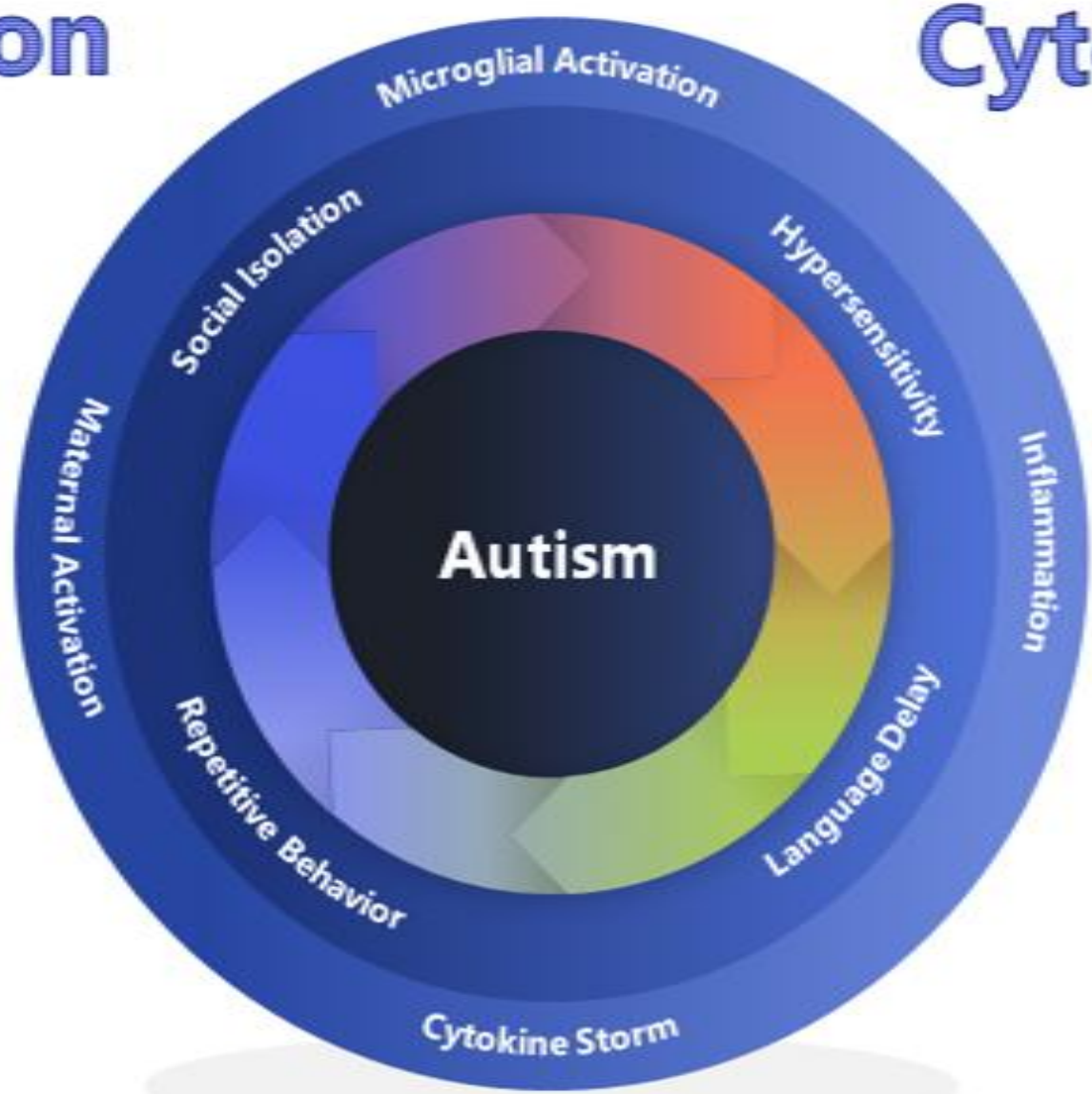
Given Vaccine at 15 months. Seizure 24 hrs. later

Marked Behavioral Changes within 2 weeks =

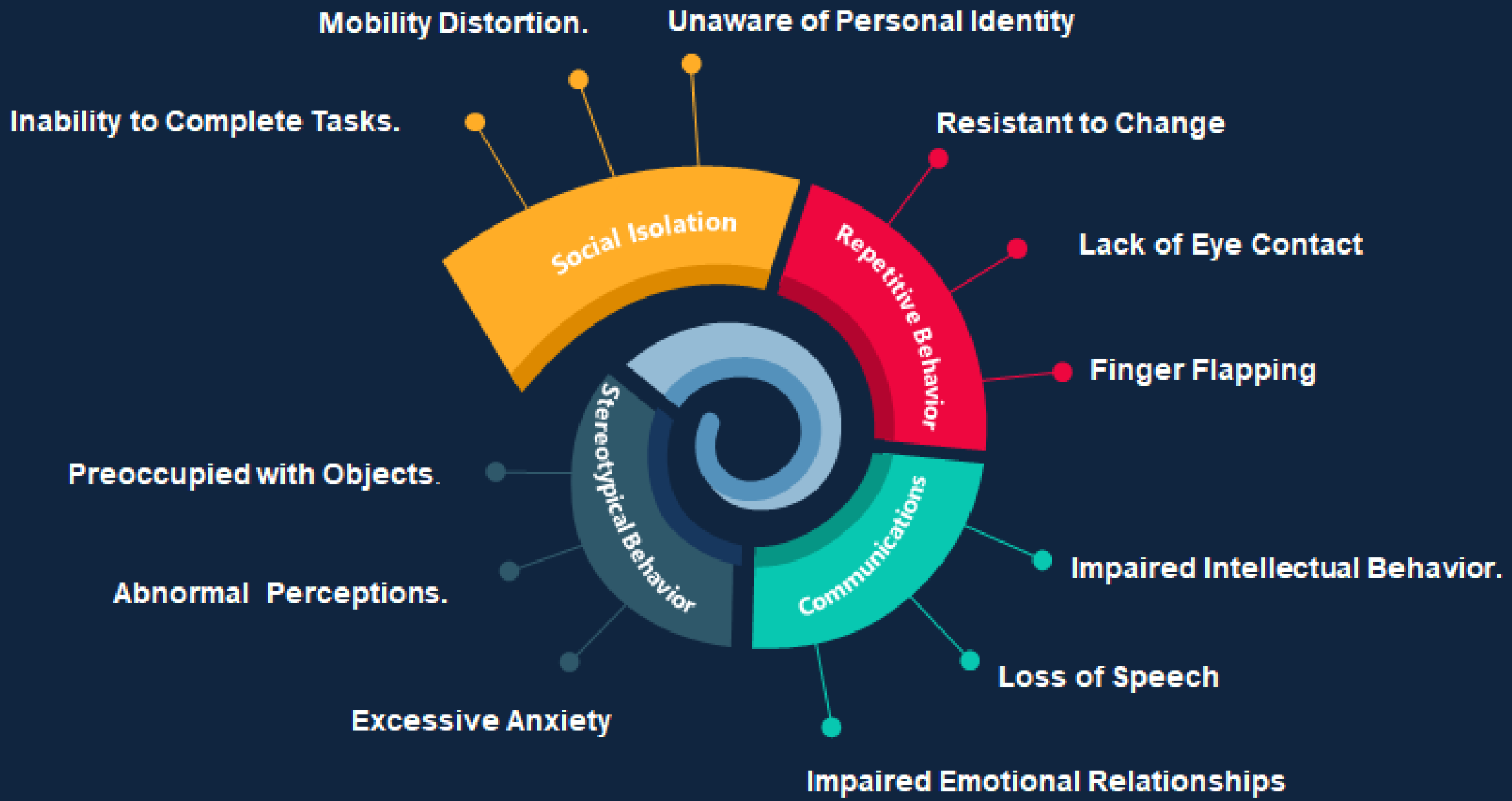
Autism

Inflammation

Cytokine Storm



Autism


Mobility Distortion.
Unaware of Personal Identity
Inability to Complete Tasks.
Resistant to Change
Social Isolation
Repetitive Behavior
Lack of Eye Contact
Finger Flapping
Preoccupied with Objects.
Stereotypical Behavior
Communications
Impaired Intellectual Behavior.
Abnormal Perceptions.
Loss of Speech
Excessive Anxiety
Impaired Emotional Relationships

Statistics

1 in 59 Children are born with ASD

Boys/girls by a factor of 3-5/1

There are No Definitive Medical Markers for ASD

Affects 1.5 million people in US

Not due to Parenting Defect

No Known Single Cause

Screening Tools

1. Autism Diagnostic Interview – Revised (ADI-R)
2. Autism Diagnostic Observation Schedule –(ADOS-G)
3. Childhood Autism Rating Scale (CARS)
4. Gilliam Autism Rating Scale – Second Edition (GARS-2)

Lab Testing for Autism

- CBC
- CMP
- Lipid Profile
  - Low Chol=Behavior Issue
- Thyroid Function Tests

  TSH, fT3, fT4

  rT3, TPO, TAG

  Ferritin, B12

- Cysteine (Glutathione marker)
- RBC-Magnesium
- RBC-Zinc
- Lead, Mercury
- C-Reactive Protein
- 25 OH Vitamin D
- HbA1c, Fasting Insulin

Specialty Lab Testing for Autism

- Heavy Metals
- Urinary Organic Acid Testing
- Comprehensive Stool Analysis
- Intestinal Permeability
- SIBO Breath Test
- MRI. CT Scan Head
- Functional MRI
- SPECT SCAN

- Hormone Evaluation
  - Testosterone, total and free
  - Androstenedione
  - Estrone, Estradiol
  - Progesterone
  - GH (before 10 a.m.)
  - IGF 1, IGF-2, IGFBP-1, IGFBP-3
  - IL-6
  - A.M. Cortisol, (rT3)
  - Fasting Insulin
  - Thyroid Function
  - DHEA, Pregnenolone
  - Prolactin
  - Oxytocin, Vasopressin
  - GABA, Serotonin

“Conventional Therapy”

Behavioral Therapies

- Applied Behavioral Analysis
- Verbal Behavior Therapy
- Cognitive Behavioral Therapy
- Developmental and Individual Differences Relationship
- Relationship Development Intervention (RDI)
- Social Skill Groups

“Conventional Therapy”

FDA Approved Medications

1. *Atypical Anti-Psychotics (Risperidone, Aripiprazole)*
    a. *Rx. ASD related Irritability*
    b. *Side Effects*
        i. *Gynecomastia (4X Increase in PRL)*
        ii. *Insulin Resistance*

“Conventional Therapy”

Frequently Prescribed Off Label Use Medications

2. SSRIs

a. Anxiety

b. Mood

c. Obsessive Compulsive Behaviors

d. “Explosive Behavior”

“Conventional Therapy”

Frequently Prescribed Off Label Use Medications

3. ADHD Medications

a. Stimulants-Methylphenidate,

- Amphetamine-Dextroamphetamine

i. Focus, Task Completion, Impulsivity

b. Non-Stimulants-Atomoxetine

i. Improve sleep

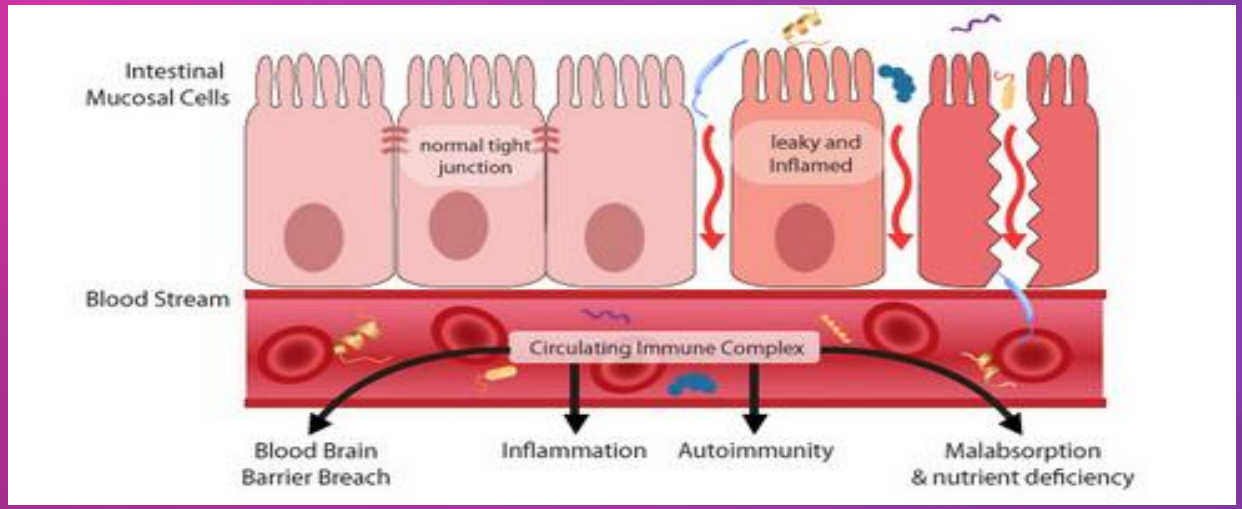
ii. Overly reactive, quick to anger

Conventional Therapy – Diet

- Gluten-Casein-Soy-Free Diet
- Lectin Free Diet
- Specific-Carbohydrate Diet
- Low Histamine
- Low-Phenol Diet
- Ketogenic Diet
- Salicylate-Free Diet
- Low-Oxalate Diet

Gluten Effects

- 1. Shifts GI Microflora to Pro-Inflammatory State
- 2. Inflammation leads to “Leaky Gut”
- 3. “Leaky gut” renders patient vulnerable to gliadin, gluten protein.



- Galland, L, The Gut Microbiome and the Brain, J Med Food. 2014 Dec 1; 17(12): 1261–1272. doi: 10.1089/jmf.2014.7000
- Trivedi MS, Shah JS, Al-Mughairy S, Hodgson NW, Simms B, Trooskens GA, et al. Food-derived opioid peptides inhibit cysteine uptake with redox and epigenetic consequences. J Nutr Biochem. 2014;25(10):1011–8. doi: 10.1016/j.jnutbio.2014.05.004.

Gluten Effects

- **4. Digestive enzymes metabolize gliadin into opioid**
  - **like peptides gliadinomorphin-7**
  - **(and) Casein, from Dairy, breaks down into Casomorphin**
- **5. Peptides are small enough to pass through BBB**
- **6. Peptides compete for opioid receptors with "normal" neurotransmitters (Serotonin, GABA, NE, Epinephrine, Glutamate)**

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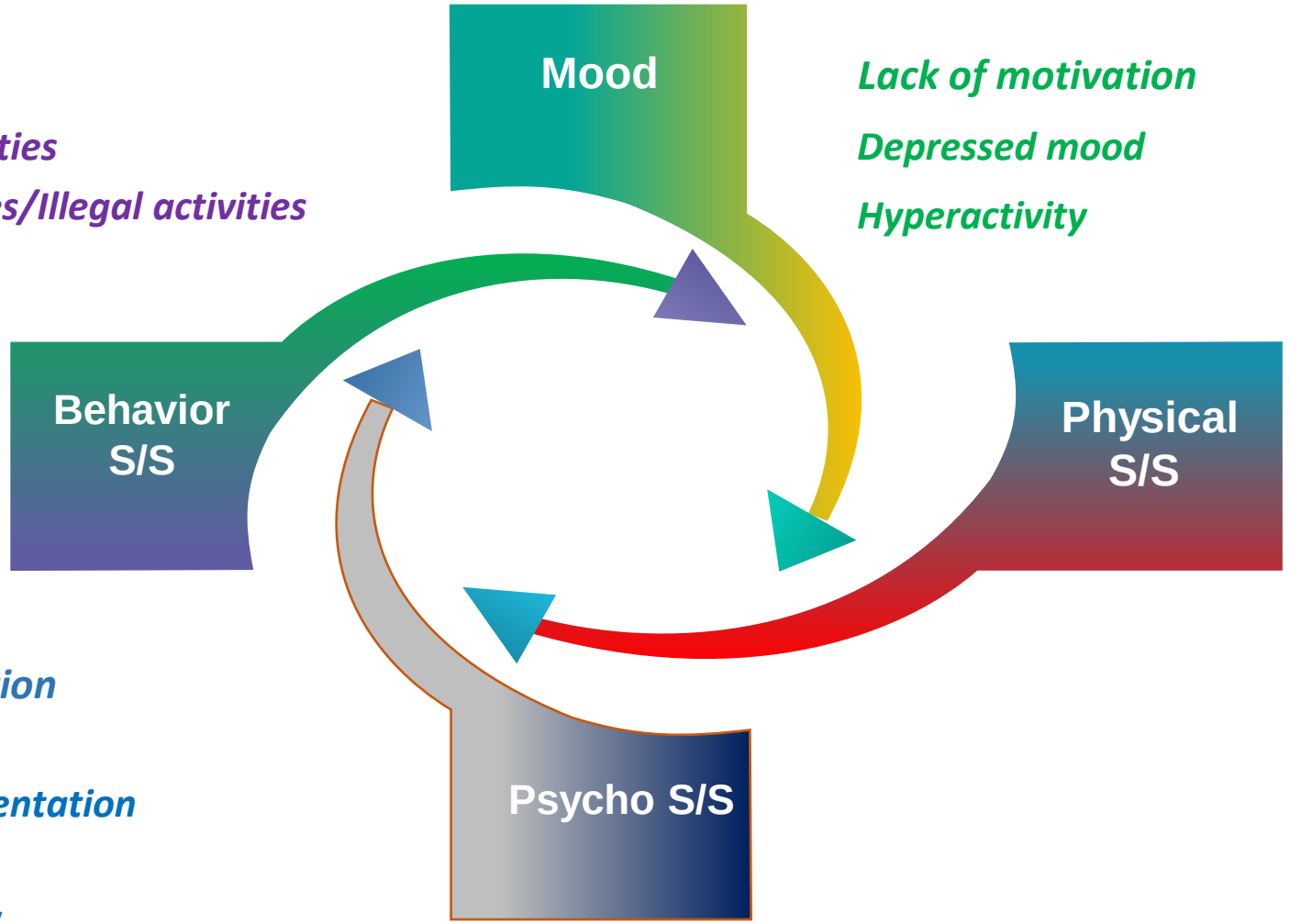
Behaviors Associated W Gluten Sensitivity

- *Socially withdrawn*
- *Slowed/Slurred speech*
- *Decreased coordination*
- *Loss of interest in activities*
- *Stealing from loved ones/Illegal activities*



Lack of motivation

Depressed mood

Hyperactivity

Lack of weight gain

Cramping

Diarrhea

Itchy skin

Joint/Muscle pain

Nausea/Vomiting

Headaches

- *Loss of concentration*
- *Apathy*
- *Confusion or disorientation*
- *Mood swings*
- *Depression/Anxiety*
- *Reality perception distorted*

.

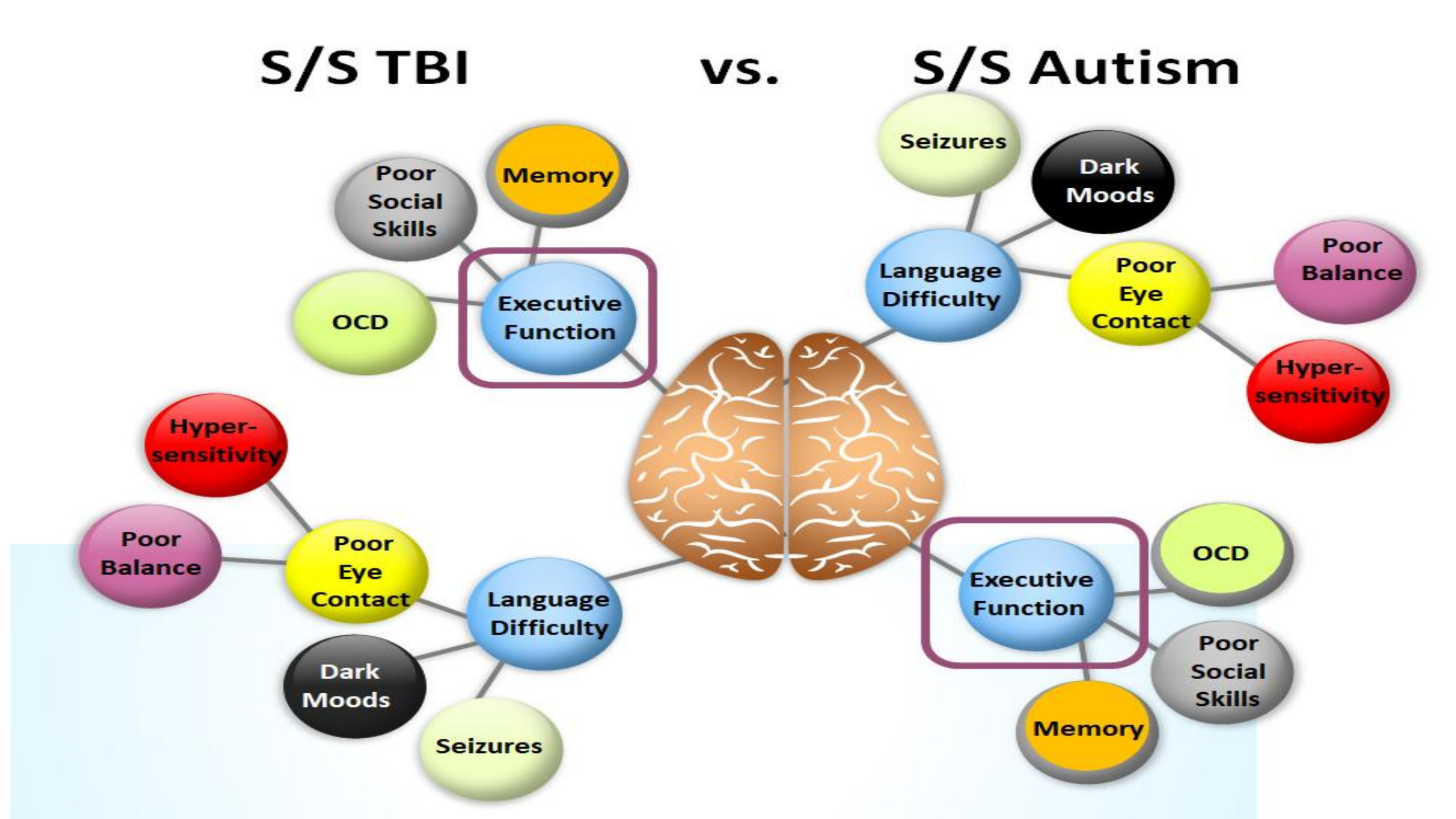
“Healing the Leaky Gut”

Where Have We Seen These Behaviors Before?

Paraphrasing Abraham Maslow circa 1966 :

"I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail."

S/S TBI vs. S/S Autism



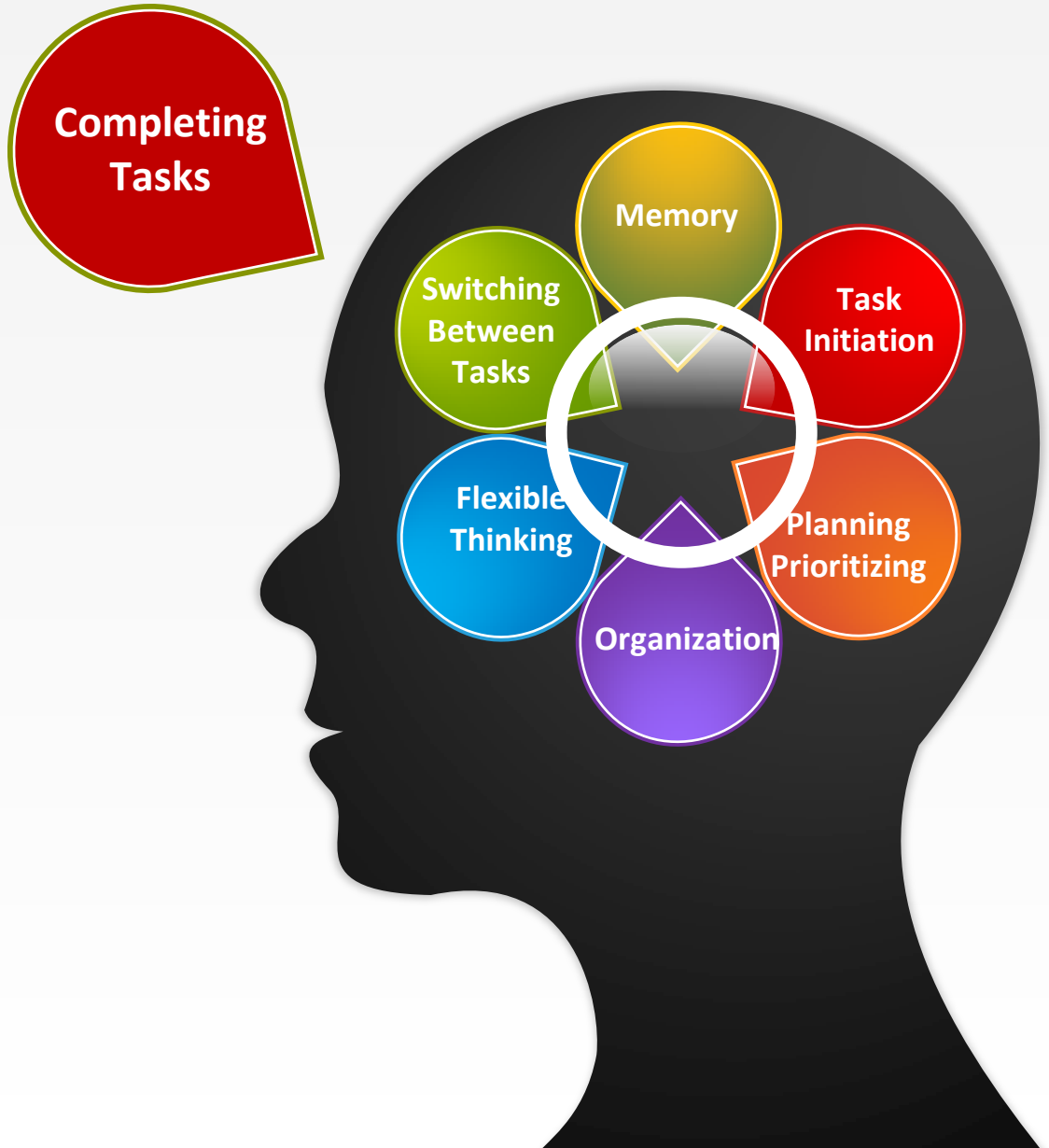
The Ah Ha! Moment

TBI and ASD are linked via "Executive Function" Deficit

Dot # 1-Executive Function

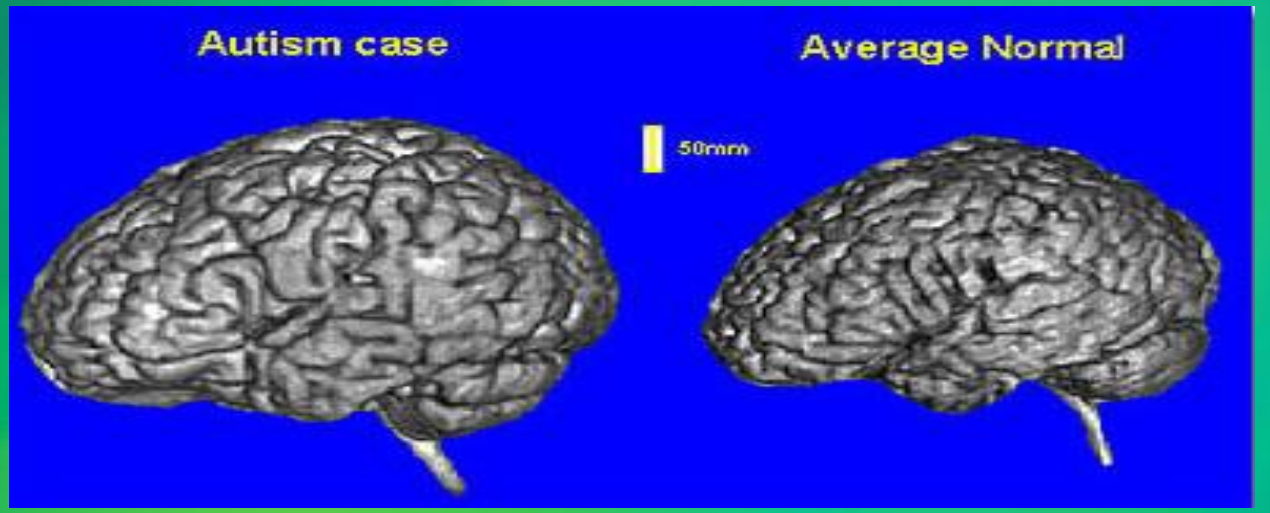
Executive Function

- *Memory*
- *Task Initiation*
- *Planning and Prioritizing*
- *Organization*
- *Flexible Thinking*
- *Ability to Switch Between Tasks*
- *Completing Tasks*



Dot # 2-Accelerated Head/Brain Growth

1st Inkling of Autism = Rapid Head Growth



- Age 1-3 months and 6-14 months
- Larger Head Circumference=Early Marker for ASD
- Higher Body Mass
- Head growth precedes diagnosis of Autism

NIH, https://www.nih.gov/news-events/news-releases/boys-autism-related-disorders-have-high-levels-growth-hormones, Friday, June 22, 2007

- Mills JL1, Hediger ML, Molloy CA, Chrousos GP, Manning-Courtney P, Yu KF, Brasington M, England LJ. Elevated levels of growth-related hormones in autism and autism spectrum disorder. Clin Endocrinol (Oxf). 2007 Aug;67(2):230-7. Epub 2007 Jun 4.

Dot # 2-Accelerated Head/Brain Growth

Frontal Lobe

- **Normal**

Concentration
Regulates Emotions
Appropriate:
- Speech
- Executive Function
- Cognition
- Problem Solving
- Abstract Thinking
- Memory
- Reasoning
- Organizing

- **Autism**

Poor Focus
Irritability
Impaired:
- Language
- Task Performed
- Facial Cognition

Increased Folds [13]
Enlarged Size [14]
- Inverse to Cerebellum Size

Parietal Lobe

Normal	Autism [15]
Temperature	Temp. Fluctuations
Language	Difficulty:
Sensory	- Reading
Functions:	- Language
- Touch	- Cognition
- Taste	- Delayed Speech
- Smell	- Spatial Concepts
- Pain	- Hypersensitivity
	Enlarged Left Lobe

Back to Maslow

Clearfield Medical Group
Brain Dysfunction/Behavioral Issues

=
Hormone
Dysfunction

Hammer.

Nail

Head
Enlargement

Hormone
Etiology of Head
Enlargement?

GROWTH
HORMONE
EXCESS!

Dot # 2-Accelerated Head/Brain Growth

- ***Rapid head growth predicts:***
- ***Age 3-4 years***
  - **Boys have higher levels of growth hormone vs. non ASD**
    - ***Serum IGF-1, IGF-2 and IGF BP3 levels higher***
  - ***Severity of clinical outcomes + Degree of brain abnormality.***

- NIH, https://www.nih.gov/news-events/news-releases/boys-autism-related-disorders-have-high-levels-growth-hormones, Friday, June 22, 2007
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Dot # 2-Accelerated Head/Brain Growth

- ***Age 4-5 ASD Brain is at "Maximum" Growth***
  - ***Brain Growth is 8-10 years sooner than "Normal"***
  - ***Brain growth is faster capacity to experience and process:***
    - ***Emotions, thoughts, and actions.***
    - ***Natural learning and exploring experiences are short circuited***
    - ***Analogous to a missile launch without a guidance system***

- ***Age 15 (Approx.)-Pattern reverses-brain volume decreases***

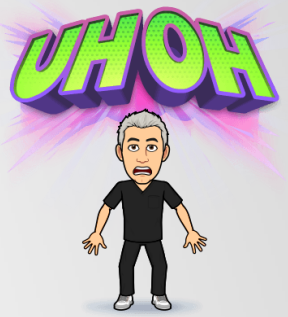
- NIH, https://www.nih.gov/news-events/news-releases/boys-autism-related-disorders-have-high-levels-growth-hormones, Friday, June 22, 2007
- Mills JL1, Hediger ML, Molloy CA, Chrousos GP, Manning-Courtney P, Yu KF, Brasington M, England LJ. Elevated levels of growth-related hormones in autism and autism spectrum disorder. Clin Endocrinol (Oxf). 2007 Aug;67(2):230-7. Epub 2007 Jun 4.

Big Head = High GH

If We Lower GH = Autism "Cured!"

Right? Easy Peasy

High Growth Hormone S/S ≠ ASD S/S

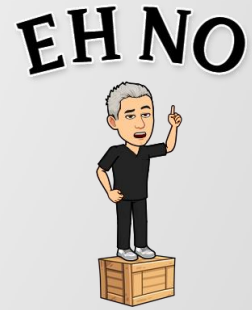


GH Excess S/S

- *Difficulty with peripheral vision*
- *Auditory/Visual Hallucinations*
- *Prominent forehead and jaw*
- *Thickening facial features*
- *Gaps between the teeth*
- *Increased sweating*
- *In girls: Irregular menstruation, galactorrhea*
- *Large hands/Feet/Fingers/Toes*
- *Weakness*
- *Sleep problems*
- *Headaches*
- *Deafness*

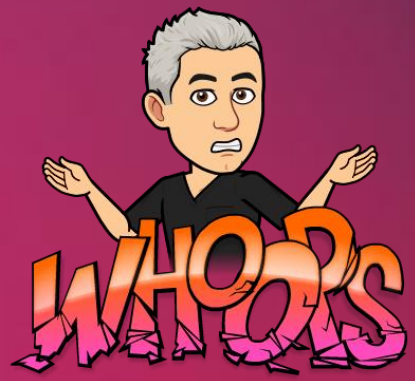
ASD S/S

- *Memory*
- *Concentration*
- *Mental clarity*
- *OCD*
- *Paranoia*
- *Poor Concentration*
- *Impulse Control*
- *Anxiety*
- *Lack of Socialization*
- *Inability to Plan*
- *Dark Moods*
- *Inability to Switch B Tasks*



EXPLAIN THIS

Studies Showing Efficacy in ASD



1. IGF-1 to Treat ASD and/or Schizophrenia [49]
2. Can IGF-1 treat autism symptoms? [50]
3. Treatment of ASD with insulin-like growth factors.

BUT WAIT

It's Low Growth Hormone S/S that = ASD S/S

HOW CAN THIS BE?

GH Deficiency S/S

- *Memory*
- *Concentration*
- *Mental clarity*
- *OCD*
- Paranoia
- Poor Concentration
- Impulse Control
- Anxiety
- Lack of Socialization
- Inability to Plan
- Dark Moods
- *Inability to Switch B Tasks*

ASD S/S

- *Memory*
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How Do We Square this Circle?

A Brief Primer on Growth Hormone (GH)

Single chain 191-amino acids linked in a specific manner, in a particular order.

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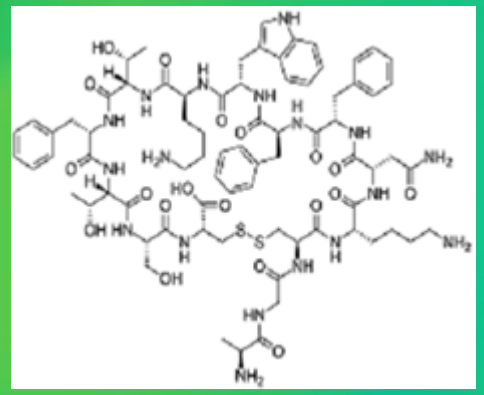
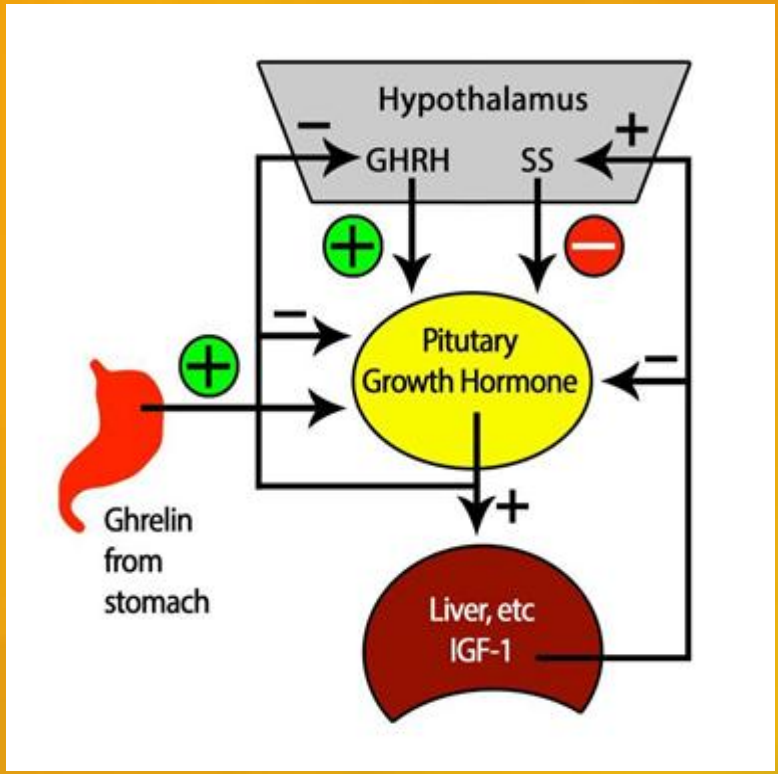


Picture a Legos ™ model snapped together to make a windmill or a car.

GH Prime Directive: Stimulate cell and growth reproduction.

Growth Hormone Physiology

1. GH released in Spurts or Waves between 10PM and 4 AM
2. Stimulated by:
   a. Hypothalamus: GH releasing factor (GHRH)
   b. GI Tract: Ghrelin (GHRP)
3. Inhibited by: Somatostatin (GHIH)
4. Synthesized in the pituitary gland



Growth Hormone Sufficiency vs. Deficiency

Sufficient GH Enhances

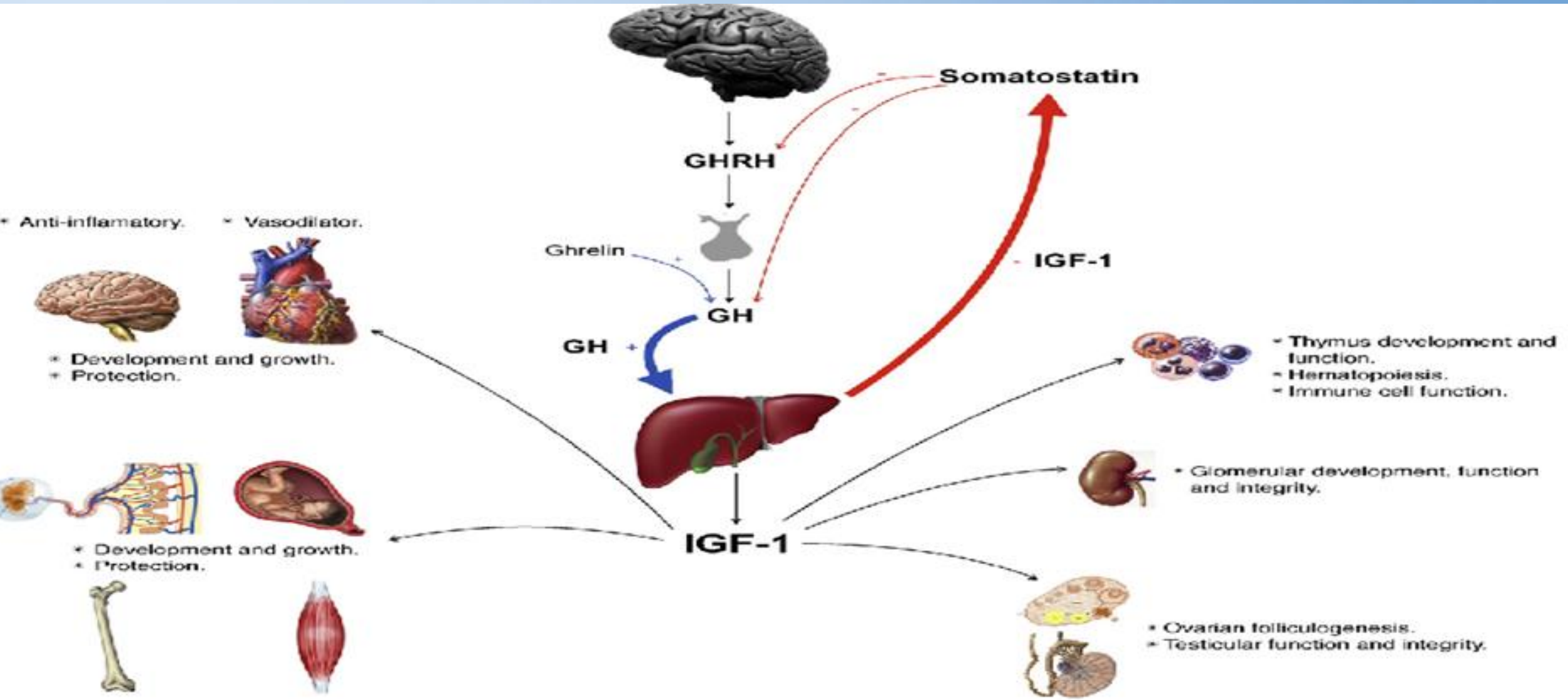
- *Memory*
- *Concentration*
- *Mental clarity*
- *Improves OCD, Paranoia S/S, Dark moods*
- *Impulse control*
- *Anxiety*
- *Sense of reality*
- ***Executive Function***
- *Energy*
- *Cardiovascular function*
  - *Reduces Il-1, Il-6, cRP*

Low GH Worsens

- *Memory*
- *Concentration*
- *Mental clarity*
- *OCD*
- Paranoia
- Poor Concentration
- Impulse Control
- Anxiety
- ***Executive Function***
  - Inability to Plan
  - Dark Moods
  - *Inability to Switch B Tasks*

Growth Hormone Physiology

Liver must convert GH to end-organ usable IGF-1 (IGF-2 Prenatal)



IGF-1

- Promotes tissue growth and maturation
- Upregulates anabolic processes
- Neurotrophic effects of IGF-1

  Promotes:

  - Neurogenesis
  - Development and maturation
  - Myelination
  - Prolonged survival and resistance to injury

IGF-1 and the Brain

↓ IGF-1 signaling = Cognitive dysfunction

- ↑ IGF-1 = ↑ Perceptual motor performance
  Information processing speed
  Fluid intelligence

- Acts in concert with BDNF to promote neurogenesis

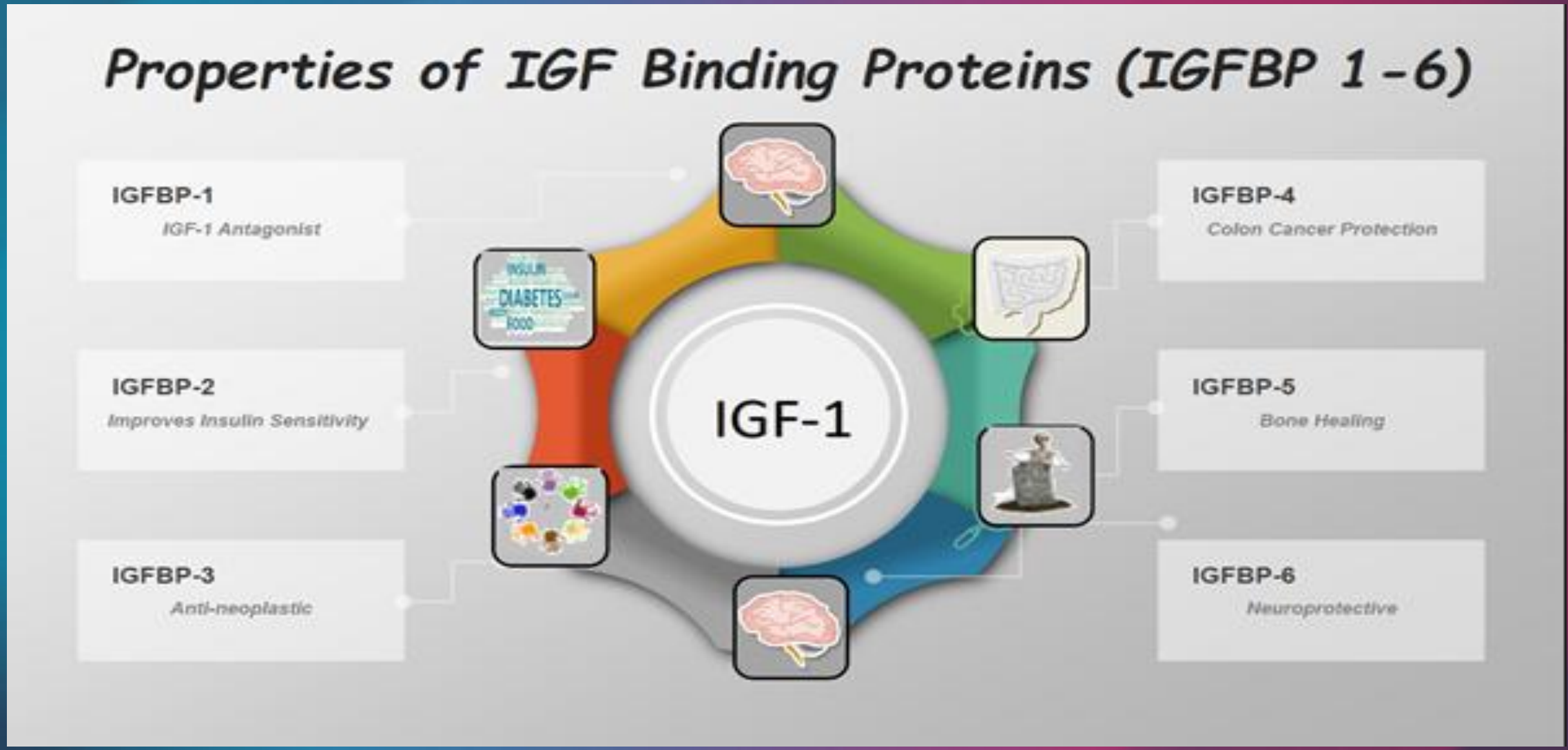
- Low-dose IGF1 treatment = ↑ neurons.
- Promotes hippocampal neurogenesis
- Exercise neuroregenesis effect mediated through IGF1 signaling

Systemic Effects of IGF-1

IGF-1

- Brain Development
- Cognitive Function
- Insulin Sensitivity
- Fertility
- Thermogenesis
- Blood Pressure
- Hepatic Glucose Output
- Appetite

IGF Circulates In Vivo Via Bound Proteins (IGFBP1-6)



IGFBP-1 has a strong, significant negative correlation with free IGF-I levels.

IGFBP-1 is Negatively Correlated with free IGF-I Levels

IGFBP-1:

Inversely related to:

Insulin resistance

BMI, waist-hip ratio

Free IGF-I levels. [63-64]

Increased by Cytokines:

Interleukin 6 (IL-6)

TNFα [66]

Elevated IGFBP-1:

Poor brain development

Reduced cognitive function

Poor verbal fluency

Poor Mini-Mental State Examination (MMSE) scores.

IGFBP-1 is Negatively Correlated with free IGF-I Levels

IGFBP-1:

Inversely related to:

Insulin resistance

BMI, waist-hip ratio

Free IGF-I levels. [63-64]

Increased by Cytokines:

Interleukin 6 (IL-6)

TNFα [66]

Elevated in ASD Patients:

- **IGFBP-1.** [65]
- **Interleukin-6 (IL-6)**
- **TNF-α**
- **Interferon-γ (IFN-γ)**[68]

IGF-1 Levels in ASD

In ASD:

Serum **IGF-1 levels are elevated**

Cerebrospinal fluid **IGF-1 levels are significantly diminished**

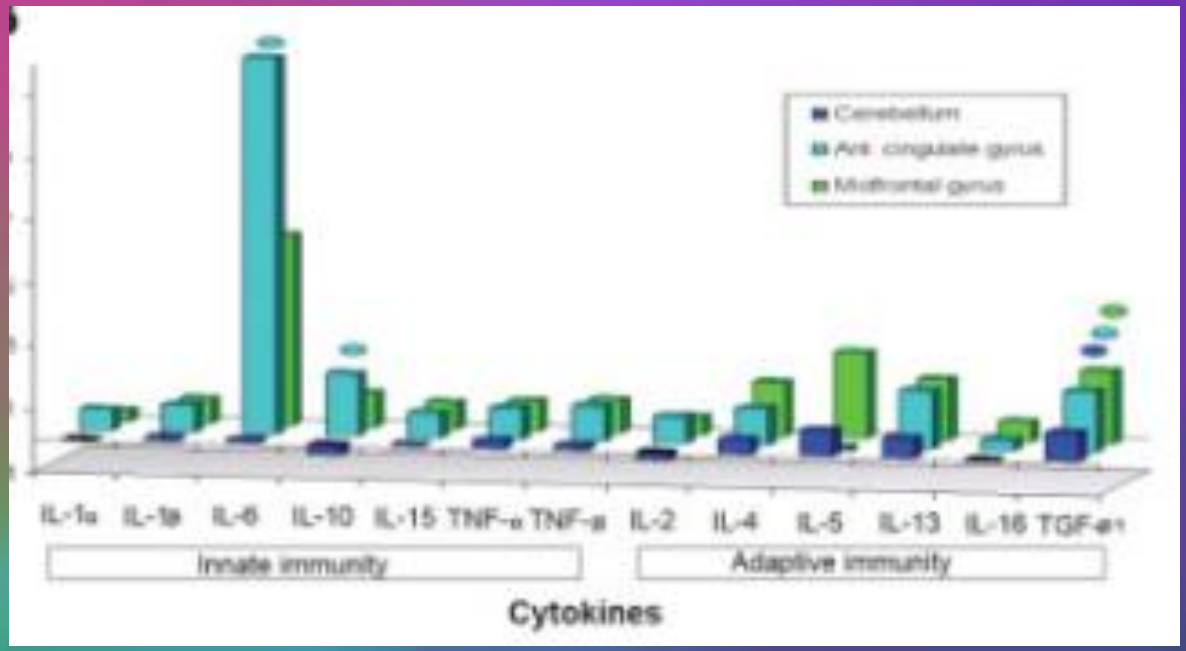
WHY?

Riikonen, Raili. "Insulin-Like Growth Factors in the Pathogenesis of Neurological Diseases in Children." International journal of molecular sciences vol. 18,10 2056. 26 Sep. 2017, doi:10.3390/ijms18102056

What Causes the Dichotomy Between High GH and Low IGF-1?

Pro-inflammatory cytokine, IL-6, is significantly elevated in the autistic brain. (73)

Growth hormone rises in the presence of IL-6, but its' conversion to IGF-1 fails. (75)



(74)

What Causes the Dichotomy Between High GH and Low IGF-1?

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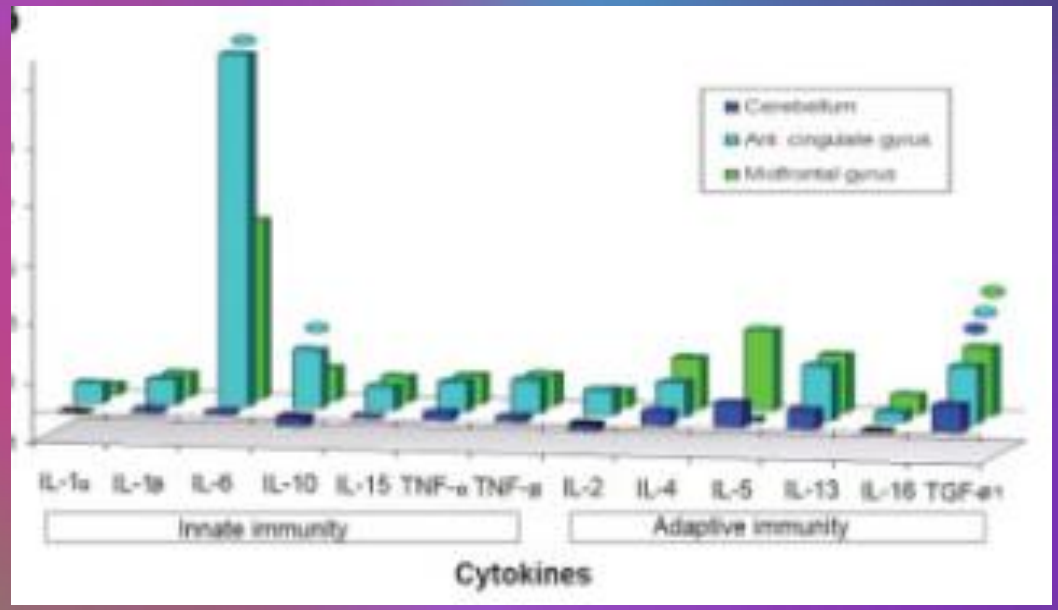


73. Wei, Hongen, et al. “IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration, and synaptic formation.” Journal of neuroinflammation vol. 8 52. 19 May. 2011, doi:10.1186/1742-2094-8-52

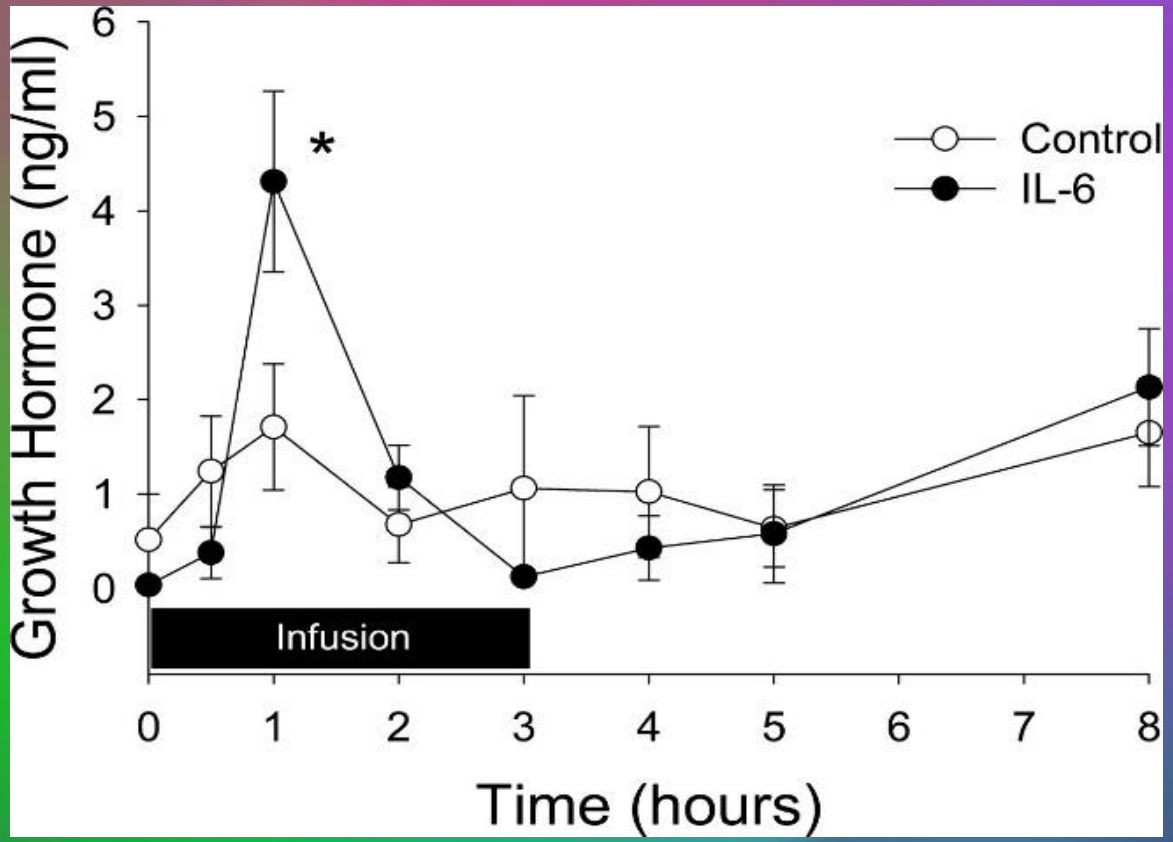
74. Jiang, Nona M, et al. “The Impact of Systemic Inflammation on Neurodevelopment.” Trends in molecular medicine vol. 24,9 (2018): 794-804. doi:10.1016/j.molmed.2018.06.008

75. Trobec, Katja et al. “Growth hormone, insulin-like growth factor 1, and insulin signaling-a pharmacological target in body wasting and cachexia.” Journal of cachexia, sarcopenia, and muscle vol. 2,4 (2011): 191-200. doi:10.1007/s13539-011-0043-5

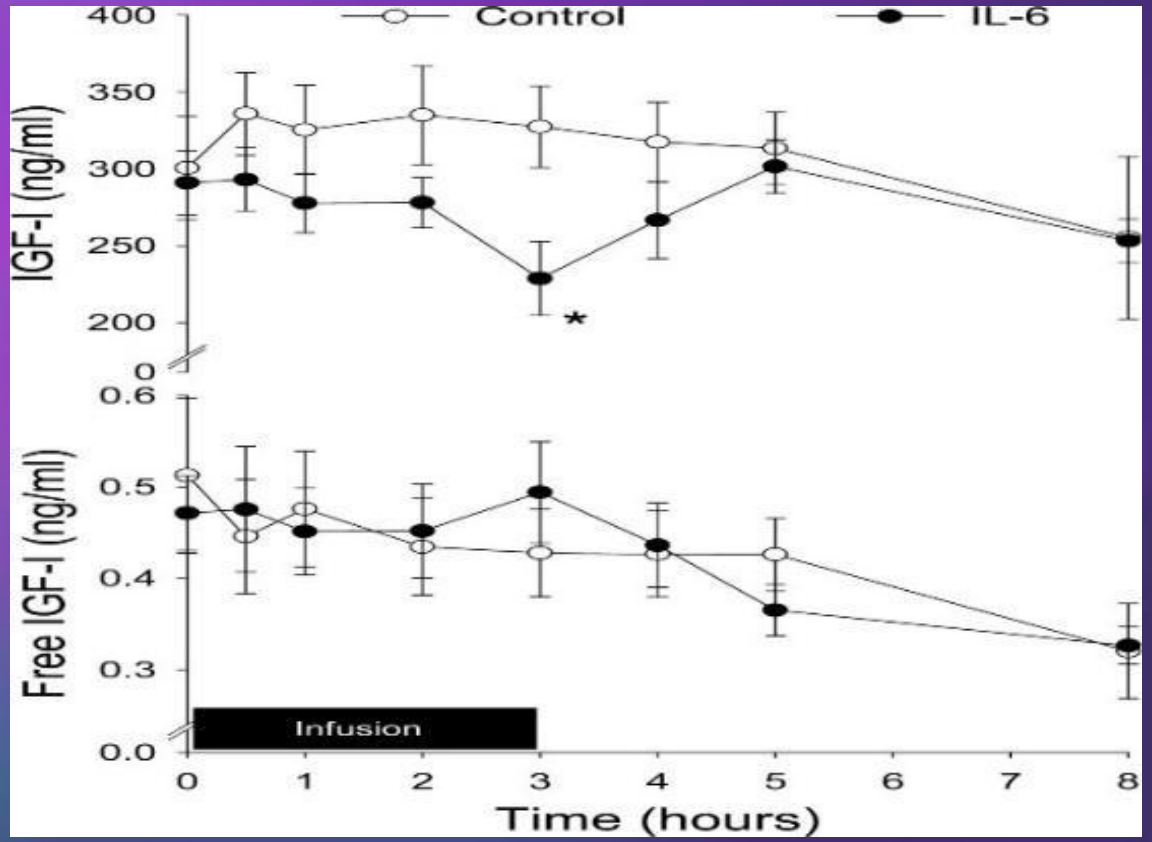
What Causes the Dichotomy Between High GH and Low IGF-1?

(74)

EFFECT IF IL-6 ON GH



EFFECT OF IL-6 ON IGF-1

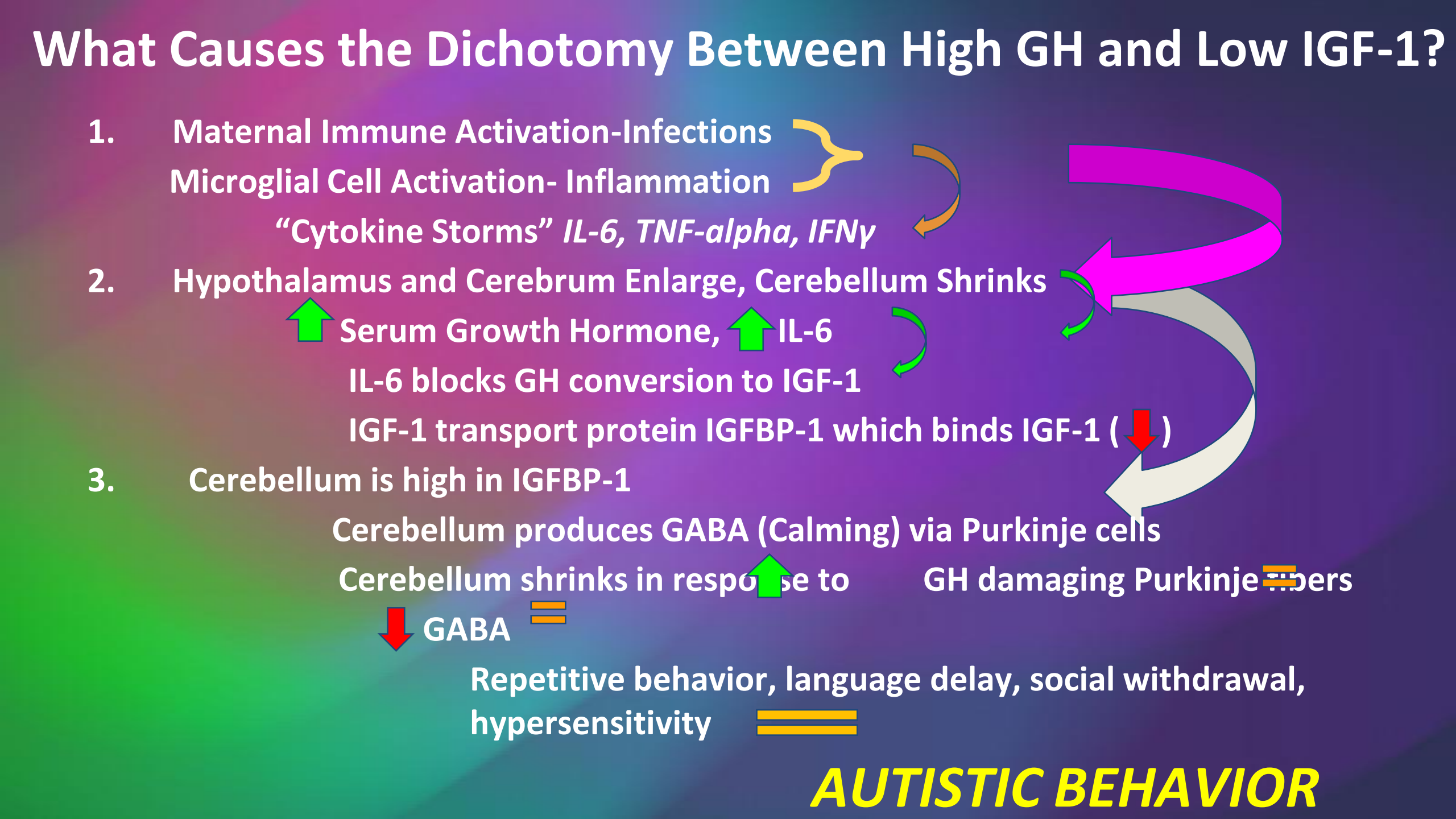


Nemet, D., Eliakim, A., Zaldivar, F., Cooper, D., Effect of rhIL-6 infusion on GH→IGF-I axis mediators in humans American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 2006 291:6, R1663-R166

Thomas, P.L., IL-6 Disrupts the GH→IGF-1 Axis in Autism; Epiphany Online Blog, Thursday, March 13, 2014

What Causes the Dichotomy Between High GH and Low IGF-1?

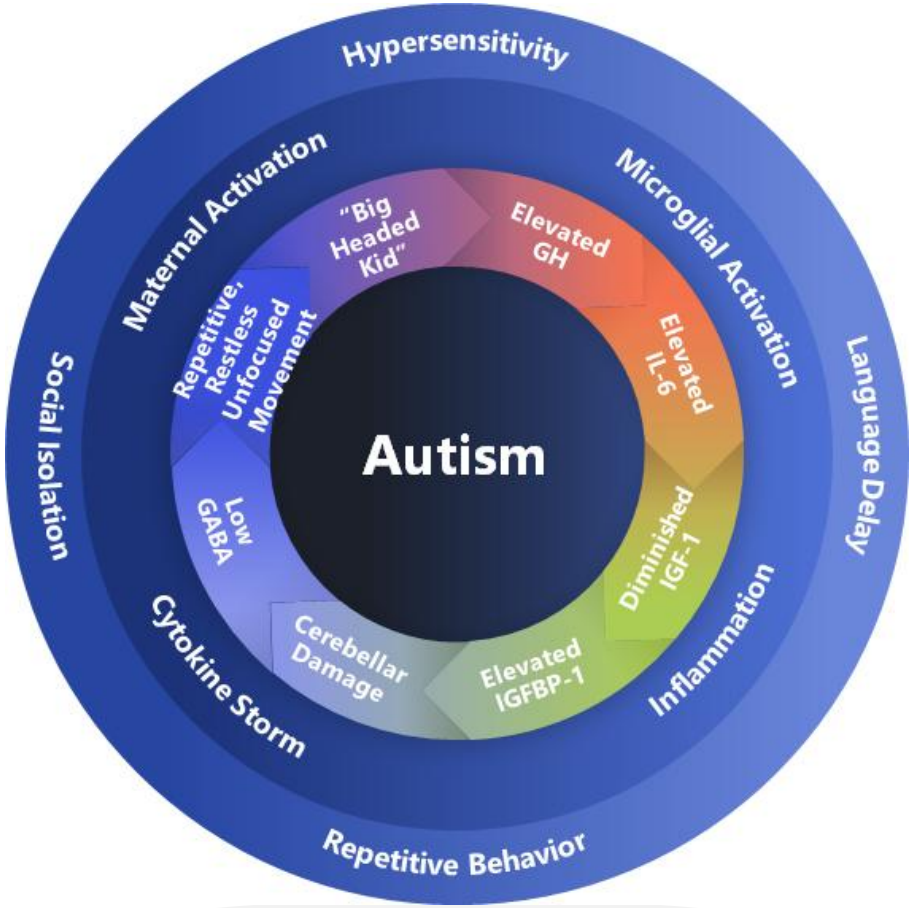
1. Maternal Immune Activation-Infections
   Microglial Cell Activation- Inflammation
   "Cytokine Storms" *IL-6, TNF-alpha, IFNγ*
2. Hypothalamus and Cerebrum Enlarge, Cerebellum Shrinks
   ↑ Serum Growth Hormone, ↑ IL-6
   IL-6 blocks GH conversion to IGF-1
   IGF-1 transport protein IGFBP-1 which binds IGF-1 (↓)
3. Cerebellum is high in IGFBP-1
   Cerebellum produces GABA (Calming) via Purkinje cells
   Cerebellum shrinks in response to GH damaging Purkinje fibers
   ↓ GABA
   Repetitive behavior, language delay, social withdrawal, hypersensitivity



AUTISTIC BEHAVIOR

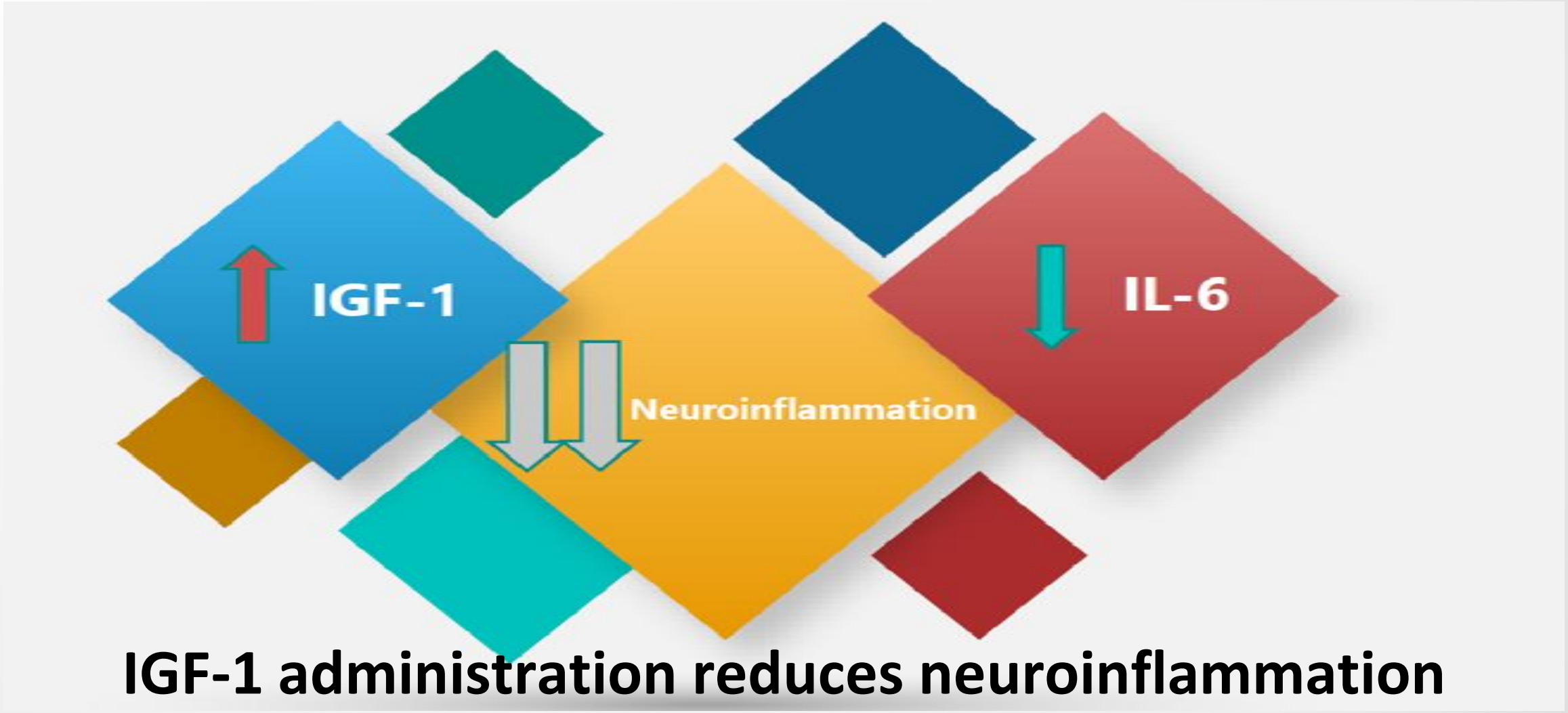
Inflammation

Cytokine Storm



Autism

IGF-1 EFFECT ON IL-6



IGF-1 administration reduces neuroinflammation

IGF-1 alters microglial function by ↓ secretion of IL-6

Lab Values: GH, IGF-1

Growth Hormone	Normal Range	Optimal Range	Median
Children	10-50 ng/ml	19.8-40.2	30 ng/ml
Adults	0-20 ng/ml	6.6-13.4 ng/ml	10 ng/ml

https://www.ucsfhealth.org/medical-tests/003706

IGF-1	Normal Male	Normal Female	Optimal M	Optimal F	Median M	Median F
< 1 yr.	16-142 ng/ml`	17-185 ng/ml	52-106 ng/ml	67-135 ng/ml	79 ng/ml	101 ng/ml
1-1.9 yr.	16-134	16-175	50-100	63-128	75	95.5
2-2.9 yr.	16-135	16-178	48.3-101	64-130	75.5	97
3-3.9 yr.	30-155	38-214	61-124	83-169	92.5	126
4-4.9 yr.	28-181	34-238	69-140	90-182	104.5	136
5-5.9 yr.	31-214	37-272	80.5-163.5	102-207	122	154.5
6-6.9 yr.	38-253	45-316	96-195	119-241	145.5	180.5
7-7.9 yr.	48-298	58-367	112.2-227.8	140-285	170	212.5
8-8.9 yr.	62-347	76-424	135-274	165-335	204.5	250
9-9.9 yr.	80-398	99-483	158-320.26	192-390	239	291
10-10.9 yr.	100-449	125-541	154.2-367.83	220-446	274.5	333

Hautakoski, Elina. “Plasma concentrations of insulin-like growth factor 1 (IGF-1) and IGF binding protein 3 (IGFBP-3) among 6- to 30-month-old rural Malawian children.” (2019). https://www.semanticscholar.org/paper/Plasma-concentrations-of-insulin-like-growth-factor-Hautakoski/047a01a81aaa8f8d08b112e0eda894ce0a4e2bf3

Lab Values: IGFBP1, IL-6

IGFBP-1	Normal	Optimal	Median
< 9 yr.	15-95 ng/ml	36-74 ng/ml	55 ng/ml
10-14 yr.	8-64 ng/ml	23.76-48.24	36 ng/ml

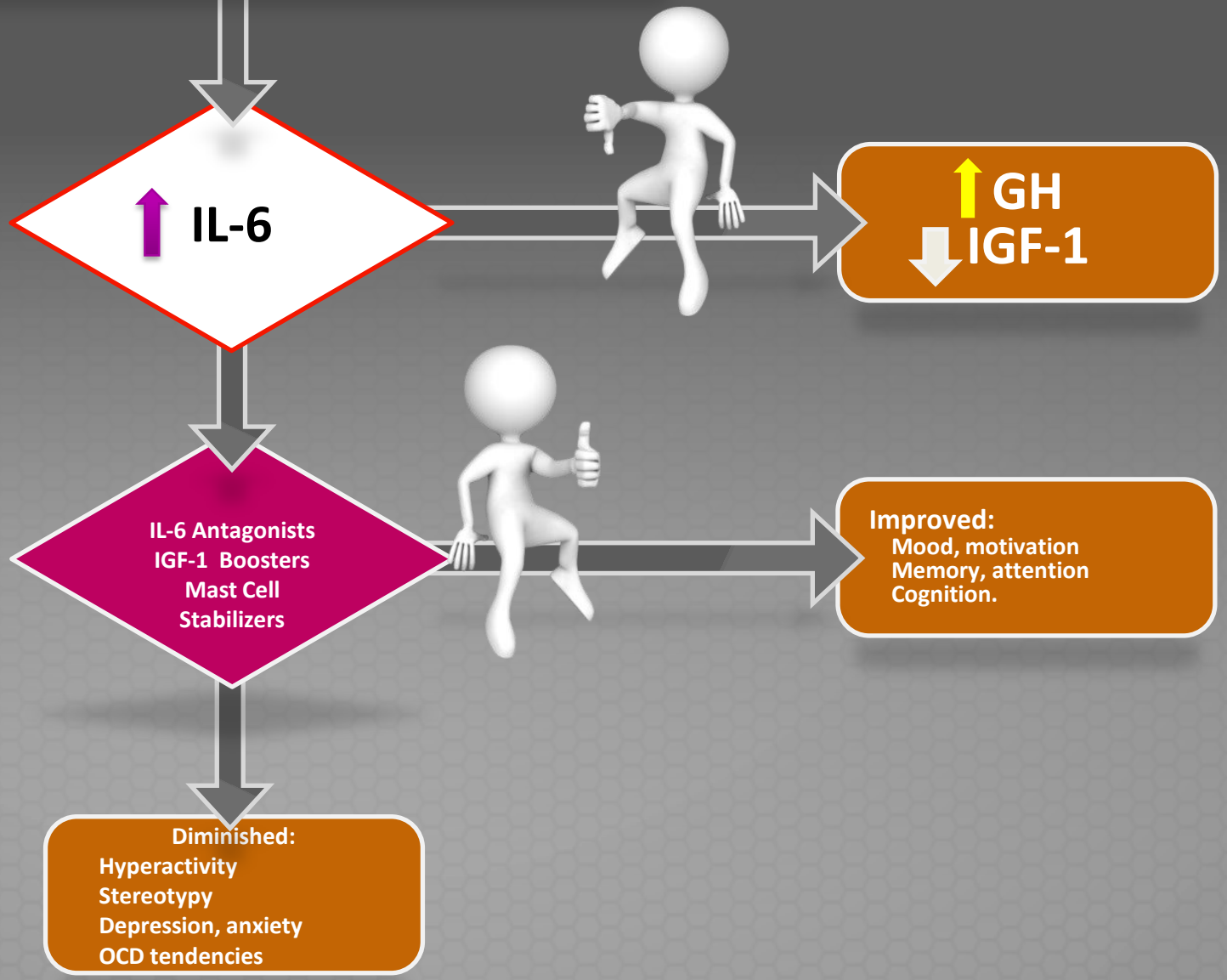
Cortés Blanco A, Labarta Aizpún JI, Ferrández Longás A, Mayayo Dehesa E. Valores de referencia de IGF-I, IGFBP-1, IGFBP-3 y osteocalcina en niños sanos zaragozanos [Reference values for IGF-I, IGFBP-1, IGFBP-3 and osteocalcin in healthy children in Zaragoza]. An Esp Pediatr. 1999;51(2):167-174.

IL-6	Normal	Optimal	Median
Vaginal Delivery	2-9.5 pg/ml	3.6-7.6	3.3 pg/ml
C section Delivery	2-12.8 pg/ml	4.9-9.9	<2 pg/ml
1 mo.-age 14	0-16 pg/ml	5.28-10.8	8 pg/ml
Adult	0-1.8 pg/ml	0.59-1.206	0.9 pg/ml

1. Barug D, Goorden S, Herruer M, Müller M, Brohet R, de Winter P (2014) Reference Values for Interleukin-6 and Interleukin-8 in Cord Blood of Healthy Term Neonates and Their Association with Stress-Related Perinatal Factors. PLoS ONE 9(12): e114109. https://doi.org/10.1371/journal.pone.0114109)
2. Child Khan, A, and Z Ali. "Normal Ranges for Acute Phase Reactants (Interleukin-6, Tumour Necrosis Factor-alpha, and C-reactive Protein) in Umbilical Cord Blood of Healthy Term Neonates at the Mount Hope Women's Hospital, Trinidad." The West Indian medical journal vol. 63,5 (2014): 465-9. doi:10.7727/wimj.2012.133
3. https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/63020

GH/IGF-1 REMEDIES

Autism/Neuroinflammation



Medications:

- IGF-1
- Intranasal Insulin
- Low Dose Naltrexone
- Pioglitazone
- Statins
- Verapamil
- Tocilizumab

Supplements:

- EPA/DHA
- EGCG
- Vitamin C
- N-Acetyl Cysteine
- Quercetin
- Luteolin
- Rutin
- Zinc
- Vitamin D

IGF-1 (Increlex, Mecasermin)

Mechanism of Action: Corrects Glutamate/GABA Imbalance

Dose: 0.04-0.12 mg/kg

Effects:

Improves social withdrawal, language delay, repetitive behaviors, hypersensitivity

Side Effects:

Hypoglycemia, allergic reactions, increased intracranial pressure (temporary), headache, nausea/vomiting, enlarged tonsils, snoring, difficulty breathing, sleep apnea, slipped capital femoral epiphysis, scoliosis due to rapid growth, benzyl alcohol toxicity.

1. Buxbaum et al. http://sfari.org/news-and-opinion/conference-news/2011/international-congress-of-human-genetics-2011/growth-factor-improves-autism-symptoms-in mice
2. Sholtis, S., "Discovery of a new drug target could lead to a novel treatment for severe autism," Penn State News; January 4, 2016. https://news.psu.edu/story/386151/2016/01/04/research/discovery-new-drug-target-could-lead-novel-treatment-severe-autism

Intranasal Insulin

***MOA*: Enhances synaptic plasticity via glutamatergic/GABAergic receptors. [93] Corrects sodium, potassium, chloride pump, malfunction resulting in excess cerebral chloride. Result is reversal of GABA depletion.**

***Dose*: 2 IU daily x 3 days, then increase to 0.5-1.5 IU/kg/d**

***Effects*: Similar to IGF-1. Gross and fine motor activities, cognitive function, and educational comprehension, nonverbal communication, cognition, and autonomy enhancement.**

1. de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis 2005;7:45-61.
2. Lioutas VA, Alfaro-Martinez F, Bedoya F, Chung CC, Pimentel DA, Novak V. Intranasal Insulin and Insulin-Like Growth Factor 1 as Neuroprotectants in Acute Ischemic Stroke. Transl Stroke Res. 2015;6(4):264-275. doi:10.1007/s12975-015-0409-7
3. Medina, Igor et al. “Current view on the functional regulation of the neuronal K(+)-Cl(-) cotransporter KCC2.” Frontiers in cellular neuroscience vol. 8 27. 6 Feb. 2014, doi:10.3389/fncel.2014.00027
4. Lee CC, Huang CC, Wu MY, Hsu KS. Insulin stimulates postsynaptic density-95 protein translation via the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway. J Biol Chem 2005;280:18543-50.
5. Benedict C, Kern W, Schultes B, Born J, Hallschmid M. Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. J Clin Endocrinol Metab 2008;93:1339-44.

Low Dose Naltrexone

MOA: **Cytokine Inhibition, Opioid Antagonist**

Dose: 1 mg/kg max. Begin at 0.1 mL (0.1 mg)

- Increase by 0.1 mL q3-7 days up to maximum dose 4.5 mg

Effects: Improvements in:

Self-injurious behavior
Communication skills
Hyperactivity, Agitation
Social withdrawal
Stereotyped behaviors
Attention
Eye contact

Side Effects: Rebound insomnia, Nausea, Nightmares

Pioglitazone (Actos)

MOA: Cytokine (IL-6) Inhibition, Anti-inflammatory

Dose: 0.75 mg/kg Begin at 7.5 mg, increase to 15 mg/d as tolerated

Improved:

- **Irritability**
- **Lethargy**
- **Stereotypy**
- **Hyperactivity**

Side Effects:

Peripheral edema, headache, sore throat, reports of bladder cancer

Statins

MOA: Anti-inflammatory, Cytokine Inhibition, Reduces cerebellar neuroinflammation

Dose: Lipophilic Statins:

Simvastatin 5-20 mg./day
Atorvastatin 10 mg/day
Lovastatin 10-40 mg/day

Effects: Decreased irritability, hyperactivity, neuroprotective, Improved affection, spontaneity

Side Effects:

Liver Issues-loss of appetite, stomach pain (upper right side), tiredness, itching, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes)

- **Headache**
- **Nausea, stomach pain, constipation**
- **Cold symptoms such as a stuffy nose, sneezing, sore throat**

1. Ridker, P.M., The JUPITER Trial. Results, Controversies, and Implications for Prevention. *Circulation: Cardiovascular Quality and Outcomes*. 2009;2:279–285. 1 May 2009 https://doi.org/10.1161/CIRCOUTCOMES.109.868299
2. Moazen-Zadeh E, Shirzad F, Karkhaneh-Yousefi M-A, Khezri R, Mohammadi M-R, Akhondzadeh S (2018) Simvastatin as adjunctive therapy to risperidone in the treatment of autism: A randomized, double-blind, placebo-controlled clinical trial. J Child Adolesc Psychopharmacol 28:82–89. doi:10.1089/cap.2017.0055 pmid:28719

Verapamil

MOA: Mast Cell Stabilization, IL-6 Inhibition

Dose : 1 mg/kg divided into two to three doses per day. Typically 10-40 mg/d

Effects: "Allergy S/S"

- **Calming, Halts rage**
- **Self-injurious behavior**
- **Agitation, Aggression,**
- **Depression/Anxiety**
- **Fear**

Side Effects: Sweating, peripheral edema, fatigue

1. Giugliano, G & Pasquali, Daniela & Notaro, A & Brongo, S & Nicoletti, G & D'andrea, Francesco & Bellastella, Antonio & Sinisi, A.A. (2003). Verapamil inhibits interleukin-6 and vascular endothelial growth factor production in primary cultures of keloid fibroblasts. British journal of plastic surgery. 56. 804-9. 10.1016/S0007-1226(03)00384-9.
2. Legrand A, Cerrina J, Bonne C, Lockhart A, Benveniste J. Inhibition of rat mast cell degranulation by verapamil. Agents Actions. 1984;14(2):153-156. doi:10.1007/BF01966635

Tocilizumab

MOA: IL-6 Inhibition

Dose: Weight: >30 Kg; 8 mg/kg
Weight < 30 kg; 10 mg/kg
Single-dose Rx. is effective for up to 2 years

Effects: Improves:
Behavior
Language

Side Effects: Upper respiratory tract infections (common cold, sinus infections)
Headache
Hypertension
Injection site reactions.

Cost: $491/dose without insurance

1. Duarte, A. "Tocilizumab, Actemra." https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Treatments/Tocilizumab-Actemra March 2019.

DHA

MOA: IL-6 Inhibition, Antioxidant

Dose: 1-2 grams EPA/DHA /d (May split the dose), EPA/DHA ratio 2/1

Effects: Improves: Hyperactivity, Stereotypy, Depression, anxiety, OCD tendencies, sleep disturbance, moodiness, nightmares, irritability, "road rage" impulsivity, adrenal fatigue, hyperactivity, self-harm, suicide ideation, being a"nattering nabob of negativity."

Side Effects: Nausea, "Fishy-taste" (Rx: Put DHA in Freezer), Bleeding, Increases blood sugar, Lowers BP

Vancassel S et al. Plasma fatty acid levels of autistic children. Prostaglandins Leukot Essent Fatty Acids. 2001;65:1–7.

Bent S et al. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. J Autism Dev Disord. 2011;41(5):545–54.

Green Tea Extract

MOA: inhibits mTor, inhibits IL-6

Dose: 9 mg/kg or fixed Dose: 338 mg. (Note: Lipton Green Tea = 70 mg EGCG/tea bag
Commercial teas contain 50-100 mg EGCG)

Effects: Improves:

Mood, socialization, memory pattern recognition, ability to follow instructions, perform ADL's, insulin resistance. Lowers cholesterol and is neuroprotective

Side Effects: Dose > 800 mg/day may result in liver damage, liver and **kidney** failure, dizziness, low blood sugar, anemia.

Tang G, Gudsnuk K, Kuo SH, et al. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron. 2014 Sep;83(5):1131-1143. DOI: 10.1016/j.neuron.2014.07.040.

Rafael de la Torre, R., de Sola, S., Hernandez, G., Farré, M., Pujol, J., Rodriguez, J., et al. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): a double-blind, randomized, placebo-controlled, phase 2 trial. Volume 15, Issue 8; P801-810, JULY 01, 2016. DOI:https://doi.org/10.1016/S1474-4422(16)30034-5

Vitamin C

MOA: Regulates Dopamine. Inadequate Vitamin C

(Dopamine increased on average 60% in ASD patients vs. Normal)

Dose:

Infants 0-12 months	**Cannot Establish**
Children 1-3 years old	**400 mg/d**
Children 4-8 years old	**650 mg/d**
Children 9-13 years old	**1200 mg/d**
Adolescents 14-18 years old	**1800 mg/d**
Adults > 19 years of age	**2000 mg/d**

Effect: Excess dopamine expresses as hyperactivity, irritability, aggression, stereotypy, and self-injury. Adequate Vitamin C needed for motivation, memory, attention, cognition.

1. Baler, R., Wise, R.A., Volkow, N.D., 16 November 2017, The dopamine motive system: implications for drug and food addiction. Nature Reviews Neuroscience volume 18, pages 741–752(2017)
1. Calne, D., Chase, T. N., & Barbeau, A. (1975). *Dopaminergic mechanisms*. Advances in Neurology, Vol. 9, New York: Raven Press.

N-Acetyl Cysteine (NAC)/Glutathione

MOA: Antioxidant, GAba/Glutamine balance

Effects: Eliminates: Stereotypy/stimming, OCD

Improves: Aggression, irritability, hyperactivity, non-compliance, sleep, speech, mood, Social Organization

Dose: 600-900 mg 1-3x/d

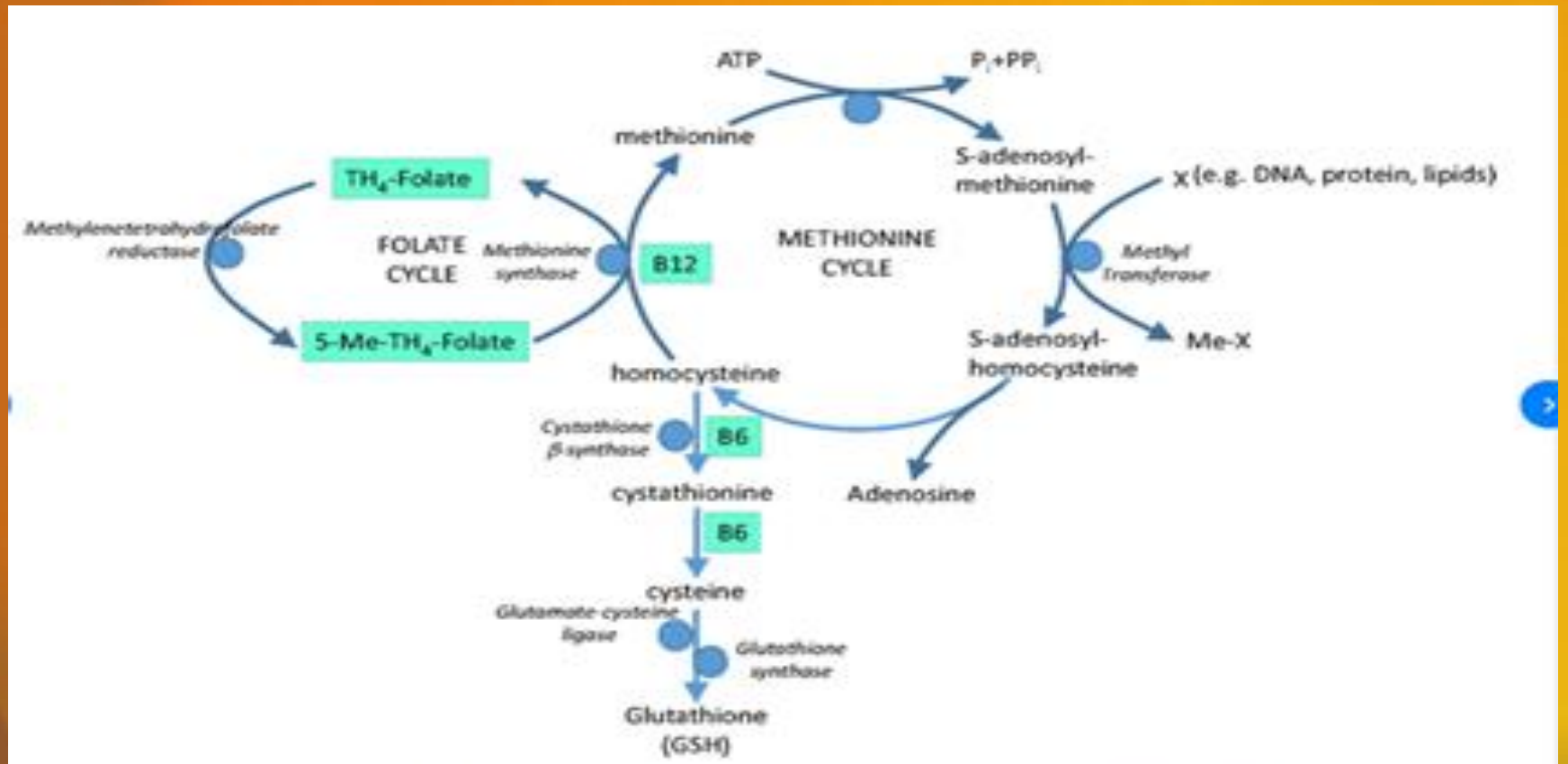
Side Effects: Nausea, vomiting, diarrhea, constipation, swelling of mouth

1. Schmaal, L., Veltman, D., Nederveen, A. et al. N-Acetylcysteine Normalizes Glutamate Levels in Cocaine-Dependent Patients: A Randomized Crossover Magnetic Resonance Spectroscopy Study. Neuropsychopharmacol 37, 2143–2152 (2012). https://doi.org/10.1038/npp.2012.66
2. Naveed, Sadiq et al. "Use of N-Acetylcysteine in Psychiatric Conditions among Children and Adolescents: A Scoping Review." Cureus vol. 9,11 e1888. 29 Nov. 2017, doi:10.7759/cureus.1888
3. Lloyd-Thomas, P., NAC for Long Term Use in Autism. https://epiphanyasd.blogspot.com/2014/08/nac-for-long-term-use-in-autism.html 22 August 2014

NAC-CLINICAL PEARLS

"NAC stops Working." **NAC outstrips Methionine Cycle 6-9 mo. after initiation**

RX: Add B6: 20-25 mg, B12, 1000 mcg, Folic acid, 800-1000 mcg



The role of vitamins B9 (folate), B6, and B12 in methionine metabolism and glutathione (GSH) synthesis.

NAC CLINICAL PEARLS-Selenium

MOA: Glutathione antioxidant activity is dependant on adequated selenium.

Selenium is diminished 18-45% in ASD patients vs. normal controls.

Inadequate selenium reserves =

1. **Brain cell membrane dysfunction.**
2. **Promoting and abetting oxidative damage in the brain.**

Selenium regulates thyroid hormone synthesis and thyroid hormone metabolism.

1. Thyroid hormones govern early brain differentiation, synaptogenesis, and myelination.

Dose: 20-200 mcg./d

Side Effects: Bad breath (garlic odor, metallic taste in the mouth, hair loss, nail loss or brittleness

1. Raymond, Laura J et al. "Potential Role of Selenoenzymes and Antioxidant Metabolism in relation to Autism Etiology and Pathology." Autism research and treatment vol. 2014 (2014): 164938. doi:10.1155/2014/164938

2. Miyuki S, Kanai H, Xu X, et al. Review of animal models for autism: implication of thyroid hormone. Congenit Anom 2006;46(1):1–9.

NAC CLINICAL PEARLS-Molybdenum

1. ***MOA:*** **Acts as a cofactor in sulfite to sulfate conversion of methionine and cysteine.**
    a. **Insufficient molybdenum results in sulfite excess.**
    b. **Sulfite excess =**
        i. **Allergic-type reactions, anemia, respiratory difficulties, skin lesions, growth retardation, palpitations, rapid heart rate, neurological problems, headaches, visual disturbances, and autistic behavior.**
    c. **Autistic patients are low in molybdenum as compared to their non-affected peers.**
        i. **Low molybdenum levels in autism =**
            i. **Communications deficiencies and disturbed general impressions.**
2. ***Dose:*** **2-35 mcg/d**
    a. **Epsom Salt Bath (**1/4 level teaspoon to 2 liters of water = 518 mg sulfate and 131 mg magnesium. [217]
3. ***Side Effects:***
    a. **Gout-like s/s, renal failure, diarrhea**

Blaurock-Busch, Eleonor et al. "Toxic Metals and Essential Elements in Hair/Severity of Symptoms among Children with Autism." Maedica vol. 7,1 (2012): 38-48.

Williams, R.J. Sulfate Deficiency as a Risk Factor for Autism. J Autism Dev Disord 50, 153–161 (2020). https://doi.org/10.1007/s10803-019-04240-5

NAC CLINICAL PEARLS-Acetaminophen

***MOA*: Depletes glutathione**

Use in children age 12 to 18 months vs. control are 8 X more likely to have ASD nearly
With regressive development use assoc. w 21 X more likely to have ASD

***Dose:* Contraindicated in ASD population**

1. Saito, Chieko, et al. "Novel mechanisms of protection against acetaminophen hepatotoxicity in mice by glutathione and N-acetylcysteine." Hepatology (Baltimore, Md.) vol. 51,1 (2010): 246-54. doi:10.1002/hep.23267

2. Heard, Kennon J. "Acetylcysteine for acetaminophen poisoning." The New England journal of medicine vol. 359,3 (2008): 285-92. doi:10.1056/NEJMct0708278

3. Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study. Autism Res. 2016;9(9):951-958. doi:10.1002/aur.1591

4. Schultz, Stephen T, and Georgianna G Gould. "Acetaminophen Use for Fever in Children Associated with Autism Spectrum Disorder." Autism-open access vol. 6,2 (2016): 170. doi:10.4172/2165-7890.1000170

Quercetin

MOA: **Mast cell stabilization, GI stabilization**

Dose**: 7-10 mg/kg/d**

Children's dose: 125 mg 2-3 times/d

Adult dose: 500 mg 1-3 times/day (Maximum 1500 mg/d)

Effects**: Anti-inflammatory, antiviral, antioxidant, anti-allergy, anti-carcinogen, neuroprotective.**

Side Effects**: Headache (oral use), numbness, tingling (oral use), shortness of breath IV use , nausea and vomiting (IV use), kidney damage (@ 1900 mg/kg/d)**

1. Maintz L[1], Novak N., Histamine and histamine intolerance. Am J Clin Nutr. 2007 May;85(5):1185-96.
2. Theoharides, T.C., Angelidou, A. Alaysantros, K. D., *et. al.* Mast cell activation and autism. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, Volume 1822, Issue 1, January 2012, Pages 34-41

Luteolin

MOA: **Mast cell stabilization, inhibits histamine, leukotrienes, interleukin-8 (IL-8), IL-6, IgE, vascular endothelial growth factor (VEGF)**

Dose: **100 mg 1-3 times/day (10 mg/kg)**

Effects:

Improves: Social interaction, neuroprotective, restores speech, reduces GI allergens.

Inhibits: Mast Cell secretions

***Side Effects*:** **1. Transient increase (1-8 weeks) of irritability. (1 report) [255]**
2. Estrogen agonist, progesterone antagonist.

Nabavi, S.F., Braidy, N., Gortzi, O., et al., Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. Brain Research Bulletin, Volume 119, Part A, October 2015, Pages 1-11. https://doi.org/10.1016/j.brainresbull.2015.09.002

Jang, Saebyeol et al. "Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1." Proceedings of the National Academy of Sciences of the United States of America vol. 105,21 (2008): 7534-9. doi:10.1073/pnas.0802865105

Rutin

MOA: **Mast Cell Stabilization, IL-6 inhibitor, improves iodide uptake**

Dose: **3 mg/kg**

Effects: **Anti-inflammatory, antioxidant, neuroprotective, protects vascular structures in the face of hyperglycemia**

Side Effects: **Headache, flushing, rashes, gastritis**

1. Colucci-D'Amato L, Cimaglia G. Ruta graveolens as a potential source of neuroactive compounds to promote and restore neural functions. J Tradit Complement Med. 2020;10(3):309-314. Published 2020 Jun 4. doi:10.1016/j.jtcme.2020.05.00

2. Vinayagam, R., Xu, B. Antidiabetic properties of dietary flavonoids: a cellular mechanism review. Nutr Metab (Lond) 12, 60 (2015). https://doi.org/10.1186/s12986-015-0057-7

3. Tsilioni, I., Taliou, A., Francis, K. et al. Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. Transl Psychiatry 5, e647 (2015). https://doi.org/10.1038/tp.2015.142

Curcumin

MOA: **IL-6 inhibitor**

Dose: **200-500 mg 1-2x/day.**

Use formulation w bioperine pepper

Effects: Anti-inflammatory, antioxidant, detox medium, antineoplastic

Restores Behaviors:

Neurologic, social, biochemical

***Side Effects*: Gastritis, nausea, vomiting, diarrhea, vertigo, skin rashes, dizziness.**

1. Suskind, David L et al. "Tolerability of curcumin in pediatric inflammatory bowel disease: a forced-dose titration study." Journal of pediatric gastroenterology and nutrition vol. 56,3 (2013): 277-9. doi:10.1097/MPG.0b013e318276977d

2. Aleks1c, A., Curcumin / Turmeric Benefits + Side Effects, Dosage. https://selfhacked.com/blog/curcumin-cures-top-15-scientifically-proven-health-benefits-with-references/, March 6, 2020.

3. Fischer CP, Hiscock NJ, Penkowa M, et al. Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. J Physiol. 2004;558(Pt 2):633-645. doi:10.1113/jphysiol.2004.066779

Vitamin D

***MOA*: 2 x as prevelant in Vitamin D deficient mothers**

***Effects:* Low Vitamin D = Brain size, altered brain shape, and enlarged ventricles**

IGF-1 and Vitamin D levels are directly related

Seizure Activity

Alexithymia-inability to identify/verbally describe feelings.

Dose: 150-300 IU in young; Up to 5000 IU in Adults

Replacement: 1000 IU *Increases 25 OH Vit D Level by 8 ng/ml*

"Normal-" 30-100 ng/ml

"Optimal" 50-80 ng/ml

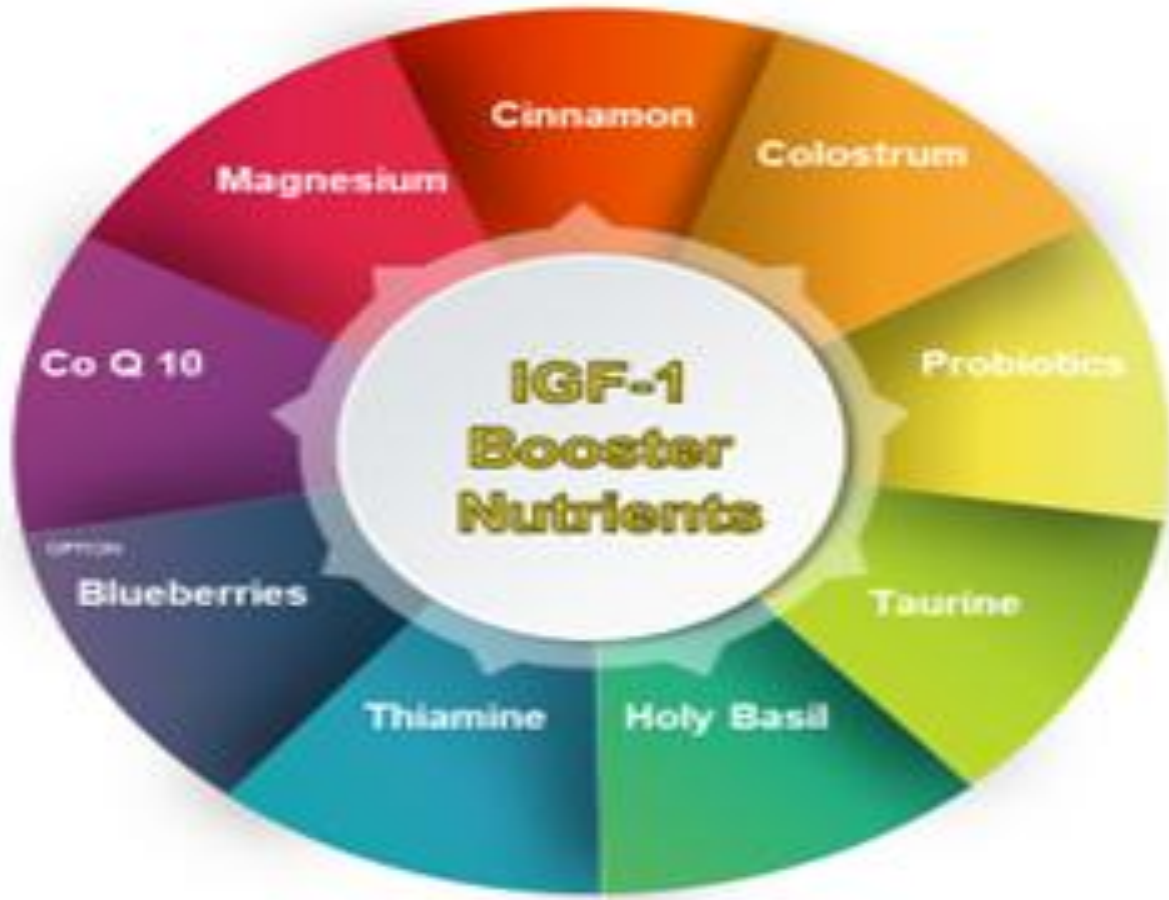
"Median" 65 ng/ml

Ameri P, et al "Interactions between vitamin D and IGF-1: From physiology to clinical practice" *Clinical Endocrinol* 2013; DOI:10.1111/cen.12268.

Feiyong Jia, Bing Wang, Ling Shan, Zhida Xu, Wouter G. Staal, Lin Du, Core Symptoms of Autism Improved After Vitamin D Supplementation. Pediatrics Jan 2015, 135 (1) e196-e198; DOI: 10.1542/peds.2014-2121

Altbäcker A, Plózer E, Darnai G, et al. Alexithymia is associated with low level of vitamin D in young, healthy adults. Nutr Neurosci. 2014;**17**(6):284–

Other IGF-1 Nutrient Boosters



Autism/Neuroinflammation

↑ IL-6

↑ GH
↓ IGF-1

IL-6 Antagonists
IGF-1 Boosters
Mast Cell
Stabilizers

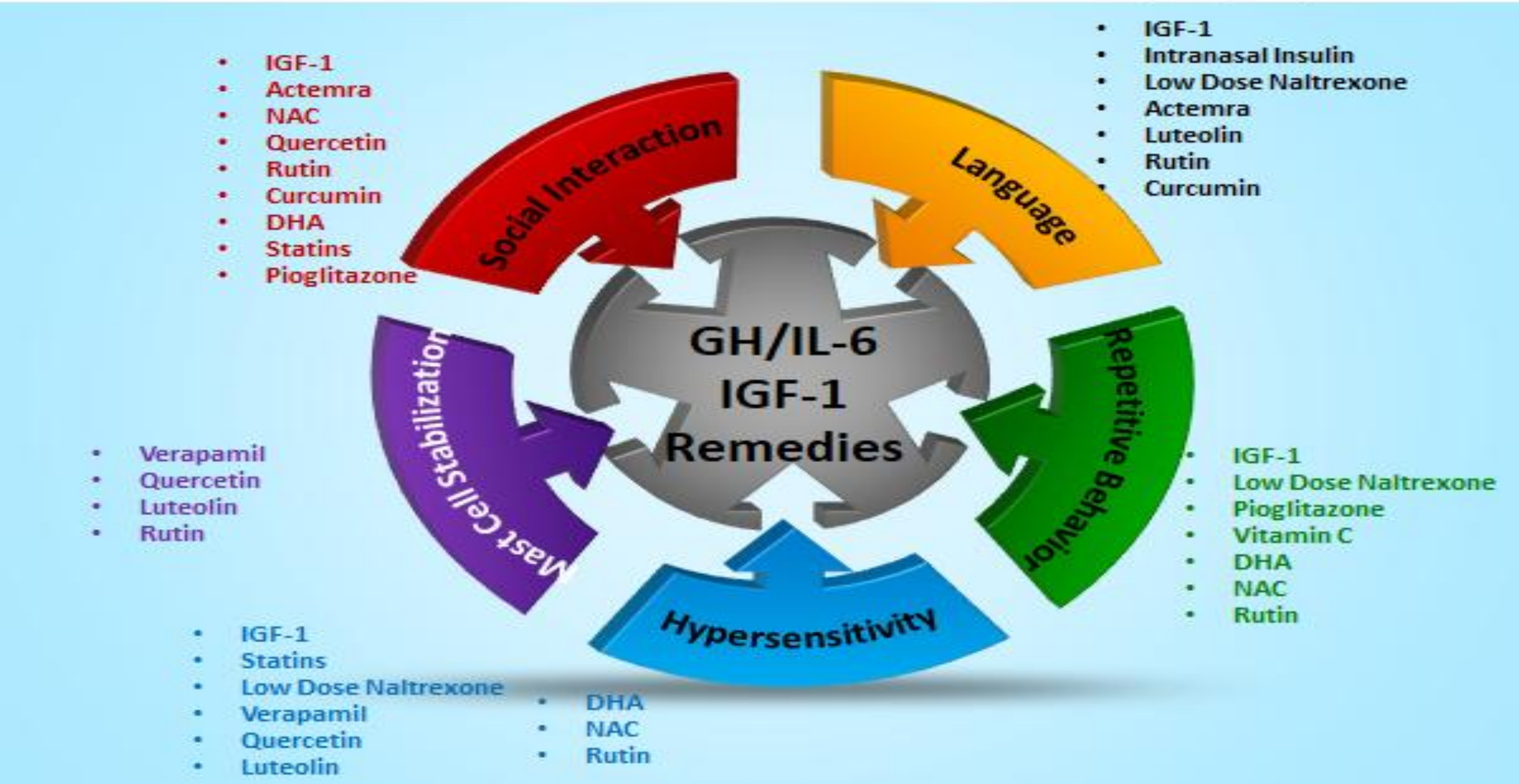
Improved:
Mood, motivation
Memory, attention
Cognition.

Diminished:
Hyperactivity
Stereotypy
Depression, anxiety
OCD tendencies

Medications:
- IGF-1
- Intranasal Insulin
- Low Dose Naltrexone
- Pioglitazone
- Statins
- Verapamil
- Tocilizumab

Supplements:
- EPA/DHA
- EGCG
- Vitamin C
- N-Acetyl Cysteine
- Quercetin
- Luteolin
- Rutin
- Zinc
- Vitamin D

GH/IL-6/IGF-1 Disconnect Remedies by Symptoms



- IGF-1
- Actemra
- NAC
- Quercetin
- Rutin
- Curcumin
- DHA
- Statins
- Pioglitazone

- IGF-1
- Intranasal Insulin
- Low Dose Naltrexone
- Actemra
- Luteolin
- Rutin
- Curcumin

- Verapamil
- Quercetin
- Luteolin
- Rutin

- IGF-1
- Low Dose Naltrexone
- Pioglitazone
- Vitamin C
- DHA
- NAC
- Rutin

- IGF-1
- Statins
- Low Dose Naltrexone
- Verapamil
- Quercetin
- Luteolin

- DHA
- NAC
- Rutin

Summary of Hormone Changes in ASD

Elevated Hormones vs. Non-ASD

- Growth Hormone
- Testosterone
- Androstenedione
- DHT
- Progesterone
- Cortisol-High Function ASD
- Pregnenolone
- Prolactin
- Insulin
- DHEA

Diminished Hormones vs Non-ASD

- Estrogen-Post natal
- IGF-1-CSF
- Thyroid
- Cortisol-Low function ASD
- Oxytocin
- Arginine Vasopressin
- Melatonin
- Vitamin D

THE ENDOCRINOLOGY OF AUTISM 2
Beyond Growth Hormone

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Nevada Osteopathic Medical Association

Las Vegas, NV. Summer 2020

Testosterone

Prepubescent-Elevated vs. “Normal” for age

Consequence –

Disruptive Behavior

Poor Impulse Control

Acne

Hirsutism

PCOS (Female)

Aggressive

Testosterone

"Extreme Male Brain" Theory

Autism Male to Female Ratio 4:1
Asperger's Syndrome M:F 10:1

Male Characteristic-Systemization (Rules/Order}
Female Characteristic-Empathy (Flexibility/Nuance)

Testosterone

Austistic Child=Oversystemization vs Empathy

EMB Children's Behavior:

- Yelling
- Crying or laughing hysterically for no apparent reason
- Disruptive or aggressive behavior including:
  - Breaking things
  - Hitting others
  - Causing self-harm him or herself.

Fun Fact-2:4 Digital Ratio
A Proxy for Prenatal Exposure to Testosterone

Length of the index finger/ Length of the ring finger.

Males: mean 0.947, standard deviation 0.029

Females: mean 0.965, standard deviation 0.026

Women DR > Male DR = ⬆ testosterone levels in amniotic fluid.

The 2D:4D ratios in autism are lower than normal children.

Manning JT, Baron-Cohen S, Wheelwright S, Sanders G (March 2001). "The 2nd to 4th digit ratio and autism". Developmental Medicine and Child Neurology. 43(3): 160–4. doi:10.1111/j.1469-8749.2001.tb00181.x. PMID 11263685.

Testosterone

Prenatal androgen levels inversely correlate with social/language skills:

- **Eye contact at 12 months**
- **Vocabulary size at 18 and 24 months**
- **Social skills at 48 months**
- **Empathy at 6—9 years.**

Fetal androgen levels are positively associated with:

- **Autistic traits**
- **Genes involved in steroidogenesis**
- **Higher rates of androgen-related conditions (PCOS) in ASD women.**

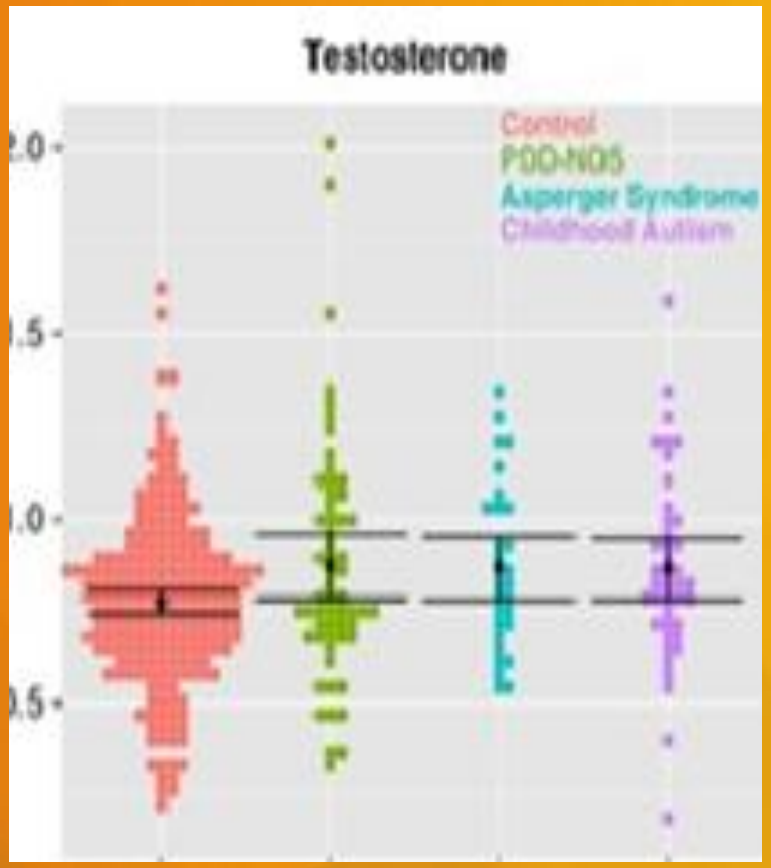
Liliana Ruta, Erin Ingudomnukul, Kevin Taylor, et al., Increased serum androstenedione in adults with autism spectrum conditions. Psychoneuroendocrinology (2011) 36, 1154—1163

Testosterone

Prepubescent testosterone levels ↑ on average, 256%.

FSH ↓ on average, 35%.

E. Ingudomnukul et al., Elevated rates of testosterone-related disorders in women with autism spectrum conditions Hormones and Behavior 51 (2007) 597–604



S Baron-Cohen, B Auyeung, B Nørgaard-Pedersen, DM Hougaard , M W Abdallah, L Melgaard, A S Cohen, B Chakrabarti, L Ruta, M V Lombardo, Elevated Fetal Steroidogenic Activity in Autism. Mol Psychiatry 2015 Mar;20(3):369-76. doi: 10.1038/mp.2014.48. Epub 2014 June 3.

Testosterone

IL-6 =

Testosterone (normal tissue)

Testosterone (damaged cells)

Chun, Jae Yeon et al. "Interleukin-6 Regulates Androgen Synthesis in Prostate Cancer Cells." Clinical Cancer Research: An Official Journal of the American Association for Cancer Research vol. 15,15 (2009): 4815-22. doi:10.1158/1078-0432.CCR-09-0640

Testosterone

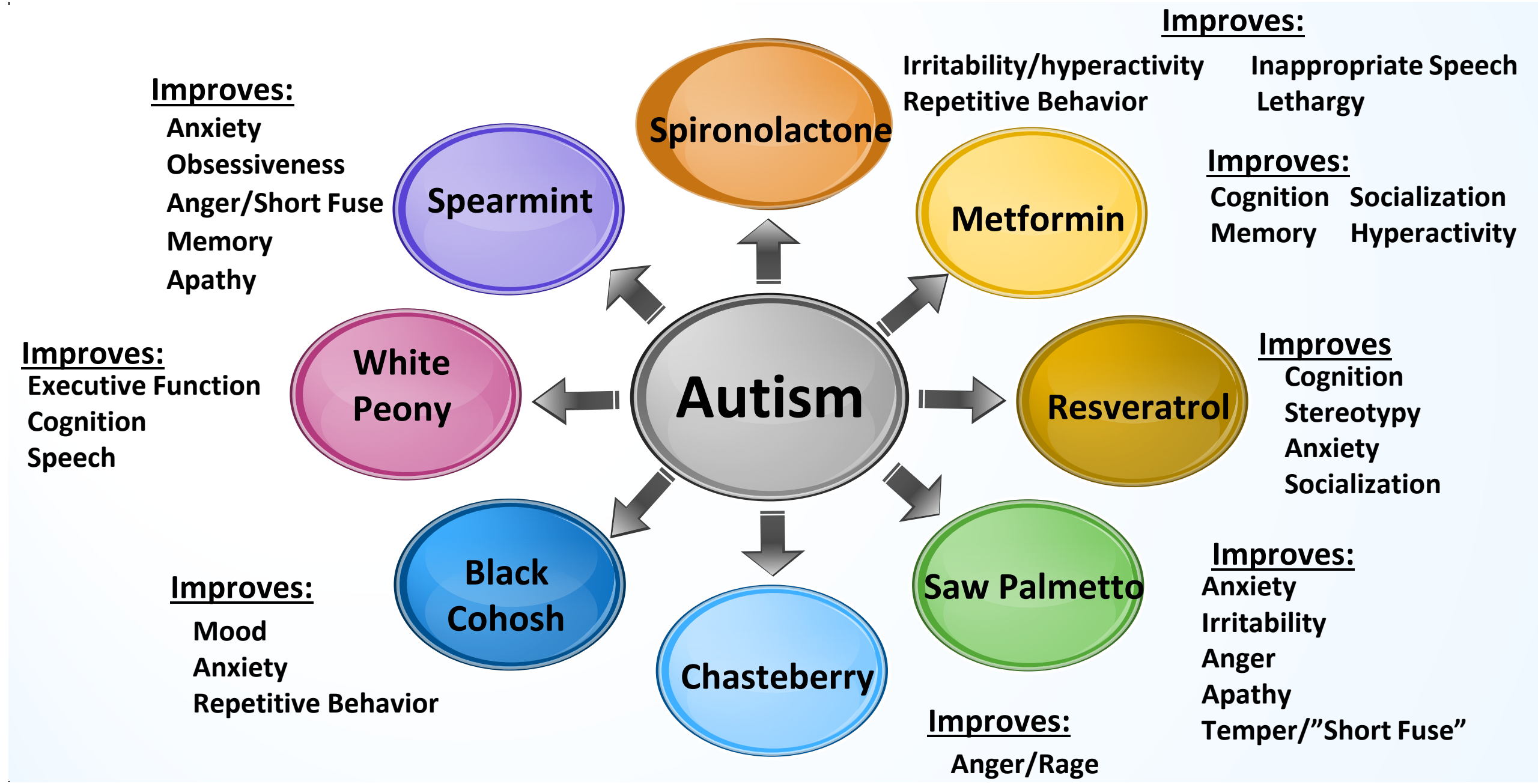
Testosterone Changes in the Autistic Spectrum

↑ Prepubescent

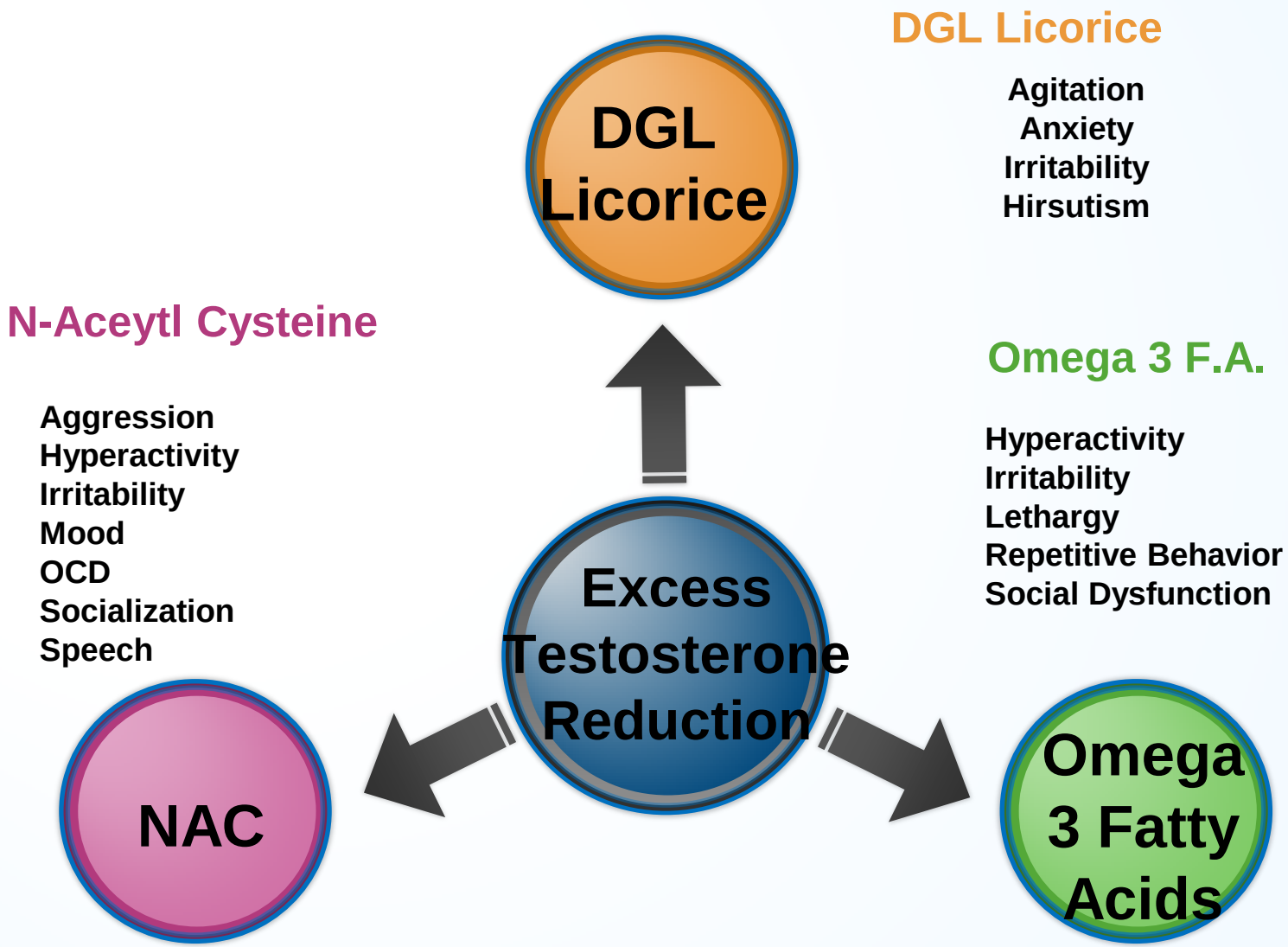
→ Post-pubescent

↓ FSH.

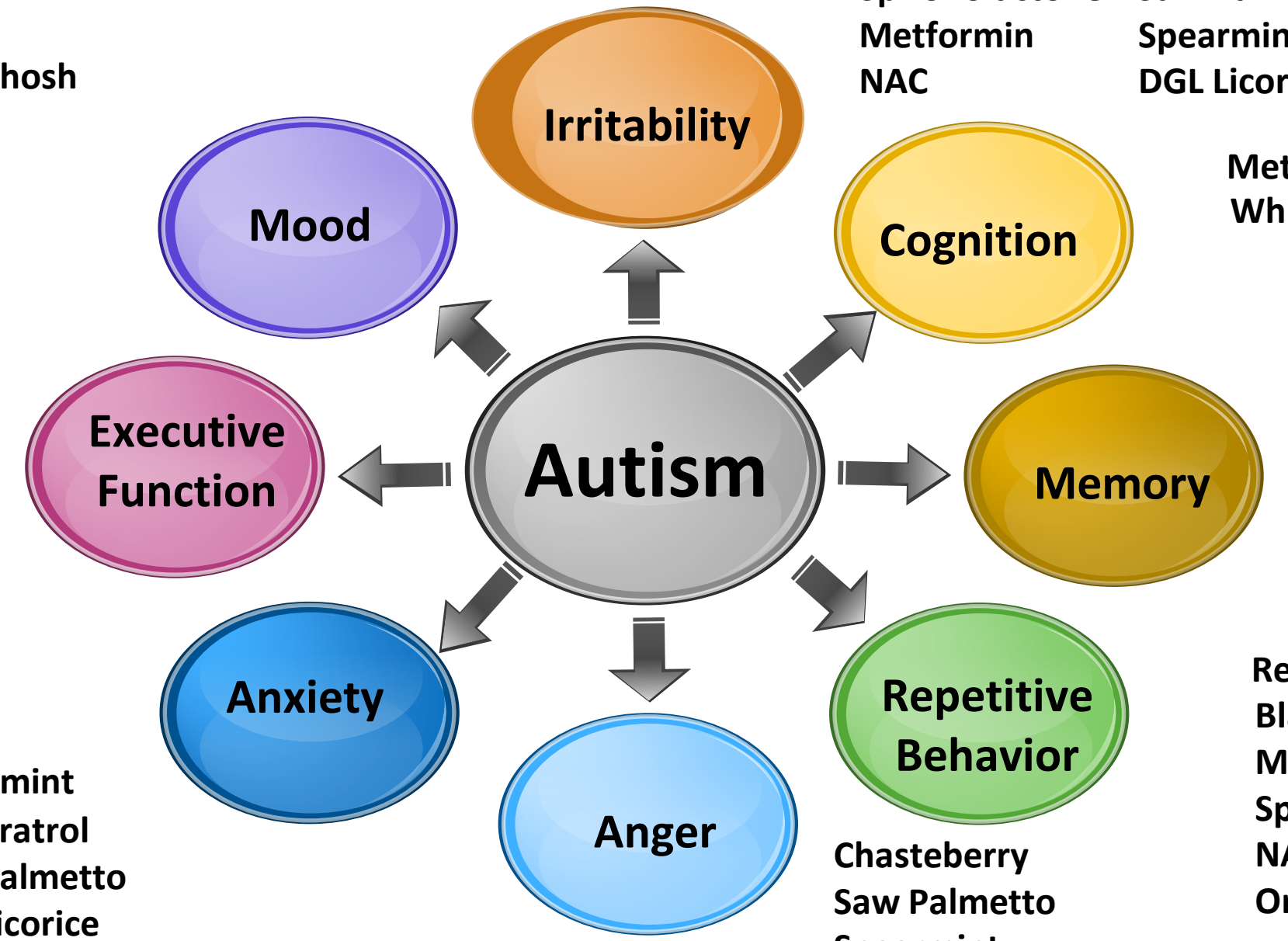
Androgen Excess Remedies



Excess Androgen Reduction-3 Bonus Supplements



Symptom Reduction w Androgen Excess Remedies



Spironolactone

MOA: Aldosterone antagonist/ Potassium sparing diuretic,
Shifts hormonal production away from testosterone and toward estrogen.
Anti-inflammatory, decreases glial activity, GI inflammation, androgenicity
Downregulates TNF-a, decreases MCP-1 and interferon-gamma

Effects: Reduces:
Irritability (79%), Lethargy (83%), Stereotypy (60%),
Hyperactivity (72%), Inappropriate speech (69%).

Dose: 2 mg/kg/d

Side Effects: Lethargy, headache, mental confusion, rash, hives
Rare is Stevens-Johnson syndrome, toxic epidermal necrolysis.

Bradstreet JJ, et al., Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders, Med Hypotheses (2006), doi:10.1016/j.mehy.2006.10.015

Berardesca E, Gabba P, Ucci G, Borroni G, Rabbiosi G. Topical spironolactone inhibits dihydrotestosterone receptors in human sebaceous glands: an autoradiographic study in subjects with acne vulgaris. Int J Tissue React 1988;10(2):115–9

Doggrell SA, Brown L. The spironolactone renaissance. Expert Opin Inv Drug 2001;10(5):943–54.

Metformin

MOA: Inhibits ovarian gluconeogenesis in the liver
Inhibits Cytochrome P450-C17-reducing LH hormone secretion

Effects: Reverses social deficits, repetitive movements, irritability, hyperactivity
Improves cognition, memory

Dose: Age: 6-9: 250 mg in am-500 mg/2d
Age 10-17:250 mg. in am-850 mg. 2/d

Side Effects: Heartburn, abdominal pain, nausea/vomiting, gas, bloating,
Diarrhea, constipation, weight loss, headache, metallic taste

Valsamakis G, Lois K, Kumar S, Mastorakos G. Metabolic and other effects of pioglitazone as an add-on therapy to metformin in the treatment of Polycystic Ovary Syndrome (PCOS) Hormones. 2013;12(3):363–78

Shegem NS, Nasir AM, Jbour AK, Batieha AM, El-Khateeb MS, Ajlouni KM. Effects of short term metformin administration on androgens in normal men. Saudi Med J. 2002;23(8):934–37.

Wang L, Cai Y and Fan X (2018) Metformin Administration During Early Postnatal Life Rescues Autistic-Like Behaviors in the BTBR T+ Itpr3tf/J Mouse Model of Autism. Front. Behav. Neurosci. 12:290. doi: 10.3389/fnbeh.2018.00290

Resveratrol

MOA: Antioxidant, anti-inflammatory, anti-aging, and phytoestrogen

Effects: Lowers testosterone levels up to 23.1%

Improves: Social impairment, stereotypy, hyperactivity, anxiety, and cognitive function. (21)

Dose: 250 mg in am, 250 mg in pm.

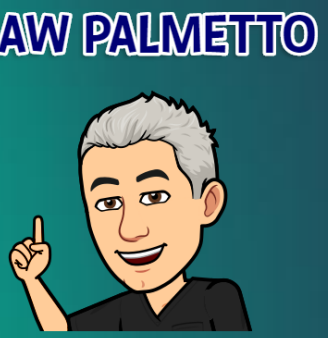
Side effects: Mild to moderate gastritis. Restlessness. Diarrhea at high dose.

1. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997;275(5297):218-220. doi:10.1126/science.275.5297.218

Banaszewska, B., Wrotyńska-Barczyńska, J., Spaczynski, R.Z., Pawelczyk, L., "Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial," http://press.endocrine.org/doi/10.1210/jc. 2016-1858.

3. Malaguarnera, Michele et al. "Resveratrol in Autism Spectrum Disorders: Behavioral and Molecular Effects." Antioxidants (Basel, Switzerland) vol. 9,3 188. 25 Feb. 2020, doi:10.3390/antiox9030188

Saw Palmetto



MOA: Reduces 5-alpha reductase.

Effect: Improves anger control, anxiety, irritability, depression, Obsessive negative thoughts, low energy, lack of motivation, "Short" fuse, quick temper.

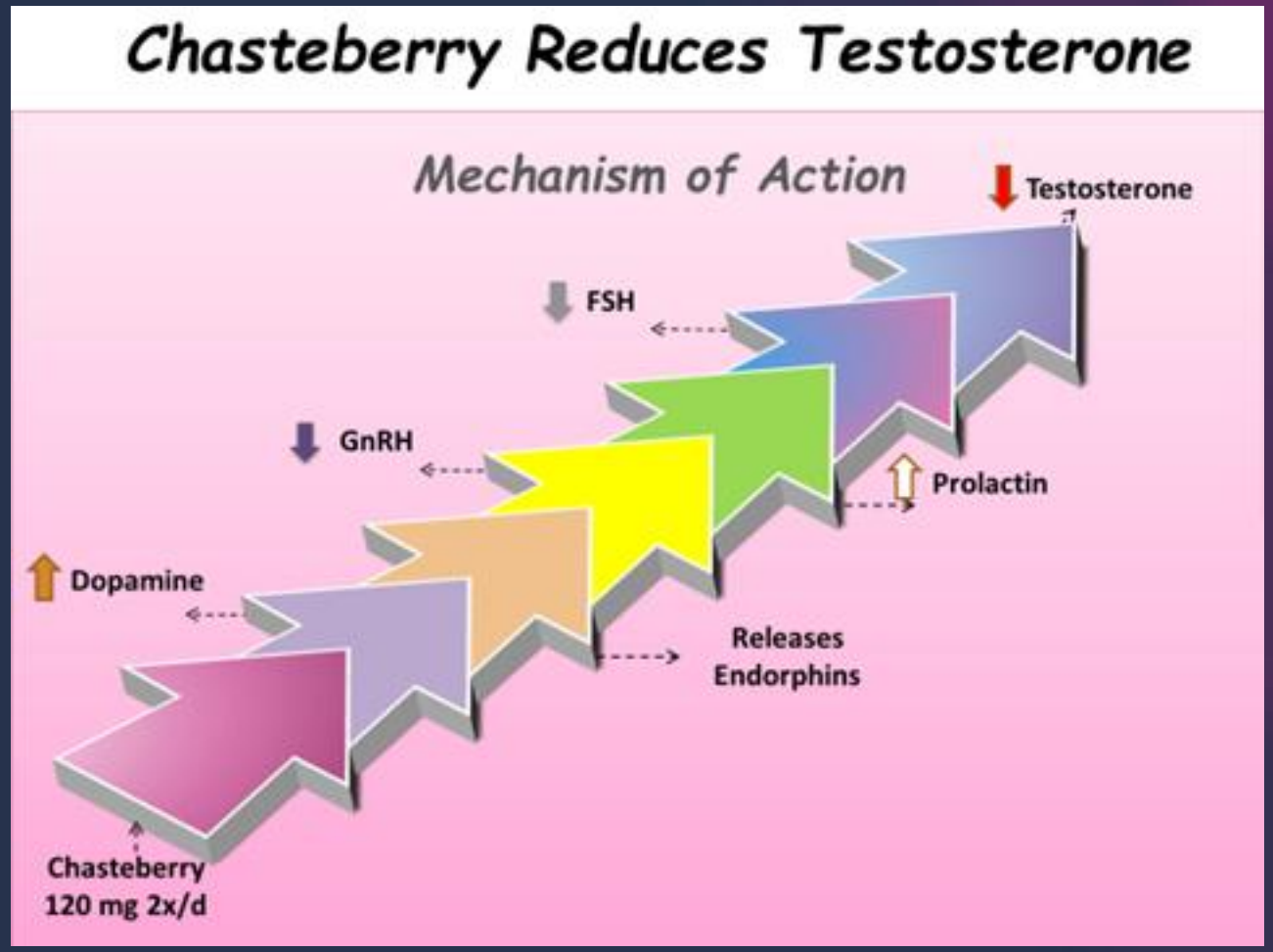
Dose: 250mg - 450 mg at bedtime

Side effects: Gastrointestinal distress, diarrhea, fatigue, headache, decreased libido, Rhinitis.

1. Ferguson, R., Our exciting discovery | Autism and PANS symptoms calm with anti-androgen herbs https://recoveringkids.com/2018/01/10/androgens/, published 10 January, 2018.
2. Yang Y, Ikezoe T, Zheng Z, Taguchi H, Koeffler HP, Zhu WG. Saw Palmetto induces growth arrest and apoptosis of androgen-dependent prostate cancer LNCaP cells via inactivation of STAT 3 and androgen receptor signaling. Int J Oncol. 2007;31(3):593-600.

Chasteberry

MOA:



Chasteberry

Effects: Decreases rage, anger

Dose: 1. **Low dose: 100-120 mg 2x/d**

High dose: 480 mg

Side Effects: Nausea, headache, GI disturbances, menstrual disorders

Acne, pruritus, erythematous rash

Black Cohosh

MOA: Mimics dopamine, norepinephrine, serotonin, and GABA.

Dopamine: suppresses GnRH leading to a decrease in LH, and ↓ testosterone.

NE: Aromatization, inhibits 5 alpha reductase

Serotonin: Antagonistic to testosterone.

GABA: regulates GRHP inhibiting T.

Effects: Acts as phytoestrogen, an anti-inflammatory, digestive aid, anxiolytic, mood stabilizer

Dose: 40 mg in am, 40 mg in pm

Side Effects: Gastritis, skin rash, nausea, vomiting, headache, dizziness, Hepatotoxicity, fluid retention, autoimmune like hepatitis, Bradycardia, hyponatremia

Wuttke W, Jarry H, Haunschild J, Stecher G, Schuh M, Seidlova-Wuttke D. The non-estrogenic alternative for the treatment of climacteric complaints: Black cohosh (Cimicifuga or Actaea racemosa). J Steroid Biochem Mol Biol. 2014 Jan;139:302-10.

2. Donnelly, P.J., Dailey, R.A., Effects of dopamine, norepinephrine and serotonin on secretion of luteinizing hormone, follicle-stimulating hormone and prolactin in ovariectomized, pituitary stalk-transected ewes. Domestic Animal Endocrinology. Volume 8, Issue 1, January 1991, Pages 87-98. https://doi.org/10.1016/0739-7240(91)90043-J

3.

White Peony

MOA: Acts on RORA (for retinoic acid-related orphan receptor-alpha) gene

RORA DECREASES TESTOSTERONE

INCREASES AROMATASE; ESTROGEN

Effects: Anti-inflammatory, Analgesic

Improvements in:

Speech

Executive function

Cognition.

Dose: 500-600 mg/d

Side Effects: Skin rash if sensitive, nausea, hormone imbalance, delayed blood clotting.

Sarachana, T., Xu, M., Wu, R.C., Hu, V. Sex Hormones in Autism: Androgens and Estrogens Differentially and Reciprocally Regulate RORA, a Novel Candidate Gene for Autism. *PLOS ONE,* February 16, 2011 https://doi.org/10.1371/journal.pone.0017116

Takeuchi T, Nishii O, Okamura T, Yaginuma T. Effect of paeoniflorin, glycyrrhizin and glycyrrhetic acid on ovarian androgen production. *Am J Chin Med*. 1991;19(1):73-78. doi:10.1142/S0192415X91000119

Spearmint

MOA: 5 alpha reductase inhibitor

Increases LH and FSH

Reduces free testosterone with no effect on total testosterone intact.

Effects: Calms the GI Tract, antioxidant, anti-bacterial, improves sleep, anger reduction

Improved: Anxiety, irritability, depression, obsessive negative thoughts,

low energy, motivation, "a short fuse," quick temper.

Dose: 150 mg/d

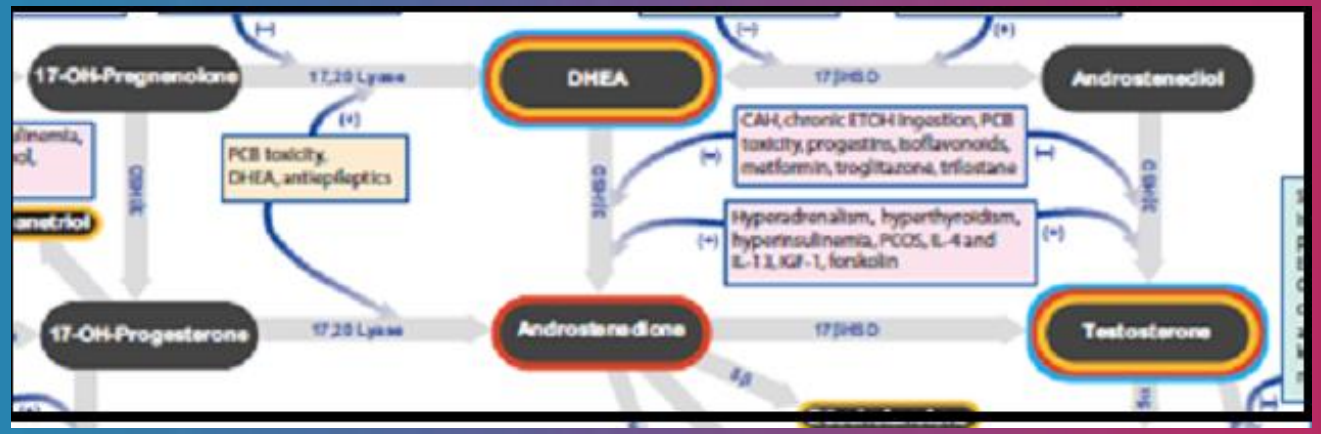
Side Effects: May exacerbate preexisting renal and hepatic disease.

1. Cirlini M, Mena P, Tassotti M, et al. Phenolic and Volatile Composition of a Dry Spearmint (Mentha spicata L.) Extract. *Molecules*. 2016;21(8):1007. Published 2016 Aug 3. doi:10.3390/molecules21081007
2. Herrlinger KA, Nieman KM, Sanoshy KD, et al. Spearmint Extract Improves Working Memory in Men and Women with Age-Associated Memory Impairment. *J Altern Complement Med*. 2018;24(1):37-47. doi:10.1089/acm.2016.0379
3. Shahbazi Y. Chemical Composition and In Vitro Antibacterial Activity of Mentha spicata Essential Oil against Common Food-

DGL Licorice

MOA: **Inhibits: (1) 17,20-lyase conversion of 17-OH progesterone to androstenedione.**

(2) 17β-OH-steroid dehydrogenase conversion of androstenedione to testosterone



Effects: **Decreases: Hirsutism, agitation, anxiety, irritability.**

DGL Licorice

Dose: 150 mg/d

Side Effects: Aldosterone-like effect-Elevated sodium, reduced potassium

Inhibits the enzyme 11-ß-hydroxysteroid dehydrogenase enzyme type 2-HBP

S/S = weakness, hypertension, cardiac arrythmias

In the exteme; congestive heart failure, renal, and hepatic failure

1. Armanini D, Bonanni G, Mattarello MJ, Fiore C, Sartorato P, Palermo M. Licorice consumption and serum testosterone in healthy man. *Exp Clin Endocrinol Diabetes*. 2003;111(6):341-343. doi:10.1055/s-2003-42724
2. Armanini D, Bonanni G, Palermo, M., Reduction of Serum Testosterone in Men by Licorice. Correspondence. *N Engl J Med 1999;* 341:1158 DOI: 10.1056/NEJM199910073411515

Omega 3 Fatty Acids

MOA : Activation of P450c17a enzymes.

- **Increased serine phosphorylation of insulin receptors.**

Effects: Decreases: Irritability, lethargy, social withdrawal, hyperactivity, stereotypy

Dose: 0.5-4 gm/d

Side Effects: Burping, "fishy" taste in mouth, bad breath, headache, heartburn, GI upset

1. Cheng, Yu-Shian et al. "Supplementation of omega 3 fatty acids may improve hyperactivity, lethargy, and stereotypy in children with autism spectrum disorders: a meta-analysis of randomized controlled trials." *Neuropsychiatric disease and treatment* vol. 13 2531-2543. 4 Oct. 2017, doi:10.2147/NDT.S147305
2. Nadjarzadeh, Azadeh et al. "The effect of omega-3 supplementation on androgen profile and menstrual status in women with polycystic ovary syndrome: A randomized clinical trial." *Iranian journal of reproductive medicine* vol. 11,8 (2013): 665-72.

N-Aceytl Cysteine/Glutathione

MOA: GABA/Glutamate Ratio

Effects: Reduces Stereotypy/stimming, OCD

Improves: Aggression, irritability, hyperactivity, non-compliance, sleep, speech, mood, social organization

Dose: <20 kg (44 pounds): 600 mg/day; > 20 kg (44 pounds), Max. 3000 mg/day

Side Effects: Nausea, vomiting, diarrhea, constipation, swelling of mouth

•

1. Oner G, Muderris II. Clinical, endocrine and metabolic effects of metformin vs N-acetyl-cysteine in women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2011;159(1):127-131. doi:10.1016/j.ejogrb.2011.07.005

https://www.healthline.com/health/glutathione-benefits

Estrogen

MOA: Estrogen Excess in Mothers

PCOS increases incidence of ASD by 59%

Deficient (Low) in Autistic Offspring

Estrogen facilitates Oxytocin

Effects: Memory Loss, depression, aggression, anxiety, psychotic S/S

Social development, establishing trust, taking social risks

Facilitation of bodily contact, partner preference

Remedy: Rx PCOS in Mother

Testosterone Control

Blood Sugar Control

“Standard” RX. of PCOS

- Cimetidine
- Ketoconazole
- Leuprolide
- Finasteride
- Progesterone
- Low GI Diet
- Estrogenic BCP
- Fiber
- HCG
- Surgery
- Ovarian wedge resection
- Laparoscopic ovarian drilling

Progesterone

Observation: Elevated Prenatally

Prenatal exposure suppresses ERβ (estrogen receptor β)

Prenatal *progestin* exposure increases the risk of infection

Gingivitis, tuberculosis, and HIV [40]

Mood Disorder, Oxidative Stress , Mitochondrial Dx.

Progesterone protects against gastrointestinal parasites. [41]

Neuroprotective

Effect: Increased:

Cortisol/Agitation, Water Retention

Insulin Resistance, Fat Storage, Appetite/Carb Cravings

Depression

Feeling “Drunk” or “Hungover”

Progesterone

Remedy:

Resveratrol-250 mg AM and PM

Reverses prenatal progestin exposure-induced ERβ suppression

Demethylates DNA and histone on the ERβ promoter in amygdala

Ling Li, Min Li, Jianping Lu, et. Al, Prenatal Progestin Exposure Is Associated With Autism Spectrum Disorders, Published online 2018 November 19. doi: 10.3389/fpsyt.2018.00611

Xie, W., Ge, X., Li, L. *et al.* Resveratrol ameliorates prenatal progestin exposure-induced autism-like behavior through ERβ activation. *Molecular Autism* 9, 43 (2018) doi:10.1186/s13229-018-0225-5

Thyroid

Thyroid hormone deficiency between weeks 3-10 of gestation, adversely affects brain development.

- **Effect:**
  - **Hyperactivity**
  - **Speech and developmental delays**
  - **Cognitive dysfunction**
  - **Hypotonia, fine motor dysfunction,**
  - **Anxiety, depression,**

GI abnormalities

Attention disorders

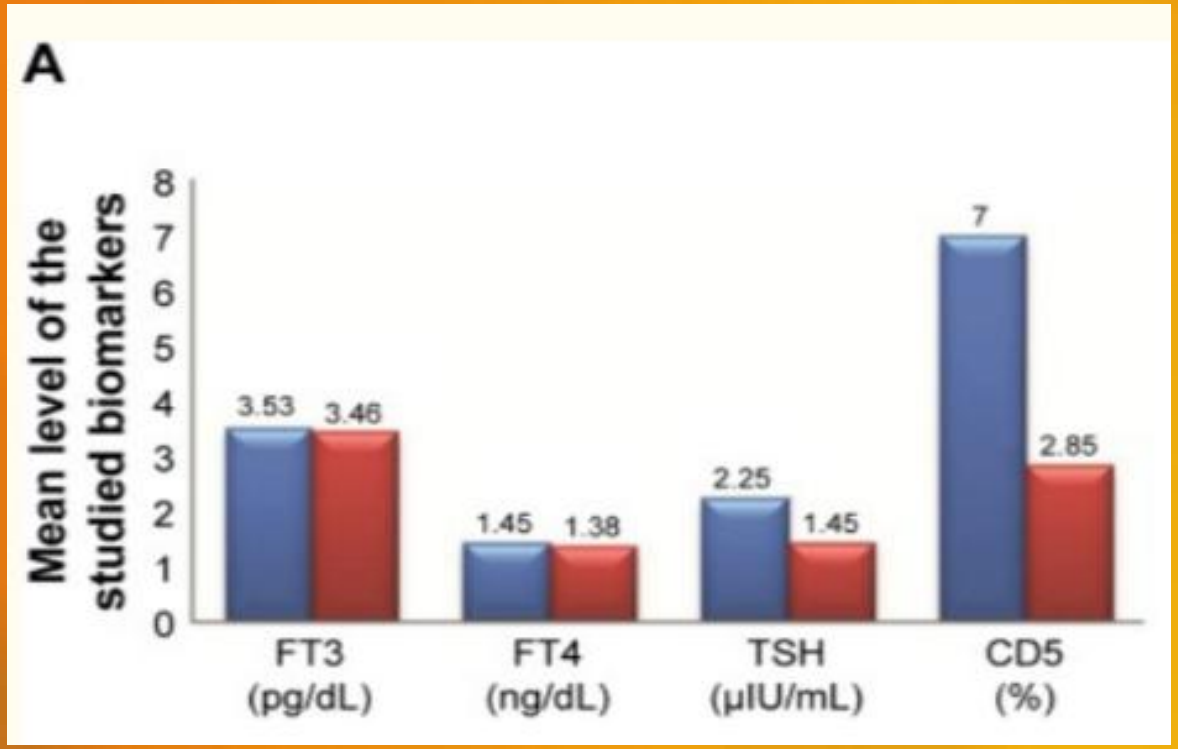
Repetitive motions

Hypersensitivity to auditory impulses

Impairment in spatial learning

Thyroid

ASD: ↑ TSH, → fT3, fT4



Thyroid

Remedies:

1. **Low "normal" fT3 and T4 benefit behaviorally from small amounts of thyroid rx.**
2. **“Normal” range Rx.=Propranolol Blocks T4 to T3 Conversion)**

   Improved language skills, cognition, memory, facial scanning, and behavior.

3. **Lithium inhibits thyroid function**

   Improves ASD behavior with frank or subclinical hyperthyroidism. [59]

4. **Ferritin**

   Protein synthesis. Typically low in ASD
   Median range 90-110. Sleep disturbance at 7 ng/ml

5. ***Note: High ferritin levels indicate hemochromatosis and coronary artery disease.***

Thyroid

" Natural Remedies:"

- Selenium-Necessary for conversion of T4 to T3
  - Present in: tuna, turkey, Brazil nuts, grass-fed beef
- Gluten-free, Sugar-free diet
- B-Complex
- Zinc
- Probiotics and Fermented Foods
  - Kefir, kombucha, some cheeses, and yogurt

Thyroid-Limit Gotrogens

3-6 times/week

Consume cooked, not raw

Collard Greens
Horseradish
Kale
Kohlrabi
Mustard Greens
Radishes
Rutabaga
Turnips

Bok Choy
Broccoli
Brussel Sprouts
Cabbage
Canola
Cauliflower
Chinese Cabbage

Soy
Pine Nuts, Peanuts
Millet
Strawberries
Pears, Peaches
Bamboo Shoots
Spinach
Sweet Potatoes

Thyroid

1. Bauer M, Goetz T, Glenn T, Whybrow PC. The thyroid-brain interaction in thyroid disorders and mood disorders. *J Neuroendocrinol*. 2008;20:1101-111

1. Khan AA. Thyroid dysfunction. Br Med J. 1970; 4:495.

1. Desoky, Tarek et al. "Biochemical assessments of thyroid profile, serum 25-hydroxycholecalciferol, and cluster of differentiation five expression levels among children with autism." *Neuropsychiatric disease and treatment* vol. 13 2397-2403. September 14. 2017, doi:10.2147/NDT.S146152

1. Siegel M, Beresford CA, Bunker M, et al. Preliminary investigation of lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder. *J Child Adolesc Psychopharmacol*. 2014;24:399-402.

1. Narayanan A, White CA, Saklayen S, et al. Effect of propranolol on functional connectivity in autism spectrum disorder – a pilot study. *Brain Imaging Behav*. 2010;4:189-197.

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In all ASD.

Ferritin

Cortisol

High Functioning ASD/Asperger's-Low CAR
Low Functioning ASD/Asperger's-High CAR

MOA: ↑ *in ASD (Low functioning ASD* ↑ *vs. high functioning)*
↑ *Cortisol =* ↑ *Estrogen =* ↑ *TBG =* ↓ *T3, T4*
↓ *Ferritin*

Effect: **Resist Change, Repetitive Motion**
Poor cognition of:
Time, Place, Self
Sugar, Salt Cravings
"Leaky Gut" Syndrome
Poor sleep
Poor learning
Depression

In all ASD.

Cortisol Remedies

- **Gluten-free, anti-inflammatory diet**
- **Adaptogenic, Calming Herbs**
  - ***Adrenal extracts (if adaptogenic herbs do not work)***
  - ***Calming herbs-L-theonine, GABA***
  - ***DGL Licorice***
  - ***Cortef (In extreme cases-low dose)***
- **Stress reduction techniques**
- **High evening cortisol: Add phosphatidylserine 300 mg**
- ***Risperidone, Aripiprazole***

In all ASD.

Cortisol Remedies

- ***Nutrients***

- Dark chocolate:
- Many fruits:
- Black and green tea:
- Probiotics and prebiotics:
- Water:

Supplements

- Zinc
- Selenium
- Copper
- Sodium
- Manganese
- DHA

In all ASD.

Cortisol References

1. Deborah J. Walder, Elaine F. Walker, and Richard J. Lewine. Cognitive Functioning, Cortisol Release, and Symptom Severity in Patients with Schizophrenia. BIOL PSYCHIATRY 2000;48:1121–1132 Departments of Psychology and Psychiatry, Emory University, Atlanta, Georgia.
2. Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): Facts and future directions. Int J Psychophysiol 2009;72(1):67–73.
3. Brosnan M, Turner-Cobb J, Munro-Naan Z, Jessop D. Absence of a normal cortisol awakening response (CAR) in adolescent males with Asperger syndrome (AS) Psychoneuroendocrinology. 2009 Aug;34(7):1095–100.
4. Metcalf, Eric, http://www.webmd.com/a-to-z-guides/features/adrenal-fatigue-is-it-real, Accessed February 16, 2015
5. Corbett BA, Schupp CW, Simon D, Ryan N, Mendoza S. Elevated cortisol during play is associated with age and social engagement in children with autism. Molecular Autism. 2010;1(13)
6. Karten YJ, Olariu A, Cameron HA. Stress in early life inhibits neurogenesis in adulthood. Trends in Neuroscience. 2005;28:171–172.
7. Corbett, Blythe A et al. "Variable cortisol circadian rhythms in children with autism and anticipatory stress." *Journal of Psychiatry & Neuroscience: JPN* vol. 33,3 (2008): 227-34.
8. Spratt EG, Nicholas JS, Brady KT, et al. Enhanced cortisol response to stress in children in autism. *J Autism Dev Disord*. 2012;42(1):75–81. doi:10.1007/s10803-011-1214-0
9. Swolin-Eide D, Ohlsson C. Effects of cortisol on the expression of interleukin-6 and interleukin-1 beta in human osteoblast-like cells. *J Endocrinol*. 1998;156(1):107-114. doi:10.1677/joe.0.1560107

Oxytocin

MOA: ***Attenuates the activity of the amygdala***

Mediates trust, cooperation, and social interactions. [118]

- Low vs. non-ASD in same age group
  - + Coorelation between low oxytocin in fathers and ASD offspring. Not w Mothers

Table 1

Plasma oxytocin levels in children with autism and controls (pg/mL)

	Children with autism (N=19)	Controls (N=44)
Mean (SD)	124.10 (90.59)	267.77 (212.37)*
Median	122.11	202.68
Range	31.77–314.35	33.21–898.76

*t=3.76, p=0.0004

Effect: **Poor socialization skills, social recognition, lack of affiliation,**

Lack of bonding, attachment, eye contact

Repetitive Behavior

Oxytocin

Dose: **Intranasal 4 IU per puff**

3 Puffs each nostril 2x/d (48 IU) total

Results: ***Improvement in:***

Social Ability, Reptitive Motion, Cognition

Largest Gain in ASD patients with lowest oxytocin levels

Side Effects: ***Fatigue, frustration, URI s/s, increased appetite, sore throat***

1. Hertoghe, T. Passion, Sex, and Long Life - the Incredible Oxytocin Adventure. ISBN 978-2-9599713-4-1, January 2010, Luxemburg, by International Medical Books/Archimedial, 4B Route d'Arlon, L-8399, Windhof, Luxembourg.
2. Weisman, O., Zagoory-Sharon, O., Feldman, R, Oxytocin administration, Salivary Testosterone, and Father–Infant Social Behavior. Progress in Neuro-Psychopharmacology and Biological Psychiatry, Volume 49, March 3, 2014, Pages 47–52
3. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal Oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry 2010;67(7):692-694.

Melatonin

MOA: ↓ ASD population

Effect: Sleep disturbances leading to mood disorders

GI abnormalities

Reduced social interaction, communication issues

Developmental regression,

Circadian rhythm abnormalities

Longer onset of sleep,

Frequent nighttime awakenings

Reduced sleep duration

Melatonin

Dose: 0.75-9 mg 2 hours before bedtime

Results: Improvements in:

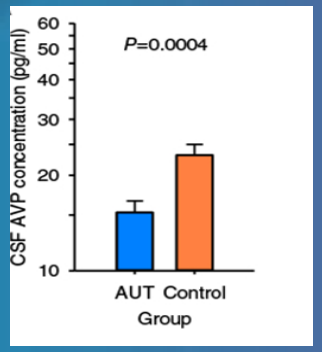
- Sleep Disturbances
- Circadian Rhythm
- Antioxidant
- Ant-inflammatory

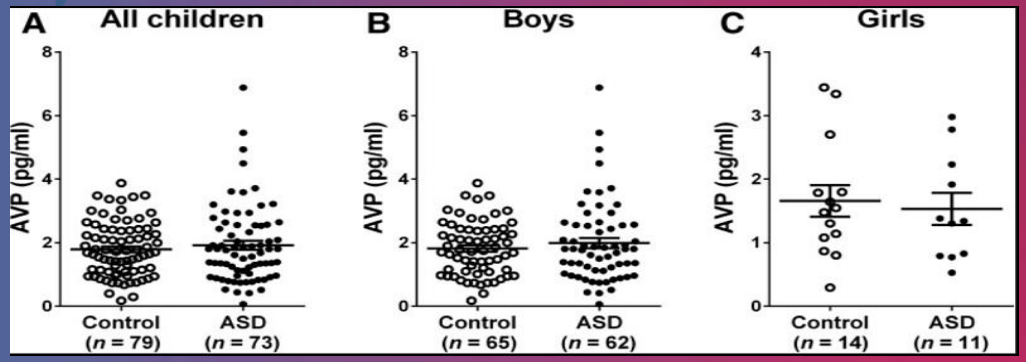
Side Effects: *AM enuresis, sleepiness*

1. Johnson KP, Malow BA Sleep in children with autism spectrum disorders. Curr Neurol Neurosci Rep 2008;8(2):155–61.
2. Srinivasan V, Lauterbach EC, Ho KY, Acuna-Castroviejo D, Zakaria R, Brzezinski A. Melatonin in antinociception: its therapeutic applications. Curr Neuropharmacol. 2012;10(2):167–178. doi: 10.2174/157015912800604489.
3. Limoges E, Mottron L, Bolduc C, et al. Atypical sleep architecture and the autism phenotype. Brain, 2005;128:1049–61.
4. Melke J, Botros HJ, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. Mol Psychiatry 2008;13(1):90–8.
5. Jonsson L, Ljunggren E, Bremer A, et al. Mutation screening of melatonin-related genes in patients with autism spectrum disorders. BMC. Med Genomics 2010;3:10

Arginine Vasopressin

- **In ASD:** ↓ CSF vs. control. ↑ Plasma Vasopressin





- **MOA:** Anti-diuretic hormone
- **Effects:**
  - Enhanced social skills
  - Diminished anxiety/depression
  - Diminished restricted/repetitive behaviors.
- **Dose:**
  - *Ages 6-9.5 12 IU 2x/d intranasal*
  - *Ages 9.6-12 16 IU 2x/d intranasal*

Arginine Vasopressin

Side Effects: ***Rare***

Bronchospasm

Urticarial

Hyponatremia

Angioedema

Rashes,

Peripheral vasoconstriction

1. *Neurology* vol. 84,4 (2018): 611-615. doi:10.1002/ana.25314
2. Hardan A. The Role of Vasopressin in the Social Deficits of Autism. National Institute of Health. [(accessed on 5, January 2020)]; Available online: https://clinicaltrials.gov/ct2/show/NCT01962870.
3. Hardan A., Parker K., Garner J. A Randomized Controlled Trial of Intranasal Vasopressin Treatment for Social Deficits in Children with Autism. 4th ed. World Summit of Pediatrics; Rome, Italy: 2018. [(accessed on January 5, 2020]. p. 35. Available online: http://www.wsp-congress.com/documenti/Abstract-Book-WSP2018-v6.pdf.

Pregnenolone

MOA: **Over age 7** ⬆ **Under age 7** ⬇

Effects: **Enhances:** ***Memory***

Excitation and inhibition of the nervous system.

Blocks: ***Cortisol, GABA-A (Anti-neuroinfammatory)***

Results: **Improves:**

- **Social/repetitive behaviors/Memory**

Dose: ***30-50 mg 2x/d Maximum dose 500 mg***

Side Effects: **Fatigue, diarrhea**

1. Sripada RK, Marx CE, King AP, *et al.* Allopregnanolone elevations following pregnenolone administration are associated with enhanced activation of emotion regulation neurocircuits. *Biol. Psychiatry* 73(11), 1045-1053 (2013).
2. Fung LK, Libove RA, Phillips J, *et al.* Brief report: An open-label study of the neurosteroid pregnenolone in adults with autism spectrum disorder. *J. Autism. Develop. Disord* 44(11), 2971-2977 (2014).
3. Kazdoba TM, Hagerman RJ, Zolkowska D, *et al.* Evaluation of the neuroactive steroid ganaxolone on social and repetitive

Insulin

Hyperglycemia
Insulin Resistance
Hyperinsulinemia
Insulin Sensitivity
Glucose Tolerance

MOA: ↑Insulin = ↑Glucose = ↑ Insulin Resistance = ↓Insulin sensitivity

Maternal diabetes leads to a 50% increased risk of delivering ASD child.

Effects: Insulin contol improves-Irritability, Sleepiness, Lethargy

***Medications Influencing Insulin*:**

SSRI's

Terbutaline

Valproic Acid- ↑ Carb. Craving = Hidden Hypo/hyperglycemia

↑ Risk of ASD 440%

High Dose Heparin

Rx. Insulin Resistance

Hyperglycemia
Insulin Resistance
Hyperinsulinemia
Insulin Sensitivity

(FBS x Fasting Insulin/405 = Insulin Resistance)

"Normal" <2.9, "Optimal" < 1.9)

Remedies

Berberine (200 mg BID)

Chromium picolinate (600-1200 micrograms)

Lipoic acid (200-600 mg)

CLA (1,000-3,000 mg)

Zinc (25-50 mg)

Taurine (1,000-3,000 mg)

Magnesium (400-800 mg)

Biotin (4-8 mg)

Vanadium (20-50 mg)

Vitamin D (Lab 50-80)

Rx. Insulin Resistance

Hyperglycemia
Insulin Resistance
Hyperinsulinemia
Insulin Sensitivity

(FBS x Fasting Insulin/405 = Insulin Resistance)

"Normal" <2.9, "Optimal" < 1.9)

Remedies

Coenzyme Q 10 (30-300 mg)

B complex (50-100 mg)

Vitamin C (1,000-3,000 mg)

Manganese (5-10 mg)

Inositol (d-chiro-inositol or d-pinitol)

N-acetylcysteine (NAC)

GABA

Lentils, chickpeas, broccoli

Fenugreek

Cinnamon

Gymnema Sylvestre

Detox

Weight Loss Surgery

•

Prolactin

MOA: ↑ *Dopamine* = ↓ *Prolactin*

Brain Damage (Autism)

↓ *Dopamine* ↑ *Prolactin*

Effects: **Edginess, agitation, aggressiveness, anxiousness, fidgetiness, panic attacks, Restlessness, and "treatment-resistant" depression.**

Results: **Gynecomastia, hirsutism, skin rashes**

Treatment-Resistant Anxiety/Depression

Etiology: **FDA approved risperidone (has high affinity for dopamine receptors results in hyperprolactinemia)**

Prolactin

Remedies:

- ✔ Bromocriptin (50 % failure rate)
- ✔ Cabergoline (17 % failure rate)
- ✔ Chasteberry-100-120 mg 2x/d
- ✔ Curcumin-250-500 mg/d
- ✔ Rhodiola 100 mg/d
- ✔ Mucuna pruriens 400 mg/d
- ✔ L-theanine 200 mg 2/d
- ✔ Vitamin B 6-(Under age 18) 30-80 mg/d
- ✔ Zinc Citrate 30-60 mg/d (Caution-raises testosterone levels!)

Vitamin D

***MOA*: 2 x as prevelant in Vitamin D deficient mothers**

***Effects:* Low Vitamin D = ⇧ Brain size, altered brain shape, and enlarged ventricles**

IGF-1 and Vitamin D levels are directly related to one another

Seizure Activity

Alexithymia-inability to identify/verbally describe feelings.

Dose: 150-300 IU in young; Up to 5000 IU in Adults

Replacement: 1000 IU *Increases 25 OH Vit D Level by 8 ng/ml*

"Normal-" 30-100 ng/ml

"Optimal" 50-80 ng/ml

"Median" 65 ng/ml

Ameri P, et al "Interactions between vitamin D and IGF-1: From physiology to clinical practice" *Clinical Endocrinol* 2013; DOI:10.1111/cen.12268.

Feiyong Jia, Bing Wang, Ling Shan, Zhida Xu, Wouter G. Staal, Lin Du, Core Symptoms of Autism Improved After Vitamin D Supplementation. Pediatrics Jan 2015, 135 (1) e196-e198; DOI: 10.1542/peds.2014-2121

Altbäcker A, Plózer E, Darnai G, et al. Alexithymia is associated with low level of vitamin D in young, healthy adults. Nutr Neurosci. 2014;**17**(6):284–288pmid:24593042

Summary of Hormone Changes in ASD

Elevated Hormones vs. Non-ASD

- Testosterone
- Androstenedione
- DHT
- Progesterone
- IGF-1 Serum
- Cortisol-High Function ASD
- Pregnenolone
- Prolactin
- Insulin
- DHEA

Diminished Hormones vs Non-ASD

- Estrogen-Post natal
- IGF-1-CSF
- Thyroid
- Cortisol-Low function ASD
- Oxytocin
- Arginine Vasopressin
- Melatonin
- Vitamin D

Takeaways from the Autistic Community

5 Pharaceutical Products Repurposed-And You Can Use Them Too!

Nevada Osteopathic Medical Association

Las Vegas, NV. Summer 2020

Verapamil

Traditional Use:

- L-Type Calcium Channel (LTCC)
- Hypertension
- CAD

Autism MOA:

- Mast cell stabilization [5]
- IL-6 inhibition

Effects:

- Improves:
  - Memory
  - Emotions, Abnormal fears, Mood swings
  - Behaviors-Limits compulsive and self-injurious behavior
  - Irritability, Hyperactivity
  - “Allergy” like S/S

Verapamil

- **Dose:**
- 1 mg/kg in 2-3 doses daily
- 10-40 mg (typically)

Side Effects:

· Blue lips and fingernails · Blurred vision · Burning, crawling, itching, numbness, prickling, "pins and needles," or tingling feelings · Chest pain · Confusion · Coughing that sometimes produces a frothy pink sputum · Dizziness, faintness, or lightheadedness when getting up from a lying or sitting position suddenly · Lightheadedness, dizziness, or fainting	· Shortness of breath · Slow or irregular heartbeat · Sore throat · Sweating · Swelling in legs and ankles · Unusual tiredness or weakness · Difficult, fast, noisy breathing, sometimes with wheezing · Increased sweating · Pale skin

Bumetanide

- ***Traditional Use:***
  - Diuretic
  - Hypertension
  -
- ***Autism MOA:***
- NKCC1/2 antagonist [1]
  - Lowers intracellular chloride
  - Stabilizes excitatory/inhibitory neurotransmitter balance
  - Attenuates GABA depolarizing action $GABA_A$ inhibitory function
- . ***Effects:***
  - Enhanced cognition
  - Accelerated acquisition of new skills.
  - IQ enhancement
  - Improved-Irritable, explosive, and social behavior [2], Language, hyperactivity

Bumetanide

Dose: **0.5-2 mg/d**

- **Use 250 mg potassium per 1 mg bumetanide**
- **2.5-3 liter/day of fluids to counteract diuresis (diuresis occurs within 1 hr. of taking pill)**
- **Add Probenecid (organic anion transporter) to slow excretion (Dose-250-500 mg/d)**
- **Onset of Action: 14 days**

Special Considerations

- **Becomes relatively ineffective in summertime**
- **Increased inflammation** due to increased inflammation = increase neuronal Cl^-
  - **i.e. Pollens, grasses**
    - **Re: Mast cell activation (accelerated degranulation)**
      - **Increased IL-6 and histamine**

Bumetanide

Remedy: **Increase dose to 2 mg**

- **Add verapamil 10-40 mg**

Lab Considerations

- **None available**
- **Negative effect of benzodiazepines warrants look at bumetanide**

Side Effects:

- **Hypokalemia**
- **Ringing in ears, Loss of hearing**
- **Unusual bleeding or bruising**
- **Severe rash with peeling skin**
- **Difficulty breathing or swallowing**
- **Hives**
- **Muscle cramps**
- **ED**

Clonazepam

- *Traditional Use:*
  - Anxietolytic
  - Panic Disorders
  - Seizures
- *Autism MOA:*
  - GABA allosteric modulator
- *Effects:*
  - Improves: [4]
    - Cognition
      - Social memory
      - Anxiety
      - Intellectual deficit

Clonazepam

- *Dose:*
- 0.03 mg/day
- Effective in 3 days
-
- *Side Effects:*
- Drowsiness
- Dizziness
- Loss of coordination
- Suicidal ideation

Low Dose Naltrexone

- ***Traditional Use:***
- Opioid antagonist
- ***Autism MOA:***
- Cytokine Inhibition
  - Shift from TH-1 (proinflammatory) to TH-2 (anti-inflammatory) cells
  - LDN reduces IL-6 and TNF-alpha production
- ***Effects:***

- Self-injurious behavior
- Communication skills
- Hyperactivity
  - Attention
- Social withdrawal
- Stereotypy
- Agitation
- Eye Contact

Low Dose Naltrexone

- ***Dose:***
  - 0.1 mg/kg
  - Increase by 0.1 mL q3-7 days up to a maximum dose of 1 mg/kg
  - Max dose 4.5 mg
  - Children > 40 kg Adult dosing

- ***Side Effects:***
  - Nausea
  - Nightmares
  - Rebound insomnia

Statins

Traditional Use:

Primary hypercholesterolemia

Combined (mixed) hyperlipidemia

Autism MOA:

Neuroprotection

Reduce neuroinflammation in cerebellum-Restoration of GABA

Effects:

Reduce irritability, hyperactivity

Improve spontaneity, affection

Statins

Dose:

Atorvastatin 10 mg/d

Simvastatin 5-10 mg/d

Side Effects:

- Liver Issues-loss of appetite, stomach pain (upper right side), tiredness,
  - itching, dark urine, clay-colored stools, jaundice
  - Headache
- Nausea, stomach pain, constipation
- Cold symptoms such as a stuffy nose, sneezing, sore throat

	Bumetanide	Clonazepam	Verapamil	LDN	Statins
Cognition	++	++			
Irritability	++		++		+++
Social Behavior	++			+++	++
Hyperactivity	+++		+	++	++
IQ	+	+		++	
Memory		++	++		
Anxiety		+++			
Mood			+++		
Allergy Like S/S Mast Cell Stabilzed			+++		
Self Injury			++	+++	
Eye contact				++	
Affection					+

	Bumetanide	Clonazepam	Verapamil	LDN	Statins
Affection					+
Allergy Like S/S Mast Cell Stabilzed			+++		
Anxiety		+++			
Cognition	++	++			
Eye contact				++	
Hyperactivity	+++		+	++	++
IQ	+	+		++	
Irritability	++		++		+++
Memory		++	++		
Mood			+++		
Self Injury			++	+++	
Social Behavior	++			+++	++

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