Medical Issues & Individuals with Autism

January 2013

Elizabeth Mumper, MD, FAAP
complexity

integration

individuality

synergy
ARI clinical treatment approach
Lecture outline Anaheim 2012

• Philosophical principles about integrating clinical signs and symptoms with pathology
• Examples of how to use laboratory assessments to integrate with history to develop logical treatment strategies
• Emphasis on tracking progress, finding complications, and fine tuning treatment plans and diet recommendations, especially how they are carried out by the families
Beyond the basics

• Good GI health
  – Excellent, whole foods diet
  – Probiotics
  – Gut healing strategies

• Immune modulation
  – Allergies
  – Immune deficiencies

• Metabolic assessment
  – Targeted nutritional supplements
Modifiable factors in immune dysfunction & chronic conditions courtesy Institute for Functional Medicine

- Diet: Pro-inflammatory vs. anti-inflammatory
  - Gluten as a highly pro-inflammatory food
- Dysbiosis
  - Probiotics, cultured foods, gut integrity
- Nutritional immunomodulation (epigenetics)
  - MB12, methylfolate, magnesium, N acetyl cysteine
- Mitochondrial dysfunction
  - Mitochondrial cocktails
- Hormonal imbalances
  - HPA axis
- Xenobiotics
  - Enhancing detoxification pathways
Treatment strategies

Use of supplements for mitochondrial support

Use of prescriptions for children who have utilized biomedical basics
Revisiting Michael
(presented in ARI lecture Oct. 2012)

- 9 yo boy with ASD
- Hx of delayed milestones in infancy/toddlerhood
  - Sat at 8.5 months
  - Did not crawl on hands and knees, but scooted on back and head until could walk
  - Walked 16 months
  - Behind peers in using scissors, crayons, etc
Floppy babies

Low muscle tone – muscle biopsies

2 months – head lags
4 months – head even
6 months – head leads
Michael

- Hx of poor feeding initially and excess drooling later
- When he was 6 yo, his doctor tested him for Ehlers-Danlos syndrome
- He started speech therapy when he was 3 yo
Michael

• Twice during infancy, he got sick with the same GI virus his older brother had, but got sicker and had to be hospitalized
  – Dehydrated, required IV fluids
Signs of dehydration

Sunken fontanelle, eyes glazed, lips dry

Poor skin turgor
What is #1 on differential diagnosis list for Michael?

• Mitochondrial disorder
  – When weakness and feeding problems present from birth – suspect classic inherited form
  – When fatigue, dysfunction in multiple organ systems or hypotonia comes later in life, suspect acquired mitochondriopathy
Mitochondria

www.mitosoc.org
Mitochondria & autism (>100 refs)

• Oliveria et al, *Dev Med Child Neurol*, 2005
  – Mitochondrial disease in 7% with ASD
  – Dysfunction in 20% with ASD
  – Indistinguishable from other groups of ASD children

  – 41 kids with ASD
  – 78% with defects of oxidative phosphorylation
  – Complex I abnormalities most common
  – 75% normal mtDNA

  – 159 kids with ASD, 94 controls
  – 38% ASD with elevated AST vs 15% controls
  – 47% ASD with increased CK
High index of suspicion for Mito Dysfunction: Clinical clues

- Weak suck and swallow
- Poor head control; floppy
- Drooling
- Hypermobile/hyperflexible joints
- Decreased activity tolerance
- Curved back when sitting
- Difficulty knowing self in space
- Gross and fine motor effects
- Eye-hand coordination poor
- Speech (expressive and receptive)

» Cohen, Mitochondrial Medicine, 2009
High index of suspicion for mitochondrial dysfunction: labs

- Isolated elevation of AST or ALT
- Low glucose
- Low BUN/creatinine
- Low B12 (MMA) and folate (RBC)
- Evidence of chronic strep or clostridia infections
- GI dysfunction
- Oxidative stress markers
  - Low reduced glutathione
  - Low cysteine
Laboratory work up of suspected mitochondrial dysfunction

• Lactate, pyruvate (serum) – tend to be elevated
• Ammonia (must be fasting, non-traumatic blood draw, no tourniquet, rapid transit to lab) - elevated
• Creatinine kinase – tends to be elevated
• Amino acids (elevated alanine:lysine ratio)
  – With mitochondrial impairment alanine builds up
  – Lysine is depleted
<table>
<thead>
<tr>
<th>Malabsorption and Dysbiosis Markers</th>
<th>Reference Range mmol/mol creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoleacetic Acid (IAA)</td>
<td>&lt;= 8.5</td>
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<tr>
<td>Phenylacetic Acid (PAA)</td>
<td>&lt;= 0.0</td>
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<tr>
<td>Dihydroxyphenylpropionic Acid (DHPPA)</td>
<td>&lt;= 1.6</td>
</tr>
<tr>
<td>Succinic Acid</td>
<td>0.5-51.0</td>
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<table>
<thead>
<tr>
<th>Fermentative Dysbiosis Markers</th>
<th>mmol/mol creatinine</th>
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</thead>
<tbody>
<tr>
<td>Citramalic Acid</td>
<td>&lt;= 9.6</td>
</tr>
<tr>
<td>Indoleacetic Acid (IAA)</td>
<td>&lt;= 8.5</td>
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<tr>
<td>Phenylacetic Acid (PAA)</td>
<td>&lt;= 0.9</td>
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<tr>
<td>Dihydroxyphenylpropionic Acid (DHPPA)</td>
<td>&lt;= 1.6</td>
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<td>Benzoic / Hippuric Acids Ratio</td>
<td>&lt;= 0.07</td>
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<td>Succinic Acid</td>
<td>0.5-51.0</td>
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<tr>
<th>Fost / Fungal Dysbiosis Markers</th>
<th>mmol/mol creatinine</th>
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<tbody>
<tr>
<td>Arabinose</td>
<td>&lt;= 63.0</td>
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<tr>
<td>d-Ketoglutaric Acid</td>
<td>&lt;= 0.0</td>
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<tr>
<td>Tartaric Acid</td>
<td>&lt;= 10.1</td>
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<tr>
<td>Citramalic Acid</td>
<td>&lt;= 9.6</td>
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<table>
<thead>
<tr>
<th>Neurotransmitter Metabolites</th>
<th>mmol/mol creatinine</th>
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</thead>
<tbody>
<tr>
<td>Vanilmandelic Acid (VMA)</td>
<td>0.9-8.6</td>
</tr>
<tr>
<td>Homovanillic Acid (HVA)</td>
<td>0.9-8.2</td>
</tr>
<tr>
<td>3-Methyl-4-OH-phenylglycol (MHPG)</td>
<td>1.0-31.4</td>
</tr>
<tr>
<td>5-OH-Indoleacetic Acid (5-HIAA)</td>
<td>1.3-13.9</td>
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<thead>
<tr>
<th>Cellular Energy and Mitochondrial Metabolites</th>
<th>mmol/mol creatinine</th>
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</thead>
<tbody>
<tr>
<td>Lactic Acid</td>
<td>3.5-37.8</td>
</tr>
<tr>
<td>Pyruvic Acid</td>
<td>1.5-22.0</td>
</tr>
</tbody>
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MP1 1416 Rev 1
Laboratory work up of suspected mitochondrial dysfunction

• Organic acids – see some elevated fatty acid metabolites
• Carnitine, free and total – tends to be low or low normal
• Maybe doctor will order skin biopsy (fibroblasts – 50% inaccurate)
• Maybe doctor will order muscle biopsy (histiopath, Electron Microscopy)

Haas, *Molecular Genetics and Metab*, 2008
<table>
<thead>
<tr>
<th>Metabolic Pathway</th>
<th>Findings</th>
<th>Intervention Options</th>
<th>Common Metabolic Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatty Acid Metabolism</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ethylmalonate</td>
<td>High</td>
<td>Carnitine, B2</td>
<td>Fatty acid oxidation</td>
</tr>
<tr>
<td><strong>Carbohydrate Metabolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyruvate</td>
<td>Very High</td>
<td>Lipoic Acid, B1, B2, B3, B5</td>
<td>Glucose oxidation, Ketosis</td>
</tr>
<tr>
<td>β-Hydroxybutyrate</td>
<td>High</td>
<td>Cr, V, Lipoic Acid, Mg, Mn</td>
<td></td>
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<tr>
<td><strong>Energy Production Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cis-Aconitate</td>
<td>High</td>
<td>Arginine, Lipoic Acid</td>
<td>Renal ammonia loading</td>
</tr>
<tr>
<td>a-Ketoglutarate</td>
<td>High</td>
<td>CoQ10, Lipoic Acid, B1, B2, B3, B5</td>
<td>Citric acid cycle, Mitochondrial ATP production</td>
</tr>
<tr>
<td>Succinate</td>
<td>Very Low</td>
<td>Isoleucine, Valine, B12</td>
<td></td>
</tr>
<tr>
<td><strong>B-Complex Vitamin Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthurenoneate</td>
<td>High</td>
<td>B6</td>
<td>Impaired Tryptophan metabolism</td>
</tr>
<tr>
<td><strong>Methylation Cofactor Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Abnormality Found</td>
<td></td>
<td></td>
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</tbody>
</table>
First do no harm: mitochondrial dysfunction - Contraindicated Medications

- Aspirin
- Acetaminophen (depletes glutathione by 21%)
- Valproic acid
- Statins (deplete CoQ10)
- Aminoglycosides, gentamicin
- MSG
- Alcohol
- Cyclosporine

Waldmeier et al, Molecular Pharmacol, 2002
Mito Treatment
Methylation Support

• Folinic Acid, 5-MeTHF
• Methyl B12 injections
• TMG (trimethyl glycine)
• Zinc picolinate
• P5P (activated form of B6)
Mito treatment
Transsulfuration support

- Glutathione
- N-acetyl cysteine
- Magnesium (consider in conjunction with P5P)
- Taurine
Mito Treatment

Antioxidants

• Essential Fatty Acids
• Minerals – zinc, selenium
• Vitamins C, D, A, E
• Melatonin
  – Increases GSH peroxidase
    • (Kotler 1999)
  – NO scavenger
    • (Reiter 2002)
Mitochondrial Dysfunction Treatment

• No long-term, randomized studies

• “Mitochondrial cocktail”
  – CoQ10
  – Carnitine
  – Riboflavin
  – Antioxidants (vitamins A, C, D, E, ALA, GSH)
  – B vitamins (B12, Folate, thiamine)
  – Creatine

» Rodríquez et al, Muscle Nerve, 2007
Mitochondrial Treatment

- Carnitine (100 mg/kg/day)
  - Required for entry of long chain fatty acids into mitochondria
  - Spares CoEnzA which gets depleted in mitochondria
  - Increases muscle strength
  - Acetyl-L-carnitine – may improve seizures
Mitochondrial Dysfunction
Treatment

• CoQ10 (10 mg/kg/day)
  – Cofactor involved in electron transfer from complex I and II to complex III
  – Functions as potent anti-oxidant
  – Rationale to bypass Complex I defects
  – Liquid/water soluble formulations better absorbed
  – Antioxidants should be given in redox couples
    • give Coq10 with vitamin C
    • 5-15 mg/kg/day with at least 10 mg/kg vitamin C
  » Wallace, Genetics, 2008
Considering getting “sick” labs when child dehydrated or ill

- Comprehensive metabolic profile – Chemistry panel
- Urinalysis – look for ketosis
- Lactate, pyruvate (lactic acid may be elevated due to acidosis from dehydration or illness)
- Ammonia
- Amino acids, plasma
  - May see elevated alanine, glycine, proline, sarcosine, tyrosine
- Organic acids, urine
  - Elevation of ethylmalonate, 3-methyl-gluconate and dicarboxylic acids
Oxidative stress: abnormal GSH and lipid peroxides
Markers of impaired methylation biochemistry
Treatment of mitochondrial dysfunction

- Methylation support
- Transulfuration support
- Antioxidants

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Looking for inflammation & oxidative stress

Going beyond what we discussed in ARI lecture Oct 2012
Consider prescription interventions in selected cases
### Neurotransmitter Metabolism Markers

<table>
<thead>
<tr>
<th>Substance</th>
<th>Status</th>
<th>Description</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanilmandeleate</td>
<td>High</td>
<td>Evaluate stress issues</td>
<td>Epi- &amp; Norepinephrine turnover stimulation</td>
</tr>
<tr>
<td>Homovanillate</td>
<td>High</td>
<td>Evaluate stress issues</td>
<td>Dopamine turnover stimulation</td>
</tr>
<tr>
<td>5-Hydroxyindoleacetate</td>
<td>Very High</td>
<td>---</td>
<td>Serotonin turnover stimulation</td>
</tr>
<tr>
<td>Kynurenic acid</td>
<td>High</td>
<td>B6</td>
<td>Receptor antagonist</td>
</tr>
<tr>
<td>Quinolinate</td>
<td>High</td>
<td>Magnesium, Immune support</td>
<td>Receptor agonist</td>
</tr>
<tr>
<td>Picolinic acid</td>
<td>High</td>
<td>Add n-3 PUFA, limit protein intake</td>
<td>Inflammatory cytokine stimulation</td>
</tr>
</tbody>
</table>

### Oxidative Damage and Antioxidant Markers

No Abnormality Found

### Detoxification Indicators

<table>
<thead>
<tr>
<th>Substance</th>
<th>Status</th>
<th>Description</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orotate</td>
<td>Very High</td>
<td>Arginine, Magnesium</td>
<td>Urea cycle overload (ammonia toxicity)</td>
</tr>
</tbody>
</table>

### Bacterial - General

<table>
<thead>
<tr>
<th>Substance</th>
<th>Status</th>
<th>Description</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoate</td>
<td>High</td>
<td>Glycine</td>
<td>Hepatic Phase II conjugation</td>
</tr>
<tr>
<td>Phenylacetate</td>
<td>High</td>
<td>Probiotics</td>
<td>Intestinal Bacterial Overgrowth</td>
</tr>
<tr>
<td>p-Hydroxyphenylacetate</td>
<td>High</td>
<td>Probiotics</td>
<td>Intestinal Bacterial Overgrowth</td>
</tr>
<tr>
<td>Tricarballylate</td>
<td>High</td>
<td>Probiotics</td>
<td>Intestinal Bacterial Overgrowth</td>
</tr>
</tbody>
</table>
Quinolinate (QUIN)

• “The last dying scream of the inflamed nervous system”
  – Richard Lord, personal communication

• QUIN is a tryptophan derivative that increases in response to IFN gamma in Central Nervous System

• Glutathione anti-oxidant system may be overwhelmed with chronic QUIN elevation
  – Chronic quinolinate elevation is **neurotoxic and oxidative**

• QUIN is a potent agonist to glutaminergic NMDA receptors
  – N methyl D aspartic acid receptors
  – May impact dopaminergic activity
    • memory, perception, mood disruption

  Journal of Neuroinflammation 2005, 2:16
Treatment strategies when QUIN elevated

• Evaluate for acute and chronic infections
• Anti-oxidants
• Immune modulation
• Anti-inflammatory support
• NMDA neuroprotective strategies
  – Magnesium
  – Low dose naltrexone?
• First do no harm
  – Avoid tryptophan supplements
Infections plus dysbiosis = inflammation

- Acute infection
- Opportunistic infection
- Pathologic response to non-pathogenic stimuli

- Gut dysbiosis
- Consider other sites
Oxidative stress: abnormal GSH and lipid peroxides

**Oxidative Stress Panel**

**Reduced Glutathione**
- Ref Range: 0 - 32 mg/dL
- Value: 29 mg/dL

**Lipid Peroxides**
- Ref Range: 0 - 10 nmol/mL
- Value: 4.7 nmol/mL

The diagram indicates values that are outside the normal range, suggesting abnormal oxidative stress markers.
Low reduced glutathione but normal lipid peroxides

This test has been developed and its performance characteristics determined by GSDL, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.
Improvement in oxidative stress markers after comprehensive nutritional rehabilitation and anti-oxidant support
Case history: ASD
years of interventions w/o language development

• 34yo mom no problems during pregnancy, 2 amalgems
• worked in school with coal fired furnace - always had coal dust on desks (2 coworkers with kids with developmental issues also
• Maternal abx for GBS. jaundice tx'd with bili lights.
• Screamed first 72 hours. Mom and baby with thrush.
• Development: Good until 9 months, after that poor eye contact, didn't point, didn't respond to name.
• At 12 to 13 months suddenly worsened. Milk introduced and had shots around that time.

• Biomedical interventions to address medical issues, years of attention to diet, using probiotics, omegas, immune enhancement, constipation measures, etc
• Pediatrician recommended SSRI – sleep and behavior problems, stims
• As soon as started namenda, she started grunting -suspected muscle pain but seemed happy, grunting turned to babbling and verbalizations have increased dramatically - now has words –
• Receptive language explosion after namenda. Now follows directions.
High quinolinic to 5HIAA ratio

<table>
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<tr>
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<th>Results</th>
<th>Remarks</th>
<th>Attach</th>
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<tbody>
<tr>
<td>32</td>
<td>Homovanillic (HVA) (dopamine)</td>
<td>≤ 14</td>
<td>4.1</td>
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<tr>
<td>33</td>
<td>Vanillylmandelic (VMA) (norepinephrine, epinephrine)</td>
<td>0.87 - 5.9</td>
<td>3.4</td>
</tr>
<tr>
<td>34</td>
<td>HVA / VMA Ratio</td>
<td>0.12 - 3.0</td>
<td>1.2</td>
</tr>
<tr>
<td>35</td>
<td>5-Hydroxyindoleacetic (5-HIAA) (serotonin)</td>
<td>≤ 7.7</td>
<td>0.57</td>
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<tr>
<td>36</td>
<td>Quinolinic</td>
<td>0.63 - 6.7</td>
<td>5.2</td>
</tr>
<tr>
<td>37</td>
<td>Kynurenic</td>
<td>≤ 4.1</td>
<td>2.1</td>
</tr>
<tr>
<td>38</td>
<td>Quinolinic / 5-HIAA Ratio</td>
<td>0.04 - 2.2</td>
<td>H 9.1</td>
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</tbody>
</table>
Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability

Michael G. Chez, MD Department of Neurology, Rosalind Franklin University/The Chicago Medical School, Chicago, Illinois, Journal Of Child Neurology

Because memantine is a moderate affinity antagonist of the N-methylD-aspartic acid (NMDA) glutamate receptor, this drug was hypothesized to potentially modulate learning, block excessive glutamate effects that can include neuroinflammatory activity, and influence neuroglial activity in autism and Pervasive Developmental Disorder Not Otherwise Specified. Open-label add-on therapy was offered to 151 patients with prior diagnoses of autism or Pervasive Developmental Disorder Not Otherwise Specified over a 21-month period. To generate a clinician-derived Clinical Global Impression Improvement score for language, behavior, and self-stimulatory behaviors, the primary author observed the subjects and questioned their caretakers within 4 to 8 weeks of the initiation of therapy. Chronic maintenance therapy with the drug was continued if there were no negative side effects. Results showed significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree. Chronic use so far appears to have no serious side effects.
A retrospective study of memantine in children and adolescents with pervasive developmental disorders
Craig A. Erickson, Psychopharmacology
Volume 191, Number 1 (2007)

• Results
  Eighteen patients (15 male, 3 female; mean age=11.4 years, range 6–19 years) received memantine (mean dosage=10.1 mg/day, range 2.5–20 mg/day) over a mean duration of 19.3 weeks (range 1.5–56 weeks). Eleven of 18 (61%) patients were judged responders to memantine based on a rating of “much improved” or “very much improved” on the CGI-I. Significant improvement was also seen on the CGI-S. Improvement was primarily seen clinically in social withdrawal and inattention. Adverse effects occurred in 7 of 18 (39%) patients and led to drug discontinuation in 4 of 18 (22%) patients. Thirteen of 18 (72%) patients received stable doses of concomitant medications during the memantine trial.

• Conclusions
  In this open-label retrospective study, memantine was effective in a number of patients with PDDs. Controlled studies are warranted to further assess the efficacy and safety of memantine in PDDs
Memantine (namenda)
Off Label for autism

• Initially developed for Alzheimer’s
• Works on NMDA receptors, shown to be a site of abnormality in a sub-set of children with autism
• Do NOT have long term studies of how well it is tolerated or potential long term side effects
• Seems well tolerated in children
Our dosing protocol

- 5 mg am x 1 week
- 5 mg am and 5 mg pm x 1 week
- 10 mg am and 5 mg pm x 1 week
- 10 mg am and 10 mg pm x 1 week

- Potential side effects: chest pain, fast heart rate, confusion, seizures, easy bruising, increased blood pressure, swelling hands or feet, rash, increased urination
- Most common in our clinical experience in children: GI – nausea, vomiting, diarrhea, constipation, loss of appetite
Modulating the nervous system

**Sympathetic:** fight or flight

**Parasympathetic:** rest & digest
ASD, several years of biomedical treatments, lots of anxiety and OCD in addition to immune dysregulation

- Problem list includes
  - ADHD
  - OCD
  - Anxiety
  - IgA Immune deficiency
  - Strep
  - Herpes
  - Chronic rhinitis
  - Fatigue
  - Candidiasis
  - Sleeps problems
  - Methionine metabolism disorder

- Mom states propranolol 'absolutely' has helped - says he handled power outage well, more interactive with relatives, less anxious, less obsessive.
- Mom chronically depressed and worn down but care of child now much more happy and feels more productive.
The noradrenergic system modulates performance on tasks dependent on semantic and associative network flexibility (NF) in individuals without neurodevelopmental diagnoses in experiments using a beta-adrenergic antagonist, propranolol. Some studies suggest drugs decreasing noradrenergic activity are beneficial in ASD. In individuals without neurodevelopmental diagnoses, propranolol is beneficial only for difficult NF-dependent problems. However, in populations with altered noradrenergic regulation, propranolol also benefits performance for simple problems. Due to decreased flexibility of access to networks in ASD, we wished to examine the effect of propranolol on NF in ASD. ASD subjects benefited from propranolol on simple anagrams, whereas control subjects were impaired by propranolol.
A decrease in interaction between brain regions is observed in individuals with autism spectrum disorder (ASD), which is believed to be related to restricted neural network access in ASD. Propranolol, a beta-adrenergic antagonist, has revealed benefit during performance of tasks involving flexibility of access to networks, a benefit also seen in ASD. Our goal was to determine the effect of propranolol on functional connectivity in ASD during a verbal decision making task as compared to nadolol, thereby accounting for the potential spurious fMRI effects due to peripheral hemodynamic effects of propranolol. Ten ASD subjects underwent fMRI scans after administration of placebo, propranolol or nadolol, while performing a phonological decision making task. Comparison of functional connectivity between pre-defined ROI-pairs revealed a significant increase with propranolol compared to nadolol, suggesting a potential imaging marker for the cognitive effects of propranolol in ASD.

Dose = 40 mg in adults 19-29 yo
Propranolol dosing protocol

• Establish BP baseline (do not start if patient has low BPs, dizziness, fainting to start with)
• Extrapolate from dosing guidelines for hypertension or migraine age 1-17 years
  – Initial: 0.5 to 2 mg/kg/day
  – Max dose = 4 mg/kg/day up to 640 mg/day divided 2 or 3 times a day
• Start low and go slow
  – Most of my patients are around 1 mg/kg/day divided morning and night
Monitoring propranolol

• Follow blood pressure (may drop) and weight (may increase)
• Have parents watch for signs of fainting, dizziness, fatigue, poor exercise tolerance, blue hands or feet, numbness or tingling
• Also may see GI side effects like nausea, vomiting, abdominal pain, trouble sleeping, unusual dreams
For most patients, basics are more successful than a succession of latest and greatest treatments.