NEW WAYS OF UNDERSTANDING AND ADDRESSING ANXIETY, OBSESSIONS, AND COMPULSIVE BEHAVIORS

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Introduction

- Anxiety, obsessions, and compulsive behaviors are common in ASD.
- Anxiety, obsessions, and compulsive behaviors are symptoms of underlying diseases and dysfunctions.
- The current explanatory model for anxiety states is lacking.
- There is a need for a more individualized, complex and holistic model.

How do children manifest anxiety?

- Avoidance of feared situations or objects (such as school refusal or avoidance)
- Temper tantrums and inflexibility
- Crying
- Freezing or standing motionless and expressionless
- Hyperactivity
- Avoiding eye contact
- Separation anxiety and clinging behaviors
- Difficulty sleeping

Disclaimer

- The vitamins, minerals, and herbs presented in this talk have not been approved by the FDA for the treatment of autism spectrum disorders or any anxiety disorder.
- The only FDA approved medications for autism spectrum disorders are risperidone and aripiprazole.

Physical signs of anxiety

- Rapid heartbeat
- Dizziness
- Shortness of breath or difficulty breathing
- Muscle tension
- GI upset
- Diarrhea
- Headache

DSM IV-TR Anxiety Disorders

- Generalized anxiety disorder
- Panic disorder
- Specific phobia
- Obsessive-compulsive disorder
- Posttraumatic stress and acute stress disorder

In Childhood:
- Separation anxiety disorder
Obsessive Compulsive Behaviors and Autism

**DSM IV Criteria for Autism:**

(C) restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least two of the following:

1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. apparently inflexible adherence to specific, nonfunctional routines or rituals
3. stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
4. persistent preoccupation with parts of objects

Post Traumatic Stress Disorder

- Criterion A: stressor
- Criterion B: intrusive recollection
- Criterion C: avoidant behaviors/numbing
- Criterion D: hyper-arousal
  - Difficulty falling or staying asleep
  - Irritability or outbursts of anger
  - Difficulty concentrating
  - Hyper-vigilance
  - Exaggerated startle response

Anxiety and PDD

- In a study of children with PDD, 43% of the children met the criteria for at least one anxiety disorder.

- Higher levels of anxiety were correlated with
  - Higher IQ
  - Functional language use
  - Higher stereotyped behaviors


A systematic review of the literature identified 31 studies involving 2,121 young people with ASD. Across studies, 39.6% of young people with ASD had at least one comorbid DSM-IV anxiety disorder, the most frequent being specific phobia (29.8%) followed by OCD (17.4%) and social anxiety disorder (16.6%).


Causes of Physiological Stress

- Emotional abuse and neglect
- Chemical toxins
- Heavy metals
- Nutritional deficiencies
- Infections
- Pain response
- High electromagnetic fields
- Excess heat

- Excess cold
- Loud noises
- Physical trauma

The Broad Autism Phenotype

Findings from an Epidemiological Survey

Autism March 2004 vol. 8 no. 1 21-37

- Depression and anxiety were significantly more prevalent in mothers of children with PDD.

- Significantly more PDD children had at least one first degree relative with anxiety and one second degree relative with OCD.
New Ways of Understanding Anxiety and Hyperactivity

Anxiety, obsessions, and compulsions are symptoms. These conditions often involve a biomedical component. Anxiety, obsessions, and compulsion behaviors involve not only imbalances in monoamine neurotransmitters but other substances in the brain, including glutamate, inflammatory markers, and brain derived neurotrophic factor. These conditions involve not only the central nervous system but also the autonomic nervous system, HPA axis, mitochondria, gastrointestinal system, and immune system.

Prevalence and Pattern of Psychoactive Medicine Use in Children with ASD

<table>
<thead>
<tr>
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<td>21.6% antidepressants</td>
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<td>10.3% OTC autism supplements</td>
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Lancto J 2004 Apr 24;363(9418):1341–5

Mechanism of SSRI Action

Antidepressants Increase Risk of Behavioural Symptoms in Children and Adolescents With Depression or Anxiety

This study examined the risk of ‘activation’ and ‘mania-hypomania’ in antidepressant trials of depressed or anxious youth. ‘Activation’ included insomnia, arousal, irritability and anger. Within drug-placebo pairs, the rates of ‘activation’ for drug versus placebo in depression and anxiety were 2.93% vs 1.08% and 11.7% vs 3.22%, respectively, with a mean onset time of 5 weeks. For mania-hypomania, the drug-placebo differences for depression and anxiety were 10.4% vs 0.45% and 1.98% vs 0%, respectively.
Pharmacologic Treatment of Repetitive Behaviors in Autism Spectrum Disorders: Evidence of Publication Bias

Meta-analysis of the published literature suggests a small but significant effect of serotonin receptor inhibitors (SRI) in the treatment of repetitive behaviors in ASD. This effect may be attributable to selective publication of trial results.

Without timely, transparent, and complete disclosure of trial results, it remains difficult to determine the efficacy of available medications.

New perspectives on the neurodevelopmental effects of SSRIs

- Limited information on neurodevelopmental consequences of early life SSRI exposure
- Assume safety from adult studies
- Early exposure studies largely focused on birth weight, pulmonary hypertension, and withdrawal syndrome.
- SSRI use in young rodents results in increased anxiety which causes a reduction in 5-HTT expression and increased anxiety, which persists into adulthood.

Black Box Warning on Use of SSRIs and Children

Side effects of SSRI medications

- Concerns on long lasting effects on brain development and behavior.
- ‘Switching’ to manic episode
- Serotonin syndrome
- Sedation
- Agitation
- Increased anxiety
- Gastrointestinal disturbances
- Discontinuation syndrome

A Systematic Review of Medical Treatments for Children With Autism Spectrum Disorders

Results: Evidence supports the benefit of risperidone and aripiprazole for challenging and repetitive behaviors in children with ASDs. Evidence also supports significant adverse effects of these medications. Insufficient strength of evidence is present to evaluate the benefits or adverse effects for any other medical treatments for ASDs, including serotonin-reuptake inhibitors and stimulant medications.
Autism Spectrum Disorders and the Autonomic Nervous System

- The activity of the sympathetic autonomic nervous system is significantly altered in children with autism. (Kostyuk, 2010)
- Results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone in children with autism (Hing, 2005)
- Children with PDD-NOS are significantly less flexible in their autonomic adaptation to attention-demanding tasks. (Althaus, 1999)
- Children with ASD exhibit a larger pupil size than age-matched controls. (Anderson, 2009)
Heart Rate Variability

Changing Heart Rhythms

Stress, Language, and Autism

- Study of 14 high functioning participants with autism and 14 matched controls.
- Participants with autism had significantly impaired category and letter fluency.
- Propranolol significantly improved category but not word fluency.
- Propranolol inhibits the sympathetic nervous system by blocking beta receptors on the nerves of the sympathetic system.
- Propranolol has been used to treat performance anxiety

Rosmarinus officinalis polyphenols activate cholinergic activities in PC12 cells through phosphorylation of ERK1/2.
Canonical acid (CA) and rosmarinic acid (RA) significantly induced cell differentiation, increased acetylcholine level, and enhanced acetylcholinesterase activity.

Activity of essential oils and individual components against acetyl- and butyrylcholinesterase.
Almost all of the essential oils showed a very high inhibitory activity (over 80%) against both enzymes, whereas the single components were not as active as the essential oils.

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Early disruptions and trauma can lead to HPA axis dysregulation

Testing

- Only the most devastating effects will be detected by serum cortisol levels as a result of the homeopathic mechanisms of the HPA axis
- Salivary cortisol measures active free cortisol and follows diurnal pattern
- Biomarker of stress in research settings
- Screening test for Cushing’s syndrome
- May be useful for more subtle forms of adrenal insufficiency, i.e. glucocorticoid replacement

Measurements at Time 1 were taken 10 min prior to a blood draw. Times 2 and 3 refer to measurements at 20 and 40 min post-draw, respectively. Subjects with autism display a higher peak response as well as a prolonged duration.

Mean salivary cortisol levels in response to a blood draw stressor in children with autism and controls

Group patterns of average cortisol response to the peer interaction in children with ASD and controls

S1 = Baseline (Preplay), S2 = Postplay, S3 = 20 minutes postplay, S4 = 40 minutes postplay

ASD is characterized by gradual decrease in salivary cortisol levels in the morning and elevated evening values.

Effects of endocrine-disrupting chemicals on adrenal function

The chemical nature of adrenal disruptors is highly varied, and there are features of the adrenal structure and function, which render it particularly vulnerable to toxic attack. However, the homeostatic mechanisms inherent in the hypothalamus-pituitary-adrenal axis mean that only the most catastrophic effects are recognized as adrenal disruption, such as in the case of etomidate. In order to detect potentially significant but milder forms of toxic disruption of adrenal function a new approach is needed; this requires the use of more sophisticated approaches than simply measuring one hormone at one time point.

Effect of chronic stress on adenals

- May be direct effect of endocrine disrupting toxins
- May be secondary effects due to stress from another system
  - Purinergic
  - Immune/infections
  - Increased excitotoxicity

Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress

Treatment with 400 mg PAS resulted in a pronounced blunting of both serum ACTH and cortisol, and salivary cortisol responses to the TSST (Trier Social Stress Test).

With regard to the psychological response, 400 mg PAS seemed to exert a specific positive effect on emotional responses to the TSST.
The Other Brain

- The GI system contains about 100 million neurons, more than either the spinal cord or the peripheral nervous system.
- 95% of the body's serotonin is in the gut.
- SSRI medications can cause nausea, diarrhea, and constipation. But, low doses of SSRIs can be used to treat nausea, diarrhea, and constipation.

Gut Brain Axis

- A bidirectional communication system between the brain and gastrointestinal systems.
- Communication occurs along immunologic, neural, and biochemical pathways.
- Gut microbiota can affect both brain development and behavior.
- Stress can also alter the composition of gut microbiota.

Stress and Friendly Bacteria

- Prenatal stress alters the bacterial colonization of the gut in infant monkeys. Stress reduced the overall numbers of bifidobacteria and lactobacilli. (Bailey, 2004)
- Exposure to stress in mice reduces the number and diversity of commensal microbial populations while leading to increased colonization by Citrobacter rodentium. (Bailey, 2010)

Stress and the Gut

- When young rats are separated from their mothers, the layer of cells that line the gut becomes weakened and more permeable.
- Dr. Mayer Emeran, professor of physiology and psychiatry at UCLA reports that 70 percent of his patients with chronic GI disorders had early childhood traumas.
- He has also found that the majority of patients with anxiety and depression have some alteration in their GI functions.

Probiotics as Psychotropics

- Emerging literature is showing the beneficial effect of oral probiotics on mood and anxiety symptoms.

  In a double blind, placebo-controlled randomized parallel group study, daily use of probiotics reduced psychological distress. (Messinaudi, 2010)

  A number of studies have shown the anti-anxiety effects of probiotic use in patients with medical conditions. (Silk, 2009; Sullivan 2009; Patel, 2008; O'Brien, 2004)
Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

- Chronic treatment with *L. rhamnosus* (JB-1) induced region-dependent alterations in GABA<sub>B1b</sub> mRNA in the brain. GABA is the major inhibitory neurotransmitter in the brain.
- *L. rhamnosus* (JB-1) reduced stress-induced corticosterone and anxiety- and depression-related behavior.
- The neurochemical and behavioral effects were not found in vagotomized mice

Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice.

- Mice infected with a noninvasive parasite, Trichuris muris, exhibited colonic inflammation and anxiety-like behavior that was associated with decreased hippocampal BDNF messenger RNA, elevated tumor necrosis factor, and an elevated kynurenine/tryptophan ratio.
- Treatment with etanercept resulted in normalized behaviors, reduced cytokine and kynurenine levels, but no change in BDNF expression.
- Treatment with *Bifidobacterium longum* normalized behavior and BDNF mRNA levels but did not affect cytokine or kynurenine levels.

Pathways involved in bidirectional communication between the gut microbiota and the brain.

- Clostrida species
- Proponic Acid
- Bartonella
- Borrelia
- Streptococcus
- PANDAS
- PITANDS
- Toxoplasma gondii

In ASD, these infections are often chronic and difficult to diagnosis with conventional tests.
**PANDAS**

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus

- Onset of obsessive compulsive behaviors and/or tics in a child following a strep throat.
- Usually has a sudden onset and episodic course
- Antibodies to strep cross react with proteins in the brain
- One study demonstrated that in mice with a propensity to autoimmune illnesses, exposure to streptococcus induced antibodies led to repetitive behaviors. (Yaddanapudi, 2010)
- Association with group A Beta-hemolytic streptococcal infection and/or elevated ASO and AntiDNAse Ab titers
- Treatment with antimicrobials and immune modulators

**Lyme Disease**

Caused by *Borrelia burgdorferi*

**Early Symptoms:**
- EM rash
- Joint pains
- Chills
- Fever
- Fatigue
- Facial palsy (paralysis)

**Late Stage or Chronic:**
- Arthritis and swelling of joints
- Cardiac abnormalities
- Central nervous system (CNS) involvement leading to cognitive (mental) disorders.

**Possible Role for Toxoplasma gondii in the Etiology of OCD**

- Toxoplasmic encephalitis (TE) is a common presentation of Toxoplasma gondii infection.
- Parasitic infection, transmitted by cats.
- In a recent study, patients with OCD (47.62%, n=42) were much more likely to have T. gondii antibodies than healthy controls (19%, n=100).

**Mitochondria and Anxiety**

- One of the major modulators of mitochondrial function is Bcl-2 proteins imbedded in the inner mitochondrial membrane.
- Mutant mice have reduced mitochondrial Bcl-2 levels, and although they have no gross behavioral abnormalities, they demonstrate a significant increase of anxiety-like behaviors.

**Mitochondrial Diseases and Psychotropic Medications**

- Patients with psychiatric symptoms and mitochondrial disorders tend to be resistant to treatment with conventional psychotropics and may deteriorate with psychotropic medications.
- Both atypical and typical antipsychotic medications have the potential to deteriorate complex I of the electron transport chain
- Valproic acid depletes carnitine and decreases β-oxidation in the liver.


**Magnesium**

- In a mouse model, plasma and brain magnesium levels were significantly correlated with several anxiety related behavioral parameters. (Laarakker, 2011)
- The NMDA/glutamate pathway has been demonstrated to be involved in the anxiolytic-like activity of magnesium. (Poleszak, 2008)
- Additionally, benzodiazepine/GABA receptors have also been shown to be involved in the anxiolytic-like effects of magnesium. (Poleszak, 2008)
Zinc Deficiency

- There is a growing body of literature supporting the association between zinc and ADHD, anorexic behaviors, depression, and anxiety.
- Zinc plays a role in serotonin and glutamate activity as well as oxidative stress.
- Zinc deficient animals exhibit anxiety like behaviors.
- Rats fed a zinc deficient diet were shown to have higher levels of corticosterone following exposure to stress.
  

Chromium and Blood Sugar Regulation

- Chromium influences neurotransmitter levels and blood sugar regulation.
- Chromium deficiency may result in symptoms of anxiety, irritability, and fatigue secondary to dips in blood sugar.
- In a study of patients with atypical depression, chromium supplementation helped with increased appetite, increased eating, carbohydrate craving, and diurnal variation of feeling. (Docherty, 2005)

Omega 6/Omega 3 Balance

- Human beings evolved on a diet ratio of omega-6 to omega-3 essential fatty acids of approximately 1:1. In Western diets, the ratio is 15/1 to 16.7. This promotes the development of numerous diseases including inflammatory and autoimmune diseases.
  
Omega-3 fatty acids have anti-inflammatory effects while omega-6 acids do not.
  
Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases.

- Vegetable oils contain high amounts of omega-6 relative to omega-3 fatty acids. The top offenders are grape seed, cottonseed, safflower, corn and sunflower oils.
  
Corn oil has an omega-6 to omega-3 ratio of 49:1

Pyridoxine

Pyridoxine (vitamin B6) is involved in the formation of neurotransmitters such as GABA, serotonin, dopamine, and norepinephrine.

In rats, pyridoxine deficiency is associated with sympathetic outflow and hypertension.

(Paulose, 1988)

Neurogenesis and Cellular Plasticity: A Final Common Pathway

- Neurogenesis the birth of new neurons. Occurs primarily in the lateral ventricles and hippocampus.
- Neurogenesis appears to be important for learning and memory formation.
- The SSRI medications increase neurogenesis
- Exercise, Rhodiola rosea, and an enriched environment also enhance neurogenesis.
Revolution in thinking in brain science

The idea of the brain as ‘plastic’ and changing replaces an earlier notion of the brain as a fixed machine.

Offers hope for a number of psychological neurological conditions in place of a ‘neurological nihilism.’

Adaptogens

- Are plant derivatives, not simple compounds such as minerals or vitamins.
- Many have been used in traditional medical systems for centuries to deal with anxiety, fatigue, or trauma.
- Are believed to normalize bodily responses to stress and to help maintain homeostasis by acting in a non-specific manner.
- May modulate the immune, antioxidant, hormonal, and nervous systems.

New Approaches To Treating Anxiety

- Approach anxiety, obsessions, and compulsions as symptoms and search for underlying disease states.
- Treatments should be individualized.
- Treat multiple systems and work on more than one level simultaneously for optimal improvement in symptoms.
- Reduce stress in the patient’s life.
- Treat the family system whenever possible.

Plant Adaptogens

- Summa (Pfaaffia paniculata)
- Golden Artic Root (Rhoiola rosea)
- Astragalus (Astragalus membranaceus)
- Tulsi or Holy Basil (Ocimum sanctum)
- Schisandra (Schisandra chinensis)
- Ashwaganda (Withania somnifera)
- Licorice (Glycyrrhiza glabra and G. uralensis)

Plant Adaptogens

- Asian ginseng (Panax ginseng)
- American ginseng (Panax quinquefolius)
- Siberian ginseng (Eleutherococcus senticosus)
- Georgian Snow Rose (Rhododendron Caucasian)
- Maca (Lepidium meyenii)
Rhodiola rosea

- In rats exposed to cold and hypoxia, Rhodiola root extract increased blood reduced glutathione and SOD activity and maintained cell membrane permeability. (Gupta, 2010)
- In depressive rats, Rhodiola rosea improved serotonin levels in the hippocampus and induced neural stem cell proliferation. (Chen, 2009)

Mitochondrial Cocktail

- CoQ10 or ubiquinone
- Alpha lipoic acid
- Riboflavin
- D-Ribose
- Niacin
- Selenium
- Thiamin
- Vitamin E
- Biotin
- Vitamin C
- Pantothenate
- L-Carnitine
- Creatine monohydrate

Nervines Herbs

- Chamomile
- Skullcap
- Hawthorne
- St. John’s wort
- Kava
- Valerian
- Lavender
- Verbena
- Lemon balm
- Passionflower
- Linden
- Oats


Vitamins, Fats, and Mineral Support for Stress and Anxiety

- Vitamin B6
- Folic acid/5MTHF
- Vitamin B12
- Pantothenic acid
- Vitamin C
- Tyrosine
- Tryptophan
- L-Theanine
- 5HTP
- Omega 3 supplements
- Lecithin
- Choline
- Phosphatidylserine
- Magnesium
- Zinc
- Chromium
- Trace Minerals
- Iodine
- Sea or Himalayan Salt

Holistic Approach to Anxiety Disorders

- Spending time in nature/grounding
- Alpha lipoic acid
- Light treatments
- Mindfulness
- Coherent breathing
- Bodywork
- Movement therapies
- Exercise
- Psychotherapy
- Spirituality/prayer
- Homeopathic treatments

It’s Not All in Your Head: Treat the Whole Body

- Assess and address:
  - Mitochondrial dysfunction
  - Possible infections and dysbiosis
  - Hormonal imbalances
  - Gastrointestinal disturbances
  - Oxidative stress
  - Detoxification and limit exposure to environmental toxins
  - Fatty acid and cholesterol imbalances
    - Omega 6/omega 3 ratio
    - Low cholesterol

- Omega 6/omega 3 ratio
- Low cholesterol
Treat the Whole Family

- Family members share similar genetics, environmental exposures, and diets.
- Consider the stress of caring for a child with chronic medical and behavioral issues as well as lack of validation by the conventional medical community of autism as a whole body based and biomedical condition.
- Consider PTSD in parents.