SCHIZOPHRENIA: A FUNCTIONAL MEDICINE APPROACH TO TREATMENT

DEVIN A. MIKLES, MD, MD(H), FACP
PEGGI S. CROSS, PHD
CHOICES FOUNDATION FOR HEALTH EDUCATION AND RESEARCH,
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LEARNING OBJECTIVES

- Define “mental illness”
- Review briefly some basics of normal brain structure and function
- Explore the epidemiologic data on the illness
- Explain the current state of things in the world of diagnosis and treatment
- Examine supplemental diagnostic procedures that can alter treatment
  - PET/ SPECT scanning
  - Genomic testing
- Discuss novel hypotheses for schizophrenia and the evidence
  - Investigate the genetic, neurological, structural, and physiological evidence
  - Describe the Fenton Reaction
  - Illustrate how dysfunctional mitochondria are related
- List and provide the evidence for the safe use of nutritional supplements
- Look at potential positive effects of some off-label use of several pharmaceuticals
- Dig into the effects of diet and food sensitivity
- Delve into the impact of toxins from the environment on the condition
- Survey potentially very helpful complementary alternatives of care-treatment
THE TERM MENTAL ILLNESS IS A MISNOMER

- The majority of humans primarily function at an emotional, not a mental level
- Some function in a mixture of emotional and mental energy
- What we mistakenly call mental illness is really a complex of a dysfunctional emotional and energetic nature [established from birth] combined with a physical brain dysfunction which arises from environmental conditions, developmental exposures, and genetic mutations, expressing as physiological aberration in metabolism and neurotransmission
- A better term is psychophysiological illness

THE BRAIN: OUR TARGET ORGAN

- The most complex and unknown organ of all
- Weighs about 3 pounds (about 2% of an average adult’s weight)
- Uses 20% of the body’s oxygen and calories (65% in newborns)
- Contains over 100 BILLION NEURONS
- Each neuron has from 1000 to over 80,000 synapses [connections with other neurons]
- Neuronal and their extensions [called “axons” ] are surrounded by myelin, which is made up of 80% fat and 20% protein
- The dry weight of the brain is 70% fat
- This fat is primarily a single omega-3 fatty acid (DHA = docosahexaenoic acid)
- Neurons transmit electrochemical signals at a velocity of about 200 mph
- The brain acts as a storage and transmission device for all of our conscious, subconscious and supraconscious thoughts, memories, behavioral and emotional states and patterns, and all actions and reactions
- These are all activated by chemicals we call neurotransmitters
- To further complicate the situation, the brain cells are not the only cells with memory or neurotransmitter function
• Pretty much all cells have some form of memory and many synthesize neurotransmitters
• Schizophrenia is associated with abnormalities of the frontal and temporal lobes, as well as the limbic system, striatum, hippocampus and hypothalamus, and lateral ventricles.

“NO PROBLEM CAN BE SOLVED FROM THE SAME LEVEL OF CONSCIOUSNESS THAT CREATED IT.” –ALBERT EINSTEIN

EPIDEMIOLOGY OF SCHIZOPHRENIA

• One percent of the population has the illness
• Each year 1 in 10 000 adults (12 to 60 years of age) develops schizophrenia
• Incidence rates have been stable across countries and cultures and over time, at least for the last 50 years
• Schizophrenic patients are not born into ecological and social disadvantage
• An early onset leads to social stagnation, a late onset to descent from a higher social status
• The main age range of risk for schizophrenia is 20 to 35 years
• In 75% of cases, diagnosis is preceded by a prodromal phase with a mean length of 5 years and a psychotic prophase of one year’s duration
• On average, women fall ill 3 to 4 years later than men and show a second peak of onset around menopause [protective effect of estrogen declines]
• Consequently, late-onset schizophrenias are more frequent and more severe in women than in men
• The gender difference in age of onset is smaller in cases with a high genetic load and greater in cases with a low genetic load
• Type of onset and core symptoms do not differ between the genders
• The most pronounced gender difference is the socially negative illness behavior of young men
EPIDEMIOLOGY OF SCHIZOPHRENIA

- The course of the illness is more benign in developing countries where treatment options are minimal.
- The incidence is 60% higher in urban than in rural areas and the urban excess is more marked in males than females.
- Higher risk if born in late winter to early spring (?infection)
- Increased maternal exposure to infectious disease at the time of fetal brain development is a possible risk factor (e.g. toxoplasmosis)
- There is definite evidence for genetic-environmental interactions including nutritional factors.
- There is definite evidence for genetically inherited risk for the illness.
- There is no single gene mutation that explains risk for the illness.
- There is reported association between a substance of abuse and schizophrenia (50%).
- Possible explanations:
  - the reported relationship is spurious
  - the substance abuse may cause schizophrenia; either de novo or by revealing a previously latent psychosis
  - schizophrenia may lead to an increased consumption of the drug; this could occur either through self-medication for unpleasant symptoms or because of the psychological and social difficulties associated with schizophrenia
  - schizophrenia and substance abuse may share common etiological factors

POSITIVE-NEGATIVE AND COGNITIVE SYMPTOMS

- Positive symptoms are psychotic behaviors: Hallucinations, delusions, thought and movement disorders.
- Negative symptoms are disruptions in normal emotions and behaviors: Anhedonia, apathy, involition, poor hygiene.
- Cognitive symptoms: loss of executive function, attention and focus issue, difficulty with working memory.
CURRENT STATE OF DIAGNOSIS

- Largely done by psychiatrists
- Based on clinical behavioral presentation and analysis
- Use of the criteria found in the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition)
- No relevant laboratory tests are in general use
- No imaging studies are in general use

CURRENT STATE OF TREATMENT

- Psychiatrists primarily act as prescribers only
- Based on clinical behavioral presentation and analysis
- Pharmaceuticals are the mainstay of treatment
- Most prescribing is based on best guess and cost considerations
- Psychosocial counseling (life skills and occupational training, some family and psychological counseling or behavioral modification)

DIAGNOSTIC PROCEDURES THAT CAN ALTER TREATMENT:
SPECT scanning (SINGLE-PHOTON EMISSION COMPUTERIZED TOMOGRAPHY)

- PET and SPECT studies that have considerably advanced understanding of the brain features of schizophrenia.
- Can significantly contributed toward the development of new and improved therapies.
- SPECT scans of the brain can differentiate between different disorders [SZ, depression, autism, ADHD TBI, BPD].
- Can be used to refine treatment and reveal toxicity patterns, or other prognostic issues related to treatment.
DIAGNOSTIC PROCEDURES THAT CAN ALTER TREATMENT:
Genomic Testing

- Genomic Testing
- Simple cheek swab
- Pharmocogenetic testing

GENETICS

- Genetics do play a role in the susceptibility to developing schizophrenia.
- A recent study showed that there were 108 different genes commonly involved in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).
- Broad categories included genes that impact the immune system, neurotransmitter receptors and function, enzyme production and function.
- The science is not evolved to the point that we know what to do to correct for most genetic weaknesses but there are a few conditions that we can test for and know how to correct or compensate

- **Genotype:**
  - What your DNA codes look like
- **Phenotype:**
  - What your genotype manifests as you
- **Genetic Polymorphisms:**
  - Where there are two or more genetic variations coding for the same thing that cannot be explained merely by recurrent mutation
P450 ENZYMES & DRUG METABOLISM

- Genes determine the activity of P450 enzymes that metabolize drugs.
- We can test for variations (polymorphisms) in most common P450 enzymes.
  - Fast metabolizers make drug active for a short time only
  - Slow metabolizers accumulate drugs which can be toxic
  - Too many drugs that use the same enzyme can also be a problem
- There is data that shows which drugs are metabolized by which enzyme (pharmacologyweekly.com).
- We can avoid drugs that are not metabolized well rather than finding out by the consequences of trial and error.
- Unfortunately the data has not been compiled (or tested) for a lot of the herbs and supplements.

MTHFR GENE
[METHYLENE TETRAHYDROFOLATE REDUCTASE]

- MTHFR C677T (Nisha et al., 2014) and the A1298C (Zhang et al., 2010) polymorphisms are associated with risk of schizophrenia.
- MTHFR is an enzyme that metabolizes folate to a usable form.
- Lack of enzyme activity causes the body to accumulate homocysteine (Agnati et al., 2006).
- Lack of MTHFR enzyme activity also causes a reduction in SAMe [S-adenosyl methionine] in the body (Liu et al., 2013).
CONSEQUENCES OF HIGH HOMOCYSTEINE LEVELS

- Increased risk for schizophrenia (not gender specific)
- Risk for more rapid acceleration of symptoms
- Increase in negative symptoms
- Risk for more rapid deterioration in health status
- Overall poorer prognosis
- Risk for other diseases, especially vascular diseases

CONSEQUENCES OF LOW SAM-E LEVELS

- Increased risk of negative symptoms
- Increased risk of depression
- Increased risk of aggressive behaviors
- Increased risk for loss in overall quality of life
MTHFR GENE

- SAMe is required for the catechol-O-methyl transferase (COMT) enzyme to metabolize dopamine.
- Abnormal dopamine levels and abnormal dopamine receptor function in the brain are thought to be one of the major components causing the symptoms of schizophrenia.
- Metabolic syndrome, commonly caused by anti-psychotics medications, is also associated with both MTHFR-677T and the COMT-158Val (Ellingrod et al., 2012).
- Thus is very important to know when selecting anti-psychotics because some are associated with higher risk for metabolic syndrome.

MTHFR CORRECTION

- Homocysteine blocks the action of the striatal D2 receptor as do most anti-psychotics (Agnati et al., 2006).
- This is very important because lowering homocysteine levels will impact the D2 receptor and this must be considered when planning the course of correction.
- N-acetyl cysteine (NAC) rapidly eliminates homocysteine and cysteine through the urine and reduces plasma homocysteine levels (Ventura et al., 1999).
- B6 (25 mg), B12 (400µg) and B9 (2 mg) lowered homocysteine levels and improved PANSS scores in a subgroup of schizophrenic patients with elevated homocysteine levels (Levine et al., 2006).
- Schizophrenic patients with MTHFR genotype (677T allele) showed improvement in negative symptoms from folate treatment even in the absence of elevated homocysteine levels or deficient folate (Hill et al., 2011).
- Different MTHFR genotypes respond differently to folic acid, increased intake of folate from the diet, or the use of the biological available form of folate, 5-MTHF (L-5-Methyltetrahydrofolate) to lower homocysteine (Zappacosta et al., 2013; Qin et al., 2012).

PANSS or the Positive and Negative Syndrome Scale is a medical scale used for measuring symptom severity of patients with schizophrenia.
COMT GENE

- The catechol-O-methyl transferase (COMT) enzyme metabolizes dopamine which is high in schizophrenia.
- The COMT158Val allele reduces the metabolism of dopamine to 40% normal (Chen et al., 2004).
- The interaction between MTHFR and COMT have been shown to influence stress reactivity in schizophrenia (Peerboms et al., 2012).
- COMT uses SAMe in the metabolism of dopamine so that supporting SAMe by insuring adequate folate metabolism is critical.
- Homocysteine levels MUST be brought down and under control first as SAMe is metabolized to homocysteine AND SAMe supplements are NOT recommended when MTHFR enzyme is low.
- Reducing dopamine production may be beneficial when the COMT activity is low.
- Lowering tyrosine intake by restricting protein intake will lower the amount of dopamine produced (Fernstrom and Fernstrom, 2007).

OXIDATIVE STRESS

- The body’s consumption of oxygen is a necessary oxidative process that creates multiple reactive oxygen species that must be dissipated.
- Oxidative stress is a condition of the imbalance whereby the body’s natural defenses to reduce toxic reactive oxygen species has been overcome.
- The brain is particularly sensitive to oxidative stress due to high oxygen consumption, low concentrations of antioxidants, high lipid concentration, high metal content and considerable formation of reactive oxygen species (Popa-Wahner et al., 2013; Ciobica et al., 2011).
- There is irrefutable evidence that oxidative damage exists in schizophrenia and considerable efforts are underway to understand the contributing mechanisms (Boskovic et al., 2011; Emiliani et al., 2014).
- Oxidative stress can be measured directly in the brain by measuring glutathione using proton magnetic resonance. Glutathione has been
found to be decreased in the cerebrospinal fluid and the prefrontal cortex of schizophrenics using this technique (Do et al., 2000).

- Persons diagnosed with schizophrenia have low glutathione levels and oxidized glutathione levels are 2-5 time higher in patients compared to controls. An analysis of diet, smoking and medication status does not explain the altered glutathione pathways in schizophrenia (Ballesteros et al., 2013).

- Peripheral blood tests include: serum thiobarbituric acid reactive substances (TBARS), malondialdehyde (an end product of lipid peroxidation), 4-HNE (an α,β-aldehyde generated by ROS production), total glutathione, reduced glutathione, nitric oxide, and the enzymes glutathione peroxidase, superoxide dismutase and catalase.

WHERE TO GET TESTS OF OXIDATIVE STRESS
GENOVA DIAGNOSTICS  WWW.GDX.NET
Oxidative Stress Analysis 2.0 (Blood and Urine)

OXIDATIVE STRESS CAUSED BY ANTI-PSYCHOTICS

- Medicated schizophrenic patients have significantly increased activity of glutathione peroxidase and malondialdehyde levels compared to controls regardless of antipsychotic medication (haloperidol, olanzapine, quetiapine and risperidone). A significant increase in superoxide dismutase was also found in haloperidol and quetiapine patients (Padurariu et al., 2010).

- Haloperidol showed significantly greater TBARS and lower antioxidant values than olanzapine and antioxidant parameters were significantly inversely correlated with TBARS in haloperidol treated patients (Singh et al., 2008).

- Antipsychotic drugs have an effect on succinate dehydrogenase (SDH) activity in the rat brain. Olanzapine inhibits SDH in the cerebellum and aripiprazole increases the enzyme in the prefrontal cortex. Clozapine inhibits the enzyme in the striatum while haloperidol inhibits it in both the striatum and hippocampus. Energy metabolism in the brain may thus be impaired by haloperidol, clozapine and olanzapine (Streck et al., 2007).
SUPPORT FOR OXIDATIVE STRESS: N ACETYL CYSTEINE

- The main anti-oxidants in the body are glutathione, vitamin C, vitamin E, carotene and the enzymes -catalase, glutathione peroxidase and superoxide dismutase (Ciobica et al., 2011).
- N-acetyl cysteine readily crosses the blood brain barrier and increases glutathione levels (Schulz et al., 2000).
- A meta-analysis performed in order to evaluate NMDA receptor modulators that may be beneficial as adjunct treatment in schizophrenia indicated that NAC has a medium effect for total and negative symptom improvements (Singh and Singh 2011).
- A randomized double-blind placebo-controlled study using 1 gram twice daily treatment with n-acetyl cysteine for 24 weeks as an adjunct treatment for medicated schizophrenic patients significantly improved PANSS total, PANSS negative, PANSS general, Clinical Global Impression (CGI) Severity and CGI-improvement scores with no significant change in the PANSS positive scores (Berk et al., 2008).

SUPPORT FOR OXIDATIVE STRESS: LIPOID ACID

- Alpha-lipoic acid increases intracellular vitamin C levels and glutathione levels (Shay et al., 2009).
- Like NAC, alpha lipoic acid rapidly crosses the blood brain barrier to increase glutathione levels (Packer et al., 1997). It has also demonstrated ability to stabilize the blood brain barrier (Schreibelt et al., 2006).
- Alpha-lipoic acid recycles vitamin C & E and is known as "the anti-oxidants of anti-oxidants."
- Human studies using lipoic acid in the treatment of schizophrenia have been limited to examining the use of ALA as an adjunct treatment to reverse weight gain caused by antipsychotic medication.
- **1200 mg daily** of ALA for 10 weeks resulted in significant weight loss (2.2 lg +/- 2.5 kg), was well tolerated and was especially effective in patients taking anti-psychotics that were strongly antihistaminic (Ratliff et al., 2013).
- A 12 week study using alpha lipoic acid (unknown dose) on patients treated with atypical anti-psychotic drugs also showed a significant weight loss and a significant reduction in cholesterol. (Kim et al., 2008).
• Cell studies have been done to examine the properties of ALA as an antioxidant. Chronic treatment by antipsychotic drugs induces up-regulation of the dopamine D2 receptors and oxidative stress. ALA reversed the increase in dopamine D2 receptor up-regulation and oxidative stress caused by the first generation antipsychotic haloperidol in SH-SY5Y neuroblastoma cells. Thus it is suggested that using ALA as an adjunct treatment with antipsychotic drugs may prevent and treat the side effect of such drugs (Delauriers et al., 2011).

• Lipoic acid has been patented for use in inhibiting or treating a central nervous system injury or disease including neurodegenerative, neurotoxicity or memory deficit by administering lipoic acid (50 to 1200 mg/day) or one of its compound in conjunction with n-acetyl cysteine, CoQ10, vitamin E, vitamin C pyruvate, melatonin, niacinamide, or glutathione before or after the injury or disease onset (Meyerhoff et al., 2006).

SUPPORT FOR OXIDATIVE STRESS: VITAMIN C&E

• Vitamin C (ascorbic acid) is an important antioxidant vitamin in the brain, protecting it from free radical-induced damage (Dakhale et al., 2005). It is present in high concentrations in brain tissues and has been shown to prevent lipid peroxidation in rat brain microsomes at physiological levels (Seregi et al., 1978).

• Vitamin C is most concentrated in the hippocampus of the human brain (Oke et al., 1987) which becomes atrophied in schizophrenic persons (Wright et al., 2000).

• Hippocampal changes are suspected of causing alterations in dopamine release in the basal ganglia (Goto and Grace, 2008) and may also account for the disturbances in memory associated with schizophrenia (Boyer et al., 2007).

• Damage to the hippocampus is also associated with hyperactivity and problems inhibiting response (Nadel et al., 1975) two symptoms associated with attention deficit hyperactive disorder (ADHD) which has been correlated with schizophrenia (Dalteg et al., 2014) and genetically linked to it (Larsson et al., 2013).

• Vitamin C (500 mg/day) decreased MDA levels and improved BPRS scores in patients on atypical medications (Dakhale et al., 2005).
Vitamin E (400 IU daily) when combined with Vitamin C and EPA/DHA restored membrane fatty acids in red blood cells to normal in atypical and typical medicated patients (Arvindakshan et al., 2002) and 800-1600 IU daily reduces tardive dyskinesia (Mahadik et al., 2006).

SUPPORT FOR OXIDATIVE STRESS: GINKGO BILOBA

- Ginkgo biloba has been found to reduce oxidative stress and improve mitochondrial function in a number of studies (Eckert 2012).
- Clinical trials have been done on patients diagnosed with schizophrenia using doses of Ginkgo biloba ranging from **120 to 360 mg/day** in conjunction with anti-psychotic medications.

<table>
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<tr>
<th>Medication/Gingko Dose</th>
<th>Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Olanzapine / 120 mg</td>
<td>Improved positive symptoms but not negative</td>
<td>Atmaca et al., 2005</td>
</tr>
<tr>
<td>Haloperidol / 360 mg</td>
<td>Improved both BPRS negative and positive symptoms</td>
<td>Zhang et al., 2006</td>
</tr>
<tr>
<td>Clozapine / 120 mg</td>
<td>Improved negative symptoms but not positive symptoms</td>
<td>Doruk et al., 2008</td>
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- Two systematic reviews and meta-analysis’ have found Ginkgo biloba to be effective as an adjunct treatment in the treatment of schizophrenia (Brondino et al., 2013 and Singh et al., 2010).
- 240 mg of Ginkgo Biloba significantly improved tardive dyskinesia movement disorder (Zhang et al., 2011; Zhang et al., 2012).
- Ginkgo biloba does not interact with the P450 enzymes (Zadoyan et al., 2012).
MITOCHONDRIUM AND SCHIZOPHRENIA

MITOCHONDRIAL DYSFUNCTION

- **Complex I and IV are dysfunctional in Schizophrenia** and the severity of the positive symptoms are highly correlated with the Complex I activity in both medicated and unmedicated patients (Ben-Shacher, 2002). NOTE: Complex I and IV are also dysfunctional in medicated Parkinson’s (Navarro & Boveris, 2010) and they naturally decline with age (Hagen et al., 2002).

- Dopamine reversibly inhibits Complex I activity in disrupted mitochondria (Ben-Shacher et al., 2002; Brenner-Lavie., 2009).

- Complex IV is reduced in the frontal cortex, temporal cortex and caudate nucleus of the schizophrenic brain (Ben-Shachar, 2002).

- Reduced ATP levels have been measured (using 31P-MRS) in the frontal lobe and in the left temporal lobe of schizophrenic patients (Fujimoto et al. 1992; Volz et al. 2000).

- “…..a shortage in ATP, and thereby the dysfunction of the heavily energy dependent Na+/K+- and Ca2+-ATPases, can cause influx of Na+ and Ca(2+) ions, and as a consequence, impaired plasma membrane potential. An increase in intracellular Ca(2+) can lead to a variety of deteriorating processes that have been implicated in schizophrenia.” (Ben-Shacher, 2002)

- Among them:
  - defective neurotransmitter transmission, including that of dopamine, glutamate and GABA (Carlsson et al. 1999)
  - apoptosis = cell suicide (Jarskog et al. 2000)
  - nitric oxide and reactive oxygen species production (Doyle and Slater 1995; Mahadik and Scheffer 1996; Bernstein et al. 1998)
  - …..all leading either to cell death or playing a role in synaptic plasticity, i.e. structural (brain) remodeling and long-term functional changes (Smythies 1999; Mattson 2000).

- Postmortem studies of schizophrenic brains indicated decreased density of the mitochondria in both the caudate and putamen compared to controls (Somerville et al., 2012).

**THEREFORE THERE SHOULD BE A PRIORITY TO MAINTAIN THE FUNCTION THE MITOCHONDRIA IN ORDER TO PRODUCE ATP.**
MITOCHONDRIAL SUPPORT

- Carnitine is essential for the transport of long-chain fatty acids across the mitochondrial membrane thus supplying nutrients for energy production.
- Carnitine supplementation must have lipoic acid as well or it causes elevated MDA levels (Hagen et al., 2002).
- This combination was shown to reverse mitochondrial aging in rats (Long et al., 2009) and decrease the decline of intact mitochondria in the hippocampus of rats (Zaitone et al., 2012).
- The Complex I Solution
  - **Succinic acid** goes around Complex I by supporting Complex II of the electron chain (Nowak et al., 2008).
  - **Niacinamide (Vit B3)** provides NAD+ for Complex I and partially restored respiration in a rat model of stroke (Klaidman et al., 2003).
  - **Riboflavin (Vit B2)** used to treat Complex I deficiency increases exercise capacity and tolerance, muscle weakness and increased Complex I activity (Marriage et al., 2003).
  - **Coenzyme Q10** supports the transport of electrons between the complexes of the mitochondrial electron chain (Marriage et al., 2003) and plays a role in the mitochondria life cycle (Shults and Hass, 2005).
  - Inhibitors of the mitochondrial electron transport chain produce excitotoxic lesions in-vivo in rats and high doses of CoQ10 block the formation of these lesion (Beal et al., 1994).
  - ALSO Schizophrenics have low red blood cell CoQ10 levels with no difference between medicated and unmedicated patients. Plasma levels do not differ from controls (Imagawa, 1989).
- Increasing Complex IV
  - Researchers of the VA Boston Healthcare system showed that near infrared light from a headcap full of LED lights increased ATP and improved Stroop test, executive function, PTSD symptoms and sleep in traumatic brain injury (Naeser at el., 2014).
  - Near IR light (808nm) increased Complex IV activity in the brain and rescues major systemic and mitochondrial defects (Vos et al., 2013).
  - Near IR light (810 nm with full width half max of 40 nm) applied to the forehead of persons with depression, anxiety and PTSD by Harvard researchers caused significant remission in symptoms after 2 weeks (Schiffer et al., 2009).
- An easier solution……sunlight.
Vitamin E increases both Complex I and IV
- A 23% and 53% decrease in frontal cortex tissue and mitochondrial respiration and decreases in the activities of complex I and IV and mitochondrial nitric oxide synthase (mtNOS) was measured in aged rats. Vitamin E supplementation dose dependently restored tissue, respiration and complex I and IV as well as mtNOS activities. Vitamin E also prevented increases in oxidation products, hydrogen peroxide and superoxide radical formation. Vitamin E also restored loss of mass in the hippocampus (Navarro et al., 2011).

Selenium and Vitamin E increases ALL complexes
- Selenium and vitamin E fed to rats (from a selenium deficient area) elevated activity of all four mitochondrial complexes (Lui, 1990).

VITAMIN B12
- B12 level standards vary from country to country and the US standards for the low end of range normals may not be high enough.
- Parenteral (IM/IV) B12 has been shown to improve clozapine resistant schizophrenia in a patient with low (but not out of range) levels within days (Raveendranatham et al., 2013).
GLUTATHIONE PEROXIDASE (GPX)

- Enzyme levels increase in order to respond to elevated levels of the molecules they metabolize.
- Glutathione peroxidase (GPx), is an enzyme that breaks down hydrogen peroxide (an oxidizer) using glutathione. Hydrogen peroxide attacks lipids, the primary component of the brain, in a process called lipid peroxidation.
- GPx was found to be significantly higher in drug-naïve first episode patients with schizophrenia (Raffa et al., 2011).
- This indicates that high hydrogen peroxide levels may exist and stimulate an increase in GPx levels early in the disease process (= ox stress).
- GPx values were normal for both schizophrenic and bipolar patients that had been on medication for years (average 12.2 and 8.7) (Raffa et al., 2012).
- **Glutathione** is low in schizophrenia (in first episode untreated patients) making it difficult for the body to convert hydrogen peroxide into water (Raffa et al., 2011).
- **Vitamin D** levels are also found to be lower in schizophrenia (Itzhaky et al 2012) and low levels are correlated with symptom severity (Graham et al., 2014). Vitamin D levels up-regulate glutathione peroxidase (Jain et al., 2013) making it imperative for proper metabolism of hydrogen peroxide.
- Post mortem myocardial selenium levels were reduced in persons taking neuroleptics that died suddenly. **Selenium deficiency causes reduced activity of glutathione peroxidase** which may contribute to oxidative stress in myocardial cells (Hamdan et al., 2012).
THE FENTON REACTION

Fe^{2+} + H_{2}O_{2} \rightarrow Fe^{3+} + OH^- + \cdot OH
Fe^{3+} + O_2 + \cdot \rightarrow Fe^{2+} + O_2
H_{2}O_{2} + O_2 + \cdot \rightarrow OH^- + \cdot OH + O_2

(Ang et al., 2010)

- Hydrogen peroxide participates in an oxidizing reaction called the “Fenton Reaction” that forms reactive oxygen species that degrade and burns through materials such as paper, skin and tissues. **AGAIN Hydrogen peroxide attacks lipids, the primary component of the brain, in a process called lipid peroxidation.**
- Transition metals such as iron, copper, zinc and aluminum act as catalysts in the Fenton Reaction to create free radicals that attack proteins and other molecules. Iron and Copper are the biggest problem.
- **Acyclovir**, an anti-viral medication used for herpes, binds to both ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron to slow down the Fenton Reaction (Muller et al., 2006).
- Acyclovir stopped 90-95% of perseverating thoughts in a single schizophrenic patient at Choices Integrative Healthcare of Sedona.

• Quinolinic acid levels are elevated in schizophrenia. The primary mechanism exerted by this excitotoxin in the central nervous system (CNS) has been largely related with the over-activation of N-methyl-D-aspartate (NMDA) receptors and increased cytosolic Ca(2+) concentrations, followed by mitochondrial dysfunction, cytochrome c release, ATP exhaustion, free radical formation and oxidative damage (Perez de-la Cruz et al., 2012).

• Quinolinic acid induces lipid peroxidation by enhancing the iron mediated Fenton reaction and the generation of free radicals such as superoxide anion.

• Acyclovir also reduced quinolinic acid induced neuronal damage in rat brain by attenuating lipid peroxide formation. The mechanism of action was attributed to Acyclovir’s ability to significantly attenuate ferrous iron (Fe2+) induced lipid peroxide and super anion production. (Muller et al., 2005).

• Acyclovir reduced the activity of the quinolinic acid catalyzing enzymes indoleamine-2,3-dioxygenase (IDO) and 3-hydroxyanthranilate-3,4-dioxygenase (3-HAO) respectively for which Fe (2+) and the superoxide anion are both cofactors (Muller et al., 2006).

**Where does the quinolinic acid come from?**

• **Toxoplasma Gondii (an intracellular protozoan parasite)**

• Toxoplasma Gondii infected mice have elevated quinolinic acid in the brain (Notarangelo et al., 2014).

• Toxoplasma Gondii has been correlated with schizophrenia (Notarangelo et al., 2013; Emelia et al., 2012).

• **The kynurenine pathway produces quinolinic acid.**
1. TOXOPLASMA GONDII

- 20% of the US population has T. gondii (Cetinkaya et al., 2007).
- The odds ratio in schizophrenia is 2.73 (Torrey and Yolken, 2007).
- Of all infectious organisms studied, T. gondii had the highest probability of association with schizophrenia based on meta-analysis (Arias et al., 2012).
- T. gondii is present in about 61-66% of persons with schizophrenia (Emelia et al., 2012; Cetinkaya et al., 2007).
- Positive symptoms are increased in schizophrenics with T. Gondii (Holub et al., 2012).
- Adverse reactions to drugs and other substances can be due to the Jarisch-Herxheimer reaction due to apoptosis of T. Gondii tachyziotes (Prandota, 2009).
- Contamination occurs by ingestion of cysts from lamb, pork, water, garden soil, sandboxes or cat feces. It can occur congenitally or later in life.
- It establishes homeostasis in which it locally survives on host tissue but does not kill the host.
- It promotes an immune response with interferon-$\gamma$ as the main mediator (Carruthers and Suzuki, 2007).
- **12 neuroleptics were tested and some were found to effectively inhibit Toxoplasma Gondii growth in vitro.** Haloperidol and the mood stabilizer Valproic acid were the most effective (Jones-Brando et al., 2003).
- Another study on rats showed that haloperidol and valproic acid normalized some of the behavior of rats infected with Toxoplasma gondii as did the pyrimethamine with dapsone used to eradicate the parasite (Webster et al., 2006).
- T. Gondii can persist in most individuals without causing clinical disease.
Anti-food antigens (bovine milk casein and wheat derived gluten) and ASCA (Anti-saccharomyces cerevisiae antibody, a marker for intestinal inflammation) were elevated in schizophrenia and even more so for recent onset cases. The anti-food antigens were correlated to both ASCA and to Toxoplasma Gondii, particularly with males with recent onset (Severance et al., 2012).

Autoimmunity, gastrointestinal (GI) disorders and schizophrenia have been associated with one another for a long time. Exposure to wheat gluten and bovine milk casein also contribute (Severance et al., 2014).

2. KYNURENINE PATHWAY

The kynurenine pathway is the main pathway of formation for tryptophan, an essential amino acid which metabolizes to form serotonin.

L-kynurenine is a central compound of this pathway since it can change to the neuroprotective agent kynurenic acid or to the neurotoxic agent quinolinic acid.

The kynurenine pathway is often systematically up-regulated when the immune response is activated (Chen et al., 2009). The biological significance is that…..

- the depletion of tryptophan and generation of kynurenines play a key modulatory role in the immune response
- some of the kynurenines, such as quinolinic acid, 3-hydroxykynurenine and kynurenic acid, are neuroactive
KYNURENIC ACID (KYNA)

While kynurenic acid is neuroprotective, excesses may be detrimental to brain function.

- Kynurenic acid (KYNA) is an astrocyte-derived metabolite of the branched kynurenine pathway (KP) of tryptophan degradation (Sathyasaikumar et al., 2012).
  - The levels are elevated in the prefrontal cortex (PFC) of individuals with schizophrenia (SZ).
  - Because endogenous KYNA modulates extracellular glutamate and acetylcholine levels in the prefrontal cortex, these increases may be pathophysiologically significant.
  - KYNA inhibits N-methyl-D-aspartate (NMDA) and α7 nicotinic acetylcholine (α7nACh) receptors.
- Elevated levels of KYNA have been found in the CSF as well as in the post-mortem brain of patients with schizophrenia.” (Erhardt et al., 2009)
  - In low concentrations, KYNA blocks the glycine site of the NMDA receptor and the nicotinic alpha(7) acetylcholine receptor.
  - Endogenous KYNA appears to tightly control firing of midbrain dopamine neurons and to be involved in cognitive functions.

What can cause KYNA to be elevated?

1. As stated above, an immune response can elevate the entire kynurenine pathway.
2. The mRNA for Tryptophan-2,3-dioxygenase (TDO2) is elevated in schizophrenia and there is an increased density of white matter TDO2-immunopositive astroglial cells containing active TDO2 (Miller et al., 2004; Schwartz and Hunter, 2007)
   a. TDO2 is an upstream enzyme responsible for forming KYNA such that this could lead to increased KYNA levels in the brain of schizophrenics.
GLUTAMATE & THE NMDA RECEPTOR

- Glutamate is the primary excitatory neurotransmitter in the mammalian brain.
- Disturbances in glutamate-mediated neurotransmission have been increasingly documented in a range of neuropsychiatric disorders including schizophrenia.
- Increased levels of kynurenic acid increase levels of extracellular glutamate in the prefrontal cortex (Sathyasaikumar et al., 2012).
- KYNA has been proposed to act as an endogenous antagonist at the glycine site of the glutamate NMDA receptor (NMDAR) and reduced KYNA improves cognitive function (Kozak et al., 2014).
- The NMDA receptor controls memory function and synaptic plasticity (Li & Tsien, 2009).
- Excessive glutamate, or excitotoxins acting on the same glutamate receptors, overactivate glutamate receptors (specifically NMDARs), causing high levels of calcium ions (Ca^{2+}) to influx into the cell. (Dubinsky, 1993).
- Overstimulation of glutamate receptors causes: neurodegeneration and neuronal damage through a process called excitotoxicity.
- Glutamate excitotoxicity leads to tinnitus (Sahley et al., 2013).

ACETYL CHOLINE & THE N-ACETYLCHOLINE RECEPTOR

- $\alpha_7$ nicotinic receptors appear to be critical for memory, including working memory, and learning, and attention (Levin et al., 2006).
- It has been proposed that Alpha 7 nicotinic receptor agonists (acetylcholine (Ach), nicotine) may have positive neurocognitive effects in schizophrenia (Olincy et al., 2006).
- However, the activation of the Alpha 7 nicotinic receptors trigger acetyl choline esterase to form in order to break down ACh. KYNA inhibition of the receptor thus blocks metabolism of ACh causing toxic levels to build-up. This leaves nicotine as the best option.
SCHIZOPHRENIA AND SMOKING

- Addiction to nicotine is the most common form of substance abuse in people with schizophrenia. They are addicted to nicotine at three times the rate of the general population (75 to 90 percent vs. 25 to 30 percent).
- Thus smoking is likely a form of self-medication in order to stimulate the metabolism of toxic levels of acetyl choline.

In general, all chemicals and foods which inhibit the enzyme that breaks down acetyl choline should be avoided as well as keeping the choline content in the diet low.

ACETYL CHOLINE ESTERASE INHIBITORS: PESTICIDES & MORE

- Many pesticides are acetyl choline esterase inhibitors meaning they prevent acetyl choline from breaking down.
- Pesticides include: Carbamates (Sevin-5), Parathion
- Others include: Caffeine, THC, Rosemary
- Other pesticides open the sodium channels which make the neurons fire irregularly.
- These include: Pyrethrins
- AVOID PESTICIDE EXPOSURE

TRPV-1 RECEPTOR

- TRP theory of involvement in schizophrenia (Chal et al., 2007)
  - “Transient receptor potential voltage channels (TRPV) channels are cell membrane receptors variously activated by several exogenous natural products such as capsaicin, as well as endogenous chemicals of different structures, including endogenous lipids or lipid metabolites and inorganic ions (Ca2+ and Mg2+).”
  - Activation of TRPV1 channels by capsaicin increases the rate of firing of dopamine neurons of the midbrain.
  - TRPV1 is involved in thermoregulation which is dysfunctional in schizophrenia.
• TRPV-1 agonists increase glutamate release
• CB1 agonists counteracts TRPV-1 agonists effect, and decrease glutamate release
• Hot peppers make some people hallucinate
• “The Homer Simpson Effect”
• See YouTUBE

www.youtube.com/watch?v=Mdfk17EKGa0

CB1 = TYPE 1 CANNABINOID RECEPTOR

• Marijuana has both TRPV-1 agonists (THC, anandamide) and the CB1 agonist cannabidiol, being tested for treatment of schizophrenia (Leweke et al., 2012).
• Cannabidiol extract can be purchased but is costly. Hemp protein contains cannabidiol and 6T equals a typical dose used in studies.

TRPV-1 RECEPTOR INHIBITOR

• Low pH (from brain trauma) and elevated temperatures also activate TRPV-1.
• Doxazosin is a TRPV-1 inhibitor used for high blood pressure, prostate cancer and PTSD.
ALTERNATIVE TREATMENTS

- **Exercise** significantly improved negative symptoms (PANSS negative) in schizophrenia but had no effect on positive symptoms.
- **Yoga** in comparison to exercise showed a better outcome for mental state (PANSS total) and better quality of life scores (Gorczynski and Faulkner, 2010).
- **Family psychosocial intervention** reduces hospital admissions, encourages compliance with medication and decreases frequency of relapse (Pharoah et al., 2010).
- Close family support is imperative.
- **Acupuncture** combined with antipsychotics showed improved Brief Psychiatric Rating Scale (BPRS) endpoint data compared to antipsychotics alone and treatment emergent adverse events were significantly lower when acupuncture was added (Rathbone and Xia, 2005).
SELF MEDICATING

- **Stimulants- definitely bad for schizophrenia**
  - Persons using methamphetamine are at higher risk for developing SZ.
  - Schizophrenics may use stimulants to counteract negative symptoms or side effects of antipsychotic medications.
  - Amphetamines significantly increase the metabolism in the left and right cerebellum and significantly decrease metabolism in the dorsolateral prefrontal cortex in schizophrenia (Nolte et al., 2004).

- **Cannabis**
  - Cannabis combined with psychosis therapy compared to psycho-education showed no difference in BPRS scores or improved social function (Rathbone et al., 2008).
  - There is substantial evidence that cannabis has to be classified as an independent risk factor for psychosis that may lead to a worse outcome of the disease.
  - Agents that interact with the cannabinoid receptor system, such as the nonpsychoactive cannabidiol, might be beneficial in the treatment of psychosis (Muller-Vahl & Emrich, 2008).
  - 33.6 % of French schizophrenics used cannabis and those using cannabis more often used opiates (17 vs 0%) and alcohol (32 vs 7.4%) (Lejoyeux et al., 2014).

- **Nicotine- self medicating**
  - Long-term smoking might partially improve the hyperactive startle reflex in schizophrenic patients (Song et al., 2014).
  - Nicotine self-medication of schizophrenics improves cognitive symptoms, possibly by facilitating nicotine-induced $\alpha_7$nACh receptor activation in the hippocampus (Hambsch et al., 2014).
  - $\beta_2$-nAChR deficits are associated with negative symptoms of schizophrenia and smokers show elevated activation in various parts of the brain (Esterlis et al., 2013).
• **Opioids**
  o Opioids may act as neuromodulators of the dopaminergic system and in general increase the synthesis, release, reuptake, and metabolism of dopamine (Schmauss and Emrich, 1985).
  o Opioid users may have schizophrenia-spectrum pathology that may emerge during detoxification or prolonged abstinence of use due to vulnerability to neuromodulation of the dopaminergic terminals (Cohen et al., 2005).

**OTHER ALTERNATIVE MEDICATIONS**

- Depressive symptoms are found in 50% of newly diagnosed schizophrenia and 33% of chronic relapsed schizophrenia. An analysis of 11 studies of the use of antidepressants showed a significant benefit in the Hamilton's Rating Scale and no evidence that they led to an increase in psychotic symptoms (Whitehead et al., 2002).
- Serotonin is formed by the metabolism of tryptophan.
- Hypermetabolism of tryptophan as indicated in an up-regulated kynurenine pathway may alter the levels of serotonin availability at critical synapses.
- 5-HTP, the precursor to serotonin, was found to be low in schizophrenia while it’s precursor, tryptophan was high (Fukushima et al., 2014).
- Thus an SSRI (Selective Serotonin Reuptake inhibitor) or 5-HTP supplementation may be helpful in this situation.

Rx: SSRI OR 5-HTP
Kynurenine Synthesis

http://flipper.diff.org/apptools/pathways/info/3321
INFECTIONOUS DISEASE CORRELATION

- A meta-analysis of studies that have assessed the possible association between detection of different infectious agents and schizophrenia showed statistically significant association between schizophrenia and …
- Toxoplasma gondii (OR=2.70; CI 95%: 1.34-4.42; p=0.005)
- Human Endogenous Retrovirus W (OR=19.31; CI 95%: 6.74-55.29; p<0.001)
- Chlamyphila pneumoniae (OR=6.34; CI 95%: 2.83-14.19; p<0.001)
- Chlamyphila psittaci (OR=29.05; CI 95%: 8.91-94.70; p<0.001)
- Human Herpesvirus 2 (OR=1.34; CI 95%: 1.09-1.70; p=0.05)
- Borna Disease Virus (OR=2.03; CI 95%: 1.35-3.06; p<0.01)

(Arias et al., 2012)

RECOMMENDED TESTS

- 25-Hydroxy Vitamin D
- Vitamin B12
- Methylmalonic acid
- RBC folic acid
- Serum selenium
- Serum copper
- Serum iron
- Serum ferritin
- Homocysteine level
- MTHFR genotype
- COMT genotype
- P450 genotype panel for drug compatibility
- Toxoplasma gondii antibodies (IgG/IgM)
- Herpes simplex type 1 and 2 antibodies (IgG/IgM)
- Oxidative stress profile
- Consider gluten sensitivity panel (IgA total; antigliadin IgG & IgA EIA, antiendomysial IgA and antitransglutaminase antibody IgG & IgA)
SUPPLEMENTS TO AVOID
AND FOOD COMPONENTS TO MINIMIZE
KEEP A JOURNAL OF DIET VS. BEHAVIOR.
DO NOT ASSUME THEY ARE NOT CORRELATED!

DO NOT SUPPLEMENT AND MINIMIZE FOODS HIGH IN:

1. Choline (eggs, choline as an ingredients in B vitamins, broccoli, cauliflower, etc. See http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/Choline/Choln02.pdf)
3. Transition metals: Iron, Copper, Zinc, Aluminum
4. Sulfites (see list on Choiceshealthcare.com under articles)

TEST TOLERANCE FOR

- Gluten
- Milk (casein)

AVOID COMPLETELY

- Capsaicin (hot peppers, mustard, radish, wasabi, etc)
- Aspartame and other artificial sweeteners (use Stevia)

DIETS THAT MAY HAVE A BENEFIT

- LOW PROTEIN - Low MTHFR and COMT allele persons may benefit from a diet low in dopamine substrates (phenylalanine and tyrosine, protein regulated diet).

MISC. For banana cravings, try potassium gluconate (595 mg/day)
OTHER THINGS TO AVOID OR MINIMIZE

1. PESTICIDES
2. ALDEHYDES

- Aldehydes cause oxidative stress
- Avoid things that metabolize to aldehydes or contain toxic aldehydes:
  - Alcohol
  - Auto exhaust
  - Cigarettes (e-cigarettes have 2.5% the aldehydes that regular cigarettes have)
  - New consumer products that out-gas formaldehyde

SUPPLEMENT SUPPORT & PROTOCOL

- Do not change any psychiatric or other medications.
- Discuss with your medical provider.
- Introduce 1 new item every 3 days and watch for negative reactions.
SUPPLEMENT SUPPORT & PROTOCOL

- Start in this order:

1) B-100 Complex with no choline (CVS brand)
2) Anti-oxidant support:
   a) vitamin E (400IU, 800-1600 IU for tardive dyskinesia),
   b) alpha lipoic acid (600 mg daily)
3) Mitochondrial support:
   a) CoQ10 (200-300 mg daily),
   b) Succinic acid (250 mg daily),
   c) L-carnitine (240 mg daily)
4) Anti-oxidant support:
   a) N-acetyl cysteine (NAC) (1200-2000 mg daily). Gradually increase the dose of NAC one capsule at a time and watch for reactions.
   b) Vitamin C (500mg daily)
5) Ginkgo (120-360 mg in divided dose daily)

- If tests indicate or/and doctor recommends:
  o Acyclovir 400 mg twice daily
  o For low MTHFR allele: 5-MTHF 1200 mcg daily
  o Vitamin D3 supplement
  o Selenium
  o B12 (in additional to that in B-100)
  o 5-HTP or an SSRI

- Notes:
  o Vitamin C can fuel the Fenton reaction so it should be started after alpha lipoic which both chelates the iron and provides antioxidant support. It is also best to start it after the Acyclovir, if that is going to be taken.
  o While NAC can give immediate relieve to symptoms (like shortness of breath accompanying “anxiety states”), it would be ideal to get the folate metabolism working and gradually lower the homocysteine levels first, as NAC will drop them rapidly and could change behavioral symptoms through the D2 receptor.
REFERENCES


58. Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of


