Orthomolecular Treatment For Schizophrenia: A Review (Part One)

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Introduction

Various segments of the schizophrenic population fall into subgroups of distinct biochemical imbalance. We often see subgroups of essential fatty acid deficiency, inadequate nutriture, dysglycemia, food intolerance, digestive compromise, malabsorption, under-methylation, vitamin B_3 deficiency, vitamin C deficiency, heavy metal toxicity, B_6 deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia. Complementary and alternative medicine (CAM) have a key role in the treatment of schizophrenia. The goal of optimal complementary treatment is to correct the biochemical imbalance. In schizophrenia, we can assess cases with lab tests and target our treatment accordingly. CAM treatment involves the use of nutritional supplements, nutraceuticals, amino acids, and botanicals. Dietary changes are also implemented in treatment. In Part One of this review we will cover the research on essential fatty acid deficiency, inadequate nutriture, dysglycemia, food intolerance, digestive compromise, malabsorption, under-methylation, vitamin B_3 deficiency, and vitamin C deficiency.

The Essential Fatty Acid (EFA) Deficient Schizophrenic

Chronic schizophrenics have increased phospholipid neuron membrane break down (oxidative stress) which concentrates in the frontal cortex and other brain areas.[1,2] Pro-inflammatory cytokine involvement in development may set the stage for oxidative stress from early development onward.[3,4] Omega 3 fats have a neuroprotective and anti-inflammatory role. Sixty percent of the dry weight of the brain is fat. EFAs, including omega-3 and omega-6, are good fats, not saturated with hydrogen, and, unfortunately, not readily provided in the North American diet. Investigators note an integral need for omega-3 supplementation for schizophrenia, mood, and behavior disorders.[3,5] EFAs are important components of nerve cell walls and they are involved in neurotransmitter electrical activity and post-receptor phospholipid mediated signal transduction.

Eicosapentaenoic acid (EPA) is an omega-3 fat that is slightly more unsaturated than omega-6 fat. Brain membrane structure is compromised in chronic schizophrenia and EPA has demonstrated some potential in keeping brain neuron degeneration at bay and in reducing psychotic symptoms.[6-12] Omega-3 EFAs may eventually gain notice as "a safe and efficacious treatment for psychiatric disorders in pregnancy and in breast feeding [moms]".[6,13] Fish have high amounts of omega-3s and high EPA supplements are derived from fish. Many EPA fish oil products contain antagonistic fats and the more pure the EPA supplement, the more useful it is for schizophrenics.[7]

A balanced essential fatty acid profile may also be mediated by vitamin B_3 but more research is needed to identify the role of B_3 on the EFA profile of schizophrenics.[14]

The Schizophrenic with Inadequate Nutriture

Neurotransmitter production is dependant on amino acid protein building blocks (phenylalanine, tyrosine, tryptophan,

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etc.) supplied from the diet. The catecholamines dopamine, norepinephrine, and epinephrine are derived from phenylalanine and tyrosine. Catecholamines are involved in executive functions and motivation. Serotonin, the 'feel good' neurotransmitter, is derived from the amino acid tryptophan. Protein nutriture is very important for schizophrenia and for general mental well-being. I have seen many schizophrenics respond when they start increasing their protein intake with each meal. A diet that has 40% protein, 40% carbohydrate, and 20% fat is ideal for most schizophrenics.

Many schizophrenics do not eat three meals a day and their diet is invariably carbohydrate dominant. Carbohydrate dominant North American diets release glucose to the bloodstream quickly. Most schizophrenics require a dietary change that incorporates complex carbohydrates. They also do well to avoid high glycemic load foods including junk food, white sugar, white rice, and white bread. If they have a poor appetite, this can lead to inadequate nutriture. Poor appetite may be associated with zinc or iron loss.

Fat nutriture is important in schizophrenia. Cold water fish with teeth have a fat profile suitable for schizophrenics. Salmon, tuna, mackerel, herring, cod, and trout provide the highest omega-3 profile. Other high EFA sources include scallops, shrimp, flaxseeds, walnuts, winter squash, and kidney beans.

Inadequate nutriture can also occur with gastrointestinal compromise, malabsorption, and low thyroid function.

The Dysglycemic Schizophrenic

The brain's demand for glucose is so immense that about 20% of the total blood volume circulates to the brain, an organ that represents only 2% of body weight. The brain demands a substantial amount of glucose to maintain its high metabolic rate. Gluco-sensing neurons regulate glucose availability in the brain as a fail-safe mechanism to ensure homeostasis of brain glucose levels.[15]

In schizophrenia, it seems likely that glucose transporters are compromised with consequent intraneuronal glucose deficits.[15] McDermott and de Silva mention that this hypoglycemic state has the potential to cause "acute symptoms of misperceptions, misinterpretations, anxiety and irritability–the usual features of prodromal and first onset schizophrenia." Epidemiological investigations show us that schizophrenics are at increased risk for dysglycemia.[17] Psychiatric meds also have some potential to induce hyperglycemic or insulin resistant states and this can be addressed, at least in part, with a nutritional adjunct.[18]

The hypoglycemic state involves a sharp rise of simple sugars in the blood followed by a sharp decline which robs the neurons of their main energy source; the sharper the decline, the greater the effect on brain cells. Typical hypoglycemic symptoms include irritability, poor memory, late afternoon blues, poor concentration, tiredness, cold hands, muscle cramping, and 'feeling better when arguing'.

Schizophrenics with hyperglycemia, much like diabetics, present with hypoglycemic mental symptoms because the glucose doesn't get into brain neurons. Brain neurons starved for energy behave differently and mental function declines.[19,20] It is not clear if dysglycemia has a causative role in schizophrenia but it can be deemed an aggravating factor.

It is said that hypoglycemia is 100% treatable in compliant patients. This emphasizes the need to address diet. The dysglycemic schizophrenic requires three solid meals (of 40% protein) a day and sometimes additional protein-containing snacks. Many schizophrenics need to be educated on complex versus fast carbohydrates and the avoidance of junk food and sugar. When schizophrenics increase their protein intake, they release glucose to the

brain at a steady rate and sugar cravings lessen. Chromium and zinc are useful for sugar balance and botanical medicine is useful in advanced hypoglycemia.

The Food Intolerant Schizophrenic

Schizophrenics, just like the general population, have the potential to exhibit mild or severe food intolerance symptoms.[21-25] The digestive tract reacts to food allergens by eliciting an immune response. Undigested food by-products can be toxic (e.g. opioid peptide exorphins), pass through the gut wall, enter the bloodstream, and reach the brain with subsequent brain function compromise.[23,26-28] I have several clients who have an increased severity and frequency of hallucinations, delusions, depression, anxiety, irritability, and insomnia when they eat an intolerant food. We see schizophrenics that experience a wide range of food related physical symptoms such as headaches, skin eruptions, palpitations, weakness, painful digestion, constipation, diarrhea, and arthralgia. In schizophrenia, gluten, dairy, and eggs are commonly not tolerated.[22,23,29] Other common food intolerances include tree nuts, citrus, fish, legumes and crustaceans. It is helpful to survey patient responses with a seven-day diet diary. Often schizophrenics are tired, weak, irritated, and moody after eating intolerant foods. Typically they either hate the intolerant food or crave it and this may be due to the toxic effects of opioid exorphin peptides. It is not uncommon to see patients that have fasted in the past and report that they feel better. This is a good indication that they have a food intolerance. An elimination diet followed by provocation is helpful to assess cases clinically. Elaborate lab testing may not need to be implemented but IgG Elisa testing can be quite useful to assess food intolerances that are less obvious.[21,30] IgG responses are provoked when there is a delayed response. IgG tests report the severity of the delayed reaction and also provide a rotation diet schedule. Many investigators have noted improvements with dietary restriction of food intolerants. In our clinic, a small but significant portion of schizophrenics experience profound improvements after removing intolerant foods. Some researchers estimate 10% of schizophrenics having severe food intolerances.[31] More research is needed to understand the pathophysiology, epidemiology, and clinical presentation of the food sensitive subset of schizophrenics.[32]

The Schizophrenic with Digestive Compromise and Malabsorption

I constantly see gastrointestinal problems in schizophrenia including constipation, spastic obstipation, bloating, cramping, abdominal discomfort, IBS, and GERD. Compromised gastrointestinal function leads to malabsorption of nutrients. These patients often require higher doses of nutrients and medications. Lack of stomach acid can reduce intrinsic factor and diminish B_{12} utilization which is essential for methylation and neurotransmitter formation. Poor bowel transit locks in toxins and they build-up, tax the immune system, and reduce the absorptive surface area. Poor bowel transit may be due to lack of peristalsis, low thyroid function, or magnesium deficiency. Adequate water intake is about two liters per day for the average adult. This is essential to keep toxins moving out and bowel contents hydrated. CAM treatment for digestive dysfunction and low thyroid function helps to alleviate digestive symptomology and also reduces the need for high nutrient dosing. Intact gastrointestinal health is a prerequisite for improved outcome in schizophrenia.

The Under-Methylated Schizophrenic

Schizophrenic researchers are well aware that certain brain tracts are overstimulated while others are understimulated (hypofrontality). If we can methyl-

ate efficiently, we have the machinery to form neurotransmitters in areas of the brain that are understimulated and neurotransmitter deficient. In our clinic, we see a good portion of schizophrenics with methylation compromise as indicated by elevated fasting homocysteine levels. Elevated homocysteine levels and methylation compromise are common in schizophrenia.[33-41] Elevated homocysteine levels have also been correlated with an increased severity of extrapyramidal symptoms.[42]

Nutritional treatment with B_{12}, folic acid, and other methylators can restore methylation status. In schizophrenia, investigators have found methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms that disrupt folic acid pathways.[43,44] These schizophrenics have a greater need for folic acid supplementation.[42] Investigators suspect a causal link between elevated homocysteine and the MTHFR genetic polymorphism.[45] Many schizophrenics have adequate dietary intake of B_{12} and folate yet their homocysteine levels are high.[46] These studies support the hypothesis that schizophrenic pathogenesis may be inherent.

Some evidence suggests that high circulating levels of homocysteine increase the level of homocysteic acid and cysteine sulphinic acid, both of which are NMDA receptor agonists that contribute to neuronal excitotoxicity.[47] It is not known if neuronal degeneration in chronic schizophrenia is due to elevated homocysteine levels. It is also unclear if NMDA-induced excitotoxicity plays a causative role in schizophrenia. More research on methylation in schizophrenia is required to fully understand the pathophysiological mechanisms.

The Vitamin B_3 and C Deficient Schizophrenic

Schizophrenics are poor at filtering the influx of sensory information and this causes perceptual dysfunction (hallucinations, illusions). Overstimulated brain pathways have excess neurotransmitter and symptoms are, in part, caused by neurotransmitter overstimulation of the prefrontal cortex. Many neurotransmitter pathways are involved; some overstimulated, others understimulated. In a schizophrenic brain, vitamin B_3 and C (ascorbate) together have the potential to intervene and limit the production and oxidation of excess catecholamines in the brain.

Vitamin B_3 is one of the few methyl acceptors in the body. As a methyl acceptor, B_3 can limit, in a regulated fashion, neurotransmitter production.[49] When under stress, B_3 can also limit adrenal gland conversion of noradrenaline to adrenaline. Peripherally, this acts as a fail-safe mechanism to prevent excessive adrenaline production and consequent readily autoxidizable catecholamine endproducts.[49]

A catecholamine rich cerebral environment is prone to oxidization and oxidized metabolites are neurotoxic and hallucinogenic to humans.[50-53] Oxidized catecholamines and toxic indoles may contribute to synaptic deletion.[54] In the healthy brain, oxidized catecholamines convert back to a stable form (neuromelanin), a process that has the effect of 'neutralizing' or 'storing' unwanted toxins.[53,54] Smythies proposes that neuromelanin neutralization is compromised in schizophrenia and it may play a causative role.[52,53] Both vitamin B_3 and C (ascorbate) have the potential to reduce oxidized catecholamine intermediates.[55] In the adrenal gland, vitamin C is found in high concentrations to keep oxidation at bay.[49]

As a separate mechanism of action, B_3 and ascorbate are physiologically antagonistic to copper. They can help to limit dopamine overproduction which overstimulates the prefrontal cortex and disturbs executive functions. Excess cop-

per is very common in schizophrenia and copper is a cofactor in dopamine production. When dopamine pathways are overstimulated, serotonin (the opposing 'feel good' master neurotransmitter system) can become downregulated. This may in part account for some of the negative symptoms of schizophrenia.

Vitamin B_3 (NAD) can be found in several supplemental forms; as niacin, niacinamide, inositol hexaniacinate, and NADH. NADH is the reduced form and it is more active than NAD. NADH is dosed in the mg range. The other forms of B_3 can be dosed in the gram range. Niacin and inositol hexaniacinate are dosed safely in the gram range in the treatment of intermittent claudication, hypercholesterolemia, and Raynaud's. Sufficient doses of B_3 for schizophrenia are also in the gram range. Niacinamide and inositol hexaniacinate are flush-free. Pure niacin causes flushing due to the release of peripheral histamine stores. When dosed in the gram range, pure niacin causes a head down flushing response during day 1 and 2 of dosing. This subsides with subsequent gram range dosings. The inositol hexaniacinate form of B_3 is well tolerated and has a great safety profile. Numerous investigators report the use of inositol hexaniacinate in the 4 gram daily range without a single adverse reaction.[56-58] Inositol hexaniacinate and pure niacin also promote brain blood flow which can be important in schizophrenic hypofrontality. Vitamin B_3 has an interesting side-effect of longevity. The Mayo Clinic found significant reductions in mortality in subjects with high baseline cholesterol who used niacin alone.[59,60]

The B_3 deficient state is typified in the disease pellagra, the rarely seen vitamin B_3-dependent disease state. Classic symptoms of pellagra include psychosis, hallucinations, depression, anxiety, confusion, memory loss, anorexia, and fatigue.[61,62] Pellagrins and schizophrenics respond well to B_3.

The positive results of B_3 treatment have been noted in six double-blind trials on schizophrenic cohorts and an optimal dosing strategy is indicated.[63-80]

Vitamin B_3 and C are anti-stress vitamins. Practitioners who treat schizophrenics with vitamin B_3 and C continue to report positive responses.[63,81-83]

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