ORTHOMOLECULAR TREATMENT FOR SCHIZOPHRENIA: A REVIEW (PART ONE)

Raymond J. Pataracchia, B.Sc., N.D.[1]

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Note

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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, combined vitamin B3 and C deficiency, heavy metal toxicity, B6 deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia. Complementary alternative medicine (CAM) has 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. Here 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, and the combined vitamin B3 and 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. 60% of the dry weight of the brain is fat. EFA's, including omega-3 and omega-6, are good fats, not saturated with hydrogen, and unfortunately, not readily provided in the American diet. Investigators note an integral need for omega-3 supplementation for schizophrenia, mood, and behavior disorders.[3,5] EFA's 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 fats. 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 EFA's 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 3's 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 B3 but more research is needed to identify the role of B3 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, etc.) supplied from the diet. The catecholamines

1. Naturopathic Medical Research Clinic, 20 Eglinton Avenue East, Suite#441, Toronto, Ontario, Canada, M4P 1A9.

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 schizophrenics and 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 schizophrenia. 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, mal-absorption, 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 the homeostasis of brain glucose.[15]

In schizophrenia, it seems likely that glucose transporters are compromised with consequent intraneuronal glucose deficits.[16] 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 the 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 intolerant foods. 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(high in copper). 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 reported feeling 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 be needed 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 guideline. 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 subsets 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 B12 utilization essential for methylation and neurotransmitter formation. Poor bowel transit locks in toxins and the build-up taxes the immune system and reduces the absorptive surface area. Poor bowel transit may be due to the lack of peristalsis, low thyroid function, and/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 methylate 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 B12, 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 polymorphisms.[45] Many schizophrenics have adequate dietary intake of B12 and folate yet their homocysteine levels are high.[46] These studies support the hypothesis that schizophrenic pathogenesis can 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 respective pathophysiological mechanisms.

The Vitamin B3 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 B3 and C (ascorbate) together have the potential to intervene and limit the production and oxidation of excess catecholamines in the brain.

Vitamin B3 is one of the few methyl acceptors in the body. As a methyl acceptor, B3 can limit, in a regulated fashion, neurotransmitter production.[48] When under stress, B3 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 end-products.[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 may play a causative role.[52,53] Together in combination, vitamin B3 and C 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, B3 and C are physiologically antagonistic to copper. They can help to limit dopamine overproduction which overstimulates the prefrontal cortex and disturbs executive functions. Excess copper 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 B3 (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 B3 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 B3 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 and head down flushing response during day 1 and 2 of dosing. This subsides with subsequent gram range dosings. The inositol hexaniacinate form of B3 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 B3 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 B3 deficient state is typified in the disease pellagra, the rarely seen vitamin B3-dependant 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 B3.

Vitamin C, on its own, is a potent antioxidant that works synergistically with vitamin E and glutathione. Vitamin C's free radical scavenging capability is associated with improved outcome in Brief Psychiatric Rating Scale (BPRS) scores in neuroleptic treated schizophrenics.[63] Vitamin C's role in converting dopamine to nor-adrenaline in the brain can further vent the biochemistry away from catecholamine oxidation.[64] Due to great metabolic demand, schizophrenics require much higher (10x) levels of vitamin C than the general population.[65,66] Low brain ascorbic acid levels are thought to cause cognitive deficits including schizophrenic psychopathology.[67]

The positive results of combined vitamin B3 and C treatment have been noted in six double-blind trials on schizophrenic cohorts and an optimal dosing strategy is indicated.[68-85]

Together, vitamin B3 and C are anti-stress vitamins that have several physiologically synergistic roles. Practitioners who treat schizophrenics with vitamin B3 and C continue to report positive response.[68, 86-88]

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Introduction

This two part review on schizophrenia describes various segments of the schizophrenic population that fall into subgroups of distinct biochemical imbalance. To recap, these subgroups include essential fatty acid deficiency, inadequate nutriture, dysglycemia, food intolerance, digestive compromise, malabsorption, under-methylation, vitamin B3 deficiency, vitamin C deficiency, heavy metal toxicity, B6 deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia. Complementary alternative medicine (CAM) has a key role in the treatment schizophrenia. Here in Part Two of this review we discuss heavy metal toxicity, B6 deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia.

Heavy Metal Toxicity in Schizophrenia

Most heavy metals are free radicals that induce oxidative stress (lipid peroxidation) and have an affinity for brain tissue.[1,2] Free radical-mediated neurotoxicity and oxidative stress are implicated as a causative factor in schizophrenia.[3,4] These free-radicals have the ability to compromise and/or destroy brain tissue and, in so doing, decrease the availability of viable brain tissue. Note that other mechanisms of brain tissue compromise are involved in schizophrenia, so the added burden of toxic metals is to be avoided.

Elevated heavy metal levels are associated with schizophrenic pathology.[4-8] It is not uncommon to see toxic levels of copper, lead, mercury, aluminum, arsenic, and cadmium in

schizophrenics. We find some of the most advanced schizophrenic cases having three or more heavy metals. Heavy metal toxicity is also associated with ADHD, anxiety, OCD, depression, bipolar disorder and dementia.

Heavy metals are excreted by using the body's metal removing protein, metallothionein.[2,9] In the process of ridding the body of heavy metals, this protein loses zinc.[10] Zinc loss in schizophrenia in turn compromises the ability to transcribe proteins and make neurotransmitters. Investigators recognize compromised brain protein transcription pathways in schizophrenia.[3,11] Zinc deficiency is associated with schizophrenia and several other psychiatric pathologies including mood dysfunction and dementia.[9]

Lead disrupts mental function.[12] Toxic lead levels are associated with psychosis.[13] Lead toxicity is also associated with behavior disturbance, mood disorder, learning disabilities, insomnia, immune compromise, brain damage, and delayed infant development. Lead has been found to disrupt the carriage of thyroid hormone (T4) into the brain.[14,15] If you are a city dweller, you are exposed to lead and the risk of lead toxicity rises with age. With widespread pesticide use, lead is accumulating in the food chain. Lead is found in paints, print colour, glass, batteries, rust protectants, alloys and old water pipes and bathtubs.[16]

Mercury is toxic and has no therapeutic use; in fact, it disrupts dopamine and norepinephrine metabolism.[17] It is not uncommon to find elevated mercury in patients with schizophrenia. Mercury is found in fluorescent lights, vaccines, thermometers, and fish, animals, and plants exposed to toxic environments. Dental fillings contain on average about 40% mercury which has the potential to leach with electrolytic decay. Mercury often causes headaches, nervous irritability, memory decline, depression, rapid fatigue, nausea, stomach aches and allergic susceptabilities.[16] Mercury has a strong affinity for the brain but also sequesters in the liver, kidney, and spleen.

Aluminum can be toxic in patients with schizophrenia, mood disorders, Alzheimer's Disease and digestive system pathologies. Aluminum disrupts enzyme function and is well-documented to disrupt cognition, learning and memory. Environmental sources of aluminum include aluminum cookware (especially from heating and deglazing with an acid such as vinegar or wine), drinking boxes, processed cheese, deodorants, and drinking water (aluminum is more soluble in our acidic magnesium deficient drinking water).[18]

In excessive concentrations, copper has a toxic effect and, in schizophrenia, contributes to excess catecholamine oxidation, the end products of which are unstable toxic hallucinogens.[6,19] We have found copper toxicity to be the most common heavy metal pattern in schizophrenia. It is also associated with ADHD, autism, depression, anxiety, bipolar disorder and paranoia. With copper toxicity we see clinical zinc deficiency.[20] Copper is abundant in food and water as it is found in soil, pesticides and animal feed. Since World War II we have been exposed to greater levels of copper due to copper piping in modern homes and the widespread use of birth control pills (estrogen based). Estrogen dominance is associated with higher circulating copper levels and copper is thought to transfer via placenta from generation to generation.[20] Other copper sources include copper tea pots, copper sulphate treated Jacuzzis or swimming pools, drinking water, dental fillings, prenatal vitamins, and copper IUD's. Neuroleptics, antibiotics, antacids, cortisone, Tagamet, Zantac, and diuretics often encourage copper dominant biochemistry.

The liver produces the copper regulating proteins metallothionein and ceruloplasmin and, with low thyroid function, their hepatic protein synthesis is diminished. The body attempts to remove excess copper by excreting it out of the liver via gall bladder excretion to the bowel. Vitamin B3, vitamin C, and zinc are helpful clinically because of their physiological antagonism to copper.

Schizophrenics relapse when thyroid function is low.[21] Poor thyroid function encourages heavy metal retention. Conversely, heavy metals seem to play a major role in blocking peripheral enzyme conversion of T4 to T3.[22-25] Heavy metal removal involves mobilizing and eliminating the metal and this is often best done after thyroid function has been optimized. The organs involved in the elimination of the metal tend to function more efficiently when thyroid metabolism is intact. It is also essential to avoid environmental exposures to heavy metals.

Zinc and B6 Deficiency in Schizophrenia

Zinc and iron are the most concentrated metals in the human brain. Zinc is important to several biochemical pathways as over 200 enzymes are zinc dependant. Zinc deficiency is very common in schizophrenia.[7-9] Insufficient levels of zinc are also associated with depression, dementia, mental retardation, learning disability, lethargy and apathy.[26] Zinc is essential for the synthesis of serotonin and melatonin.[20] It is crucial to brain development because it plays a major role in protein synthesis.[20,26] In the brain, zinc lowers excitability by moderating NMDA receptor release of excitatory glutamate. Zinc is involved in the synthesis of inhibitory GABA by the modulation of glutamate decarboxylase activity. Among the zinc-dependant proteins are metallothionein which is essential for heavy metal regulation and zinc bioavailability. The synthesis of Zn-thionein and CuZnSOD are essential in preventing oxidative damage.[20] Zinc protects against fatty acid peroxidation which destroys neuron structure and function. Zinc is involved in neuronal plasma membrane structure and functioning and, may play a key role in blood-brain-barrier integrity.[27] Zinc is involved in storing biogenic amines in synaptic vesicles and, in axonal transport. The biogenic amine histamine regulates nucleus accumbens activity, which is responsible for filtering sensory information and communicating with the amygdala, ventral tegmentum, and hypothalamus. In the limbic system, zinc is involved in the metabolism of emotional regulation. In the hypophysis and hypothalamus, zinc is involved in hormonal metabolism.

Vitamin B6 (pyridoxine) is involved in the decarboxylation of tyrosine, tryptophan, and histadine into the neurotransmitters nor-epinephrine, serotonin, and histamine respectively.[28] B6 deficiencies are associated with schizophrenia, depression, and behavior disorders. It is a cofactor in homocysteine re-methylation.[29] B6 has been found useful in memory acquisition, with just a 20mg dose.[30] It has demonstrated usefulness in controlling neuroleptic-induced akathisia and drug-induced movement disorders.[31-33] B6 is essential for the synthesis of antioxidants such as metallothionein, glutathione, and CoQ10 which help prevent neuronal oxidative stress. B6 (and zinc) are involved in the synthesis of glutamic acid decarboxylase (GAD) which blocks excitotoxicity with eventual secondary oxidative damage. B6 is essential for glutathione peroxidase and glutathione reductase which are helpful in preventing mitochondrial decay.

The major neurotransmitters of the brain are derived from protein building blocks and precisely assembled according to messenger RNA (mRNA) transcription of neuronal DNA templates. Brain tissue samples of schizophrenics have been assessed with high-

dimensional biology and found to be compromised in basic mRNA transcription and protein synthesis.[3] These perturbations influence an array of neuronal changes in the schizophrenic brain among which are, neurotransmitter synthesis and mitochondrial functioning. Oxidative stress can cause these perturbations and the ensuing changes in neuronal structure and function may be integral in understanding schizophrenic pathophysiology.

It is interesting to note here that zinc and vitamin B6 together are needed by the body as cofactors for neurotransmitter synthesis; zinc is needed for transcription and B6 is needed for transamination. Previous investigators have described B6 and zinc depletion in the context of pyrolluria. In this metabolic syndrome, B6 and zinc interact with 2,4-dimethyl-3-ethylpyrrole and are readily excreted.[34-42]

Hypoadrenia in Schizophrenia

Thyroid and adrenal function are compromised in many schizophrenics.[21,43] The thyroid and adrenal are pivotal endocrine glands. Many symptoms common to adrenal dysfunction are seen in thyroid dysfunction and vice versa. The adrenal works in concert with the thyroid gland and often both glands need to be supported together.[44,45]

Hypothalamic-Pituitary-Adrenal axis dysregulation is integrally associated with schizophrenia.[21,43] The adrenal glands are involved in stress response, sugar metabolism, electrolyte balance, peripheral epinephrine synthesis, blood pressure regulation, and sex hormone metabolism. Many schizophrenics who are heavy coffee drinkers have low adrenal function. Low adrenal symptoms include sluggishness on waking, stress intolerance, lack of enjoyment, post-traumatic stress, addiction, dizziness, low blood pressure, fluctuant body temperature, insomnia at 4am, immune compromise, hypoglycemia, dermatitis, PMS, phobia and poor libido. Schizophrenics can be warm at times and at other times cold with trouble adapting to daily temperature extremes. Fluctuant body temperatures and heat intolerance are a sign of low adrenal function which often accompanies low thyroid function.[46] Adrenal symptoms are a good indicator of adrenal status. In some cases, saliva testing is useful to assess the adrenal hormones DHEA and cortisol. Cortisol is part of the stress response but elevated cortisol disturbs mental function. Cortisol levels are commonly elevated in schizophrenics and depressives.[47,48] Adaptogens and supplements can be used effectively to support adrenal function without elevating cortisol.

Hypothyroidism in Schizophrenia

Active thyroid hormones are responsible for enabling cells, at the DNA level, to maintain their metabolic rate. Thyroid hormones also maintain oxygen availability in the brain and elsewhere. With healthy thyroid hormone function, our cells produce energy and complete their tasks efficiently. When tissue cells including neurons have energy, they work efficiently. When thyroid function is low, cells remain in a state of hypofunction. Hypofunctioning cells work slowly and produce minimal energy. Consequently, fewer enzymatic reactions occur, cells don't give off heat and core body temperature decreases. Intolerance to cold is a typical complaint in low thyroid function.[21] When body temperature is insufficient, enzymatic reactions do not occur as readily yet these reactions are needed throughout the body for, among other things, neurotransmitter synthesis. It is not uncommon to have schizophrenics report that they feel warm despite having low average body temperature.

Low thyroid symptoms are seen often in psychosis.[21,49-51] In treatment refractory depression, psychiatric 'thyroid augmentation' treatment is frequently implemented.[52,53] The most obvious low thyroid symptoms include impaired cognition, easy weight gain, fatigue, pain, headache, irritability, anxiety, panic, PMS, depression, poor memory, poor concentration, insomnia, constipation, indigestion, hair loss, high cholesterol and frequent infection.[21,52,54,55] The digestive tract of a low thyroid patient has poor motility and slow stool transit which results in constipation and inefficient nutrient absorption.[56] In low thyroid patients, core body temperatures are often so low that digestive enzymes do not reach their reaction threshold. Patients with varied non-specific complaints often have low thyroid function.

Classic hypothyroidism, occurring in a small percentage of schizophrenics, is a problem with the inability to produce adequate thyroid hormone. In classic 'conventional' hypothyroidism, blood tests show low output of thyroid hormone T4 with elevated thyroid stimulating hormone (TSH) levels. Immune involvement as in Hashimoto's thyroiditis is usually seen in 80% of classic hypothyroid cases. Othman et al. assessed a sample of 249 chronic schizophrenics and reported a prevalence of thyroid antibodies in 20% of cases.[57] Many blood thyroid imbalances are found to correlate with the degree of symptom presentation, as for example, in acute psychotic episodes.[58]

The reliance on thyroid blood tests in schizophrenia leads practitioners astray because a large portion of schizophrenics are euthyroid with 'normal' blood test measures but, paradoxically, have a low core body temperature and low thyroid symptoms (fatigue, psychosis, depression, etc). There is no accepted diagnostic agreement on this physiological state, however Wilson's Temperature Syndrome (WTS) has emerged as a condition that meets this criteria. WTS factors in the possibility of inefficient peripheral conversion of T4 to active T3 despite having adequate circulating thyroid hormone T4.[52,53,59] In classic hypothyroidism and WTS, we can implement desiccated thyroid, sustained release T3 (T3-SR) and botanical medicine.

Brain hypothyroidism

The brain is highly dependent on thyroid hormone for the regulation of dopamine, norepinephrine, and serotonin pathways.[50,60,61] Brain hypothyroidism has been described by Hatterer et al. as a state that occurs when systemic T4 does not readily cross into the brain.[62] Active thyroid hormone T3 is synthesized in the brain by brain typeII 5'-deiodinase conversion of T4 to T3.[53,63] Brain neurons therefore depend on a ready supply of T4. The choroid plexus of the brain produces transthyretin (TTR), a transport protein that binds T4 and transports it across the blood-cerebral spinal fluid barrier to the brain.[63] Transthyretin is significantly downregulated in the cerebral spinal fluid (CSF) of schizophrenics versus healthy controls.[64] This suggests that schizophrenics lack adequate amounts of T4 in the brain. Without adequate T4, brain cells remain hypo-metabolic and this may, among other things, reduce neurotransmitter synthesis and disrupt the regulation of dopamine, norepinephrine, and serotonin.

Huang et al. suggest that low CSF transthyretin may prove useful as a biomarker for early diagnosis of schizophrenia.[65] Also of interest is the fact that lead has been linked to the reduction of CSF transthyretin in humans.[14,15] Reduced CSF transthyretin is also seen in depression and suicidal propensity.[66,67] Many schizophrenics and depressives relapse when thyroid function drops.[21]

Peripheral blood thyroid levels can be normal in the context of brain hypothyroidism. T4 to T3 conversion by brain typeII 5′-deiodinase can be inhibited by cortisol.[68,69] This is important because cortisol levels are commonly elevated in schizophrenics, especially during stress. Cortisol is an adrenal stress hormone and, during stressful periods, we tend to conserve energy by shutting down thyroid hormone production.

Anti-thyrodal adrenochrome

Adrenochrome is a quinone and many molecules in this class are anti-thyroidal. In schizophrenia, a ready supply of oxidized adrenaline may account for thyroid compromise. Adrenochrome has the ability to induce oxidative stress and functional changes in thyroid tissue and peripheral metabolism.[70-78] It is not known to what degree adrenochrome damages the thyroid gland. Skoliarova suggests that functional changes can be inferred from the structural "deterioration" of the thyroid and hypophysis of chronic schizophrenics autopsied 20 minutes to 5 hours post-mortem.[79]

Thyroid treatment

There are some remarkable studies reporting the outstanding efficacy of thyroid therapy in acute and chronic schizophrenia. A study by Danziger reported in 1958, showed that 100 days of optimally dosed desiccated thyroid or thyroxine with B-complex lead to the full recovery of 54 (45%) of 80 schizophrenics.[80] Twenty of the 80 patients were given thyroid therapy alone while 60 of the 80 patients were given thyroid plus shock (ECT) therapy. Fifteen (75%) of the 20 patients given thyroid therapy recovered fully and, 39 (65%) of the 60 patients given thyroid therapy plus ECT recovered fully. Of the 15; two were sick for 60 or more months, two were sick 24-59.9 months, three were sick 12-23.9 months, two were sick 12-23.9 months, and six were sick less than 6 months. Of the 39; six were sick for 60 or more months, five were sick 24-59.9 months, five were sick 12-23.9 months, six were sick 12-23.9 months, and 17 were sick less than six months. After discharge, the incidence of relapse was very small with a maintenance treatment that kept the basal metabolic rate (BMR) in check. Full recovery was defined appropriately; that is, being 'symptom-free, returning to a former place in society/occupation and accepted as well by family, friends and co-workers'. The prognosis of the 80 patients at the onset of the study was "generally unpromising" as they were treatment refractory to ECT, psychoanalysis, and psychotherapy (all were neuroleptic naïve).

Many of the 80 schizophrenic patients reported by Danziger required high doses of desiccated thyroid (128 to 1280mg) or racemic thyroxine (1-9mg). Of the 54 patients that recovered with thyroid therapy or thyroid plus ECT, only 4 required 640mg or more of desiccated thyroid and, only 2 required up to 4mg of thyroxine. Such doses were probably required to combat adrenochrome's anti-thyroid metabolic effects and, to make up for the lack of T4 transport from the CSF to the brain ('brain hypothyroidism'). Hoskins and others report on the tolerance of schizophrenics for even higher doses of desiccated thyroid than those used by Danziger.[81,82] To enable good treatment outcome, the BMR is raised to a level that likely improves the function and production of respiratory enzymes in the cerebrum.[83] In Danziger's study, first-episode cases had the best response however, one third of the chronic cases (5 plus years post-onset) experienced full recovery as well.

A double-blind efficacy study reported by Lochner et al. in 1963 used T3 (L—triiodothyronine) treatment in a six-week trial on 30 chronic male schizophrenics eight plus

years post-onset.[84] Typical tranquilizers prescribed at the time were discontinued in a wash-out period several weeks prior to treatment. Patients were included if they tolerated withdrawal without exhibiting aggressive behavior. 15 subjects were randomly assigned to the thyroid group and another 15 subjects to the placebo control group. Red blood cell uptake of I^{131}-T3 was normal for all subjects at baseline; they were euthyroid according to blood tests. The treatment group received 50mcg of T3 b.i.d. for one week, then 100mcg b.i.d. (200mcg per day) for six weeks.

In this short treatment period, seven of the 15 patients treated with T3 responded very well. They had improved motor activity, work performance, spontaneity, sociability and logical/relevant thinking. Some reported they were "more lively" and could "think better". Mood improved and they showed interest in their environment. They showed improvements in executive functioning; some voiced "plans for the future" and wanted to visit relatives, return to work and resume family relationships outside of the hospital. Five of the 15 patients had some worsening. Two of these five patients were responsive and cooperative with generally better mood but, exhibited hallucinations and delusions that had been repressed and were tense, restless, and loquacious. Another two of these five patients became non-conversive and tense with masked facies and motor retardation. The last of these five patients became incoherent, irritable, and explosive with increased hallucinations, delusions, and activity. The remaining three of the 15 experienced no change. All schizophrenics returned to their previous state shortly after discontinuation of treatment. Lochner's study was reproduced by Scheuing and Flach with the same cohort and, a consensus of results was determined.[85] The results with T3 are impressive when you consider the short treatment duration, the chronicity of the cohort and, the failure to implement optimal dosing strategy. Doses of 200mcg of T3 may have been too high for those patients that aggravated in the given six-week time-frame of the study. Conversely, 200mcg may not have been a high enough dose for those schizophrenics that did not respond. To this author's knowledge, the use of T3 in first-episode schizophrenia has not been fully investigated.

Hoffer also reports on 12 schizophrenic patients treated on nicotinic acid and optimally dosed desiccated thyroid.[71] Of the 11 patients that completed the treatment, nine had benefited. Six of the nine were moving toward rapid recovery and had very much improved. The remaining three were improving consistent with increasing doses of desiccated thyroid. The average maintenance dose of desiccated thyroid was 300mg per day.

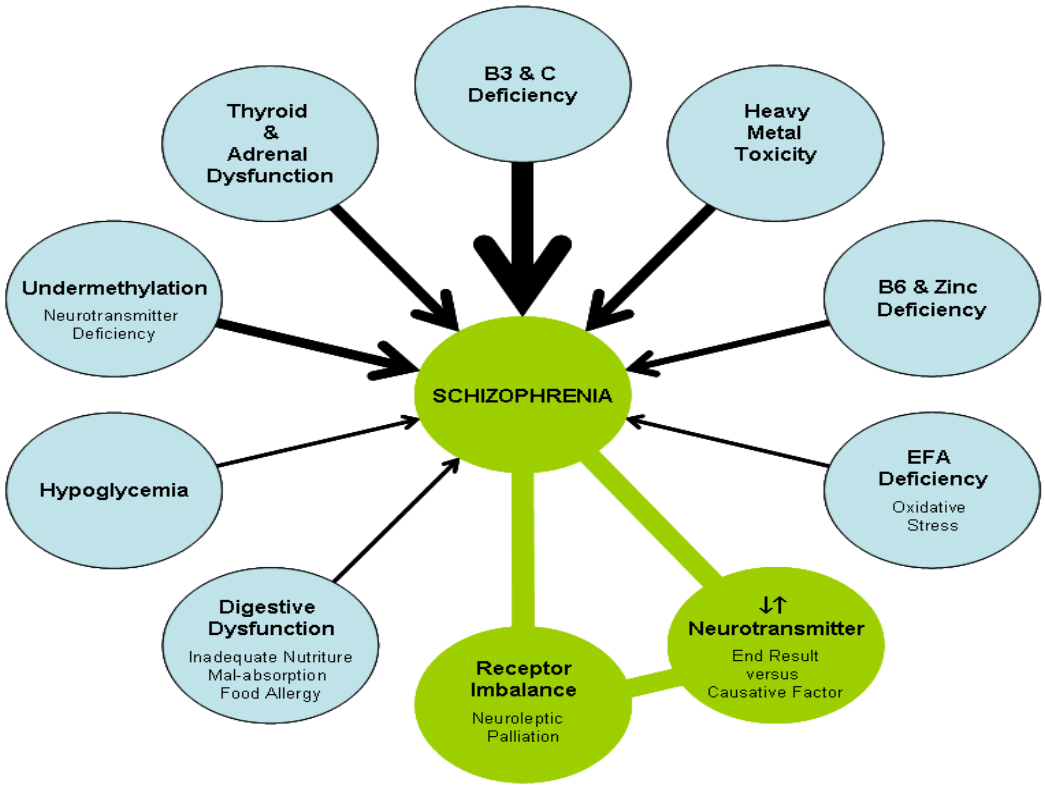
As adrenochrome reducing nutrients, vitamin B3 and C play a key role in reducing the oxidative stress on the thyroid gland. This thyroid link may explain in part, why vitamin B3 and C yield such good success in treatment. As a final note on thyroid function, blood testing can help rule out the hyper-functioning state typical of Grave's Disease.[58] Grave's, in its active phase, is a state of thyroid hyperfunction and botanicals are very useful in calming thyroid function and preventing surgery and irradiation. In low thyroid states, botanical interventions are very useful to help support and restore the thyroid gland and peripheral conversion.

Overview

Figure 1 is a schematic of the key causative factors of schizophrenia. Modern research continually confirms that these factors are important to schizophrenic pathophysiology. This is why, in support of Dr Hoffer's original work, we now see down-regulated niacin receptors

in the anterior cingulate cortex of schizophrenics.[86] The list of assessments and treatments described herein are not exhaustive but, represent the core considerations of optimal complementary treatment for schizophrenia. Orthomolecular treatment can be implemented safely as an adjunct to conventional psychiatric therapy. Schizophrenics treated with orthomolecular medicine experience positive changes. Response is based on the degree of severity and the duration of illness. We see schizophrenics who have been sick for a year or two who start responding within weeks. Schizophrenics sick over 5 years are less responsive initially but, improve with long term care. The pathological deterioration of brain tissue in schizophrenia should impel us to use orthomolecular treatment to keep oxidative stress at bay. The necessity of early screening and early intervention is important for both orthomolecular and conventional psychiatric treatment. In first-episode cases, a cocktail of desiccated thyroid (or T3-SR), vitamin B3, and vitamin C may the best early detection-intervention program ever developed. Complementary treatments for schizophrenia have been in the workings since the 1930s. A large outcome study is needed to compare the efficacy of orthomolecular treatment versus psychiatric medication. Orthomolecular treatment should play a key role in mainstream mental health care and schizophrenic patients/families constantly express their desire to see that happen.[87,88] Conventional mental health costs are exorbitant in comparison to orthomolecular treatment costs and the potential for improved quality of life should empower practitioners to be steadfast in addressing core underlying biochemistry.[89]

Figure 1. Schizophrenia: Summary of Causative Factors



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