ORTHOMOLECULAR TREATMENT FOR DEPRESSION, ANXIETY, & BEHAVIOR DISORDERS

 Dr. Raymond J. Pataracchia B.Sc., N.D.

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

(416)944-8824 (T); (647)439-1551 (F); www.nmrc.ca; info@nmrc.ca

Orthomolecular medicine can be helpful in treating the biochemical imbalances of mood and behaviour disorders. This broad grouping of disorders includes anxiety, severe depression, bipolar disorder, postpartum depression, hormonal depression, other endogenous depressions (cyclothymia, seasonal affective disorder), OCD, ADHD, ODD and, addictive behavior.

Mood and behavior disorders have similar nutritional imbalance profiles and there is much overlapping of diagnoses. Anxiety for example, often coexists with depression. Depression often involves negative thought rumination and sadness. Stoic depressives rarely smile and are locked in despair often with suicidal thoughts. Suicidal propensity is global in patients with depression, anxiety, and behaviour disorders. Obsessive thinking is commonly found in anxiety disorder but, is not diagnostic for obsessive compulsive disorder (OCD) unless it is so severe that it profoundly interferes with thinking and behaviour. People with addictive behaviour are often having co-existing mood dysfunction, behavior disorders, or schizophrenia. Addictive behaviour ranges from the realm of illicit substance use and alcoholism to the compulsive behaviours of gambling and sexual addiction. Anxiety is often an over-stimulated state and, in advanced stages, becomes disruptive. Anxiety can be associated with phobic disorders and schizophrenia. Over-stimulated states of anxiety are typically not productive. Conversely, in bipolar/manic depression, over-stimulated states (mania) are often productive and patients report accomplishing tasks with immense intensity and creativity; great artists for example, could paint a masterpiece overnight. In bipolar disorder, patients cycle with a deep depressive burn out phase. In depression and anxiety we often see inattention which can be mild or, in severe cases, interfere with thought processing. Advanced inattention can be seen as a pure component of ADHD (childhood or adult). Inattention can be due to thought blocking which is an interruption in the processing of thoughts for periods of time; thought blocking is common in heavy metal toxicity. Irritability is found globally in all mental illness categories. Anger and irritability are often linked to the 'stuckedness' of depression and hypoglycemia. Anger can extend into the realm of criminal behaviour.

Neurotransmitter deficiency syndromes are common in mood and behaviour disorders. Depression is used here as a classic example of a neurotransmitter deficiency syndrome. Based on current research, mixed neurotransmitter theory states that depression (including bipolar depression) is caused by reduced numbers of brain neurotransmitters. Serotonin and the catecholamines are master neurotransmitters. The

catecholamines include dopamine, norepinephrine, and epinephrine. Conventional drug treatments attempt to increase synaptic availability of one or both neurotransmitter pathways with SSRI's, NRI's, or SNRI's. However, these drugs depend on having enough neurotransmitter to do the job.[1] In clinical practice we see many patients on medications that either are not working or have been working less effectively with increased use and, in such cases, there is often an increase in dosage, medication change or, another medication added. Conventional medication does not act to increase the total number of neurotransmitters and, in an attempt to increase synaptic levels - by keeping neurotransmitters in the cleft - there is further neurotransmitter depletion. As these medications increase the synaptic concentration of neurotransmitters, there is an opposing natural breakdown of neurotransmitters mediated by MAO and COMT homeostatic regulation. The end result is a further depletion of already low neurotransmitter levels. Many mood and behaviour disorder patients are caught up in this neurotransmitter deficiency state.

Biochemical syndromes of importance in mood and behaviour disorders are those that ultimately influence neurotransmitter production, release, inhibition, and signal transduction.[1]Various segments of the mood and behaviour disorder 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 B3 deficiency, vitamin C deficiency, heavy metal toxicity, B6 deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia. Orthomolecular medicine has a key role in the treatment of mood and behaviour disorders. The goal of orthomolecular medicine is to correct the causative factors that influence biochemistry.

UNDER-METHYLATED MOOD & BEHAVIOR DYSFUNCTION

The brain requires efficient methylation status to form neurotransmitters on demand. Methylation is a basic chemical reaction involving among other things, neurotransmitter manufacturing at the DNA promoter region.[2] Poor methylation status is quite common in mood and behaviour disorders.[2-5] The under-methylated syndrome are a neurotransmitter deficiency syndrome.

In our clinic, we see a good portion of mood and behaviour disorder patients with methylation compromise as indicated by elevated fasting homocysteine levels. In mood and behaviour disorders, researchers are aware that certain brain tracts are overstimulated while others are understimulated. Every patient is different and some are low in serotonin versus the catecholamines (dopamine, norepinephrine, epinephrine), and vice versa. If we can methylate efficiently, we have the machinery to form neurotransmitters in brain areas that are understimulated and neurotransmitter deficient.

Orthomolecular treatment with B12, folic acid, and other methyl donor nutrients can restore methylation status.[5] Methyl donor treatment respects the brain's innate ability to 'decide' what specific pathways need more neurotransmitter. This "innate specificity" is in direct contrast to conventional psychotropic medication whose influence on given brain pathways is fixed, non-flexible and, often with side-effects due to lack of specificity.

In mood and behaviour disorders, investigators have found genetic polymorphisms that disrupt folic acid pathways.[6] These patients have a greater need for folic acid supplementation. High homocysteine levels are an excellent indication of B12 and folic acid deficiency status.[7] Depressed patients with low folic acid levels that do not respond well to anti-depressants often, improve significantly with folic acid supplementation. High B12 levels are similarly associated with improved outcome in depression.

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. This type of excitotoxicity with its corresponding mood and cognitive deficits is associated with aging and dementia.[8]

HEAVY METAL MOOD & BEHAVIOR DYSFUNCTION

It is not uncommon to see toxic levels of lead, mercury, aluminum, and copper on lab test results of mood and behaviour disorder patients. Most heavy metals are free radicals that induce oxidative stress (lipid peroxidation) and have a direct affinity for brain tissue.[9,10]Heavy metal free-radicals have the ability to compromise brain tissue structure and metabolism. Toxic metal imbalances are associated with mood and behavior disorders.[11-13]

Heavy metals make the body's metal removing protein, metallothionein, work hard to excrete them.[11,14,15] In the process of ridding heavy metals, this protein loses zinc which further compromises the ability to transcribe brain proteins including neurotransmitters. Zinc deficiency is a well know condition associated with central nervous system disorders and mental health.

If you are a city dweller, you have been exposed to lead. Lead is found in paints, glass, baterries, rust protectants, alloys, water pipes, and old bathtubs. Lead levels can be toxic to patients with behavior dysfunction, mood disorder, insomnia, and immune compromise.[16]Lead toxicity readily disrupts opiod neurotransmitter and neurohormonal function.[13] The opioid system has physiological role in the regulation of mood and stress responses, pain, locomotion, thermoregulation, respiration, diuresis, cardiovascular function, and digestion.Lead has a negative effect on verbal memory and motor movement.[17] Lead's antagonism with calcium interferes with neurotransmitter release, second messenger systems, calcium channel transport, and mitochondrial uptake.[15]

Mercury can be toxic in patients with mood and behavior disorders, nervous irritability, and memory decline.[16] Lab results are often confirming the mercury toxicity. Mercury toxicity is associated with reduced neuronal uptake of dopamine and norepinephrine.[18] Mercury is found in dental fillings, flourescents, vaccines, thermometers, fish, animals, and plants. Selenium is useful in combating mercury toxicity.[15]

Aluminum can be toxic in patients with mood and behavior disorders and, digestive pathologies. Aluminum sources include aluminum cookware (especially when you heat and deglaze with an acid like vinegar or wine), drinking boxes, processed cheese, deoderants, and drinking water.[16,19] Aluminum is more soluble in our acidic magnesium deficient drinking water.

Copper toxicity is prevalent in behaviour disorders, depression, and anxiety.[12,16,20,21] Copper toxicity is routinely found on lab results of this patient population. Copper's role in the formation of oxidized serotonin intermediates may play a role in altering mood, behaviour, and sleep.[12] It seems that serotonin's opposing neurotransmitter system, the catecholamine system, is elevated in copper toxicity. Copper excess causes dopamine levels to rise because copper is a cofactor of dopamine synthesis. Copper can therefore over-stimulate the brain and paranoia is also associated with copper elevation. In ADHD and learning disability, we see right brain copper dominance which is associated with visuo-spatial creativity; conversely, left brain dominance is associated with the verbal-analytical intellectual skills that are highly regarded in schools for evaluating academic performance. Blood estrogen levels rise when copper is in excess and may be associated with female hormonal depression.[22] Copper toxic patients typically have adrenal and thyroid compromise and therefore retain copper. Niacin, vitamin C, and zinc are important nutrients in copper toxic cases because they are physiologically antagonistic to copper. 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 implemented in modern homes and, due to widespread use ofbirth control pills (estrogen) which maintain high systemic copper levels that are thought to transfer via placenta from generation to generation. Other sources include copper tea pots, copper sulphate treated jacuzzi's or swimming pools, drinking water, prenatal vitamins, and copper IUD's. Drugs such as neuroleptics, antibiotics, antacids, cortisone, Tagamet®, Zantac®, and diuretics can exacerbate copper overload.

Orthomolecular medicine can be used to eliminate heavy metals. In most cases, the elimination of metal toxins must be done gradually to avoid excessive over-spill of toxins into the blood. Metals that are mobilized in the bloodstream need to be eliminated efficiently and, this job falls on the liver, kidneys, and bowel. In clinical practice, we support the thyroid, adrenal, liver, kidneys, and bowel to maximize the

efficient removal of the metal via gastro-intestinal routes, biliary routes, etc. Patients with toxic metals need to avoid specific environmental exposures and food supply sources.

'Brain Hypothyroidism' and Hypoadrenic Mood & Behavior Dysfunction

The thyroid and adrenal glands are compromised in the majority of mental health cases. Both the thyroid and the adrenal gland are grouped together here because they are influential endocrine glands that work together by negative feedback mechanisms. Typically both glands are sluggish and many symptoms common to adrenal dysfunction are seen in thyroid dysfunction, and vice versa.

The adrenal glands play a major role in stress response, sugar metabolism, electrolyte balance, blood pressure regulation, and sex hormone metabolism. Hypothalamic-Pituitary-Adrenal axis dysregulation is integrally associated with anxiety and depression.[23,24] The adrenal works in concert with the thyroid gland and often both glands need support.[25,26]Many people who are heavy coffee drinkers have weak adrenals. Low adrenal function symptoms include sluggishness on waking, stress intolerance, lack of enjoyment, post-traumatic stress, addiction, dizziness, low blood pressure, fluctuant body temperature, insomnia at 4am, multiple chemical sensitivity, hypoglycemia, skin conditions, PMS, phobias, and poor sex drive. Adrenal symptoms and orthostatic blood pressure are good indicators of adrenal status and, in some cases, saliva testing is useful.

Low thyroid symptoms are commonly seen in mood disorder cases and often in psychosis.[23,27-33] Stress influences thyroid metabolism and we tend to conserve energy by shutting down active thyroid hormone production. Active thyroid hormone is responsible for enabling our cells to maintain high metabolic rates. Thyroid hormone also maintains oxygen availability. With healthy thyroid hormone functioning, our cells produce energy and complete their tasks efficiently. When cells have energy, body systems work optimally. The brain is highly dependent on thyroid hormone for the regulation of dopamine, norepinephrine, and serotonin pathways.[28,34,35]

The most common symptoms of low thyroid function are fatigue, insomnia, depression, anxiety, impaired cognition, irritability, poor memory, easy weight gain, pain, headache, indigestion, hair loss, high cholesterol, frequent infection, constipation, and in women, PMS.[23,29,36,37] Many patients with varied non-specific complaints have low thyroid function. Chronic fatigue and fibromyalgia are not uncommon in mood disorder patients. Muscle pain syndromes (such as fibromyalgia) are also often associated with low thyroid function because muscle cells require ATP (the energy molecule provided indirectly by peripheral thyroid hormone metabolism) to relax. Chronic fatigue symptoms, at least in part, are also often explained by low thyroid function.

The digestive system of a low thyroid patient has poor motility and slow stool transit which cause constipation and inefficient nutrient absorption.[38] In low thyroid patients, core body temperatures are often so low that digestive enzymes do not reach the reaction threshold to enable efficient food breakdown. With optimal thyroid treatment, mood and behaviour dysfunction patients do not require as high a dose of nutrients because absorption improves. Magnesium can be used to help improve peristaltic movement, draw water into the lower bowel, and avert tenesmus.

Thyroid support is becoming accepted as an integral part of the assessment and treatment of refractory depression.[29,39] The brain is highly dependent on thyroid hormone for the regulation of dopamine, norepinephrine, and serotonin pathways.[28,34,40] "Brain hypothyroidism" has been described by Hatterer et al as a state that occurs when systemic T4 does not readily cross into the brain.[40] Active thyroid hormone T3 is synthesized in the brain by brain typeII 5'-deiodinase conversion of T4 to T3.[39,41] 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.[41] Reduced cerebral spinal fluid (CSF) transthyretin is seen in depression and suicidal propensity.[42,43] CSF Transthyretin is also downregulated in schizophrenia.[44] Many schizophrenics and depressives relapse when thyroid function drops.[23] This suggests that mood and perceptual dysfunction are associated with a lack of adequate T4 in the brain. Without adequate T4, brain cells remain hypo-metabolic and this can, among other things, reduce neurotransmitter synthesis and disrupt the regulation of dopamine, norepinephrine, and serotonin.

Huang et al suggested that low CSF transthyretin could prove useful as a biomarker for early diagnosis of bipolar disorder and psychotic depression.[45] Also of interest is the fact that lead toxicity has been linked to the reduction of CSF transthyretin in humans.[46,47]

Peripheral blood thyroid levels could be normal in the context of brain hypothyroidism. T4 to T3 conversion by brain typeII 5'-deiodinase can be inhibited by cortisol.[38,48] This is important because cortisol levels are commonly elevated in mood dysfunction, especially during stress. Cortisol is a stress hormone and, during stressful periods we tend to conserve energy by shutting down thyroid hormone production.

The faster the metabolic rate, the higher the temperature and therefore, one of the best methods for assessing thyroid function is measuring body temperature.[49] When the body temperature is adequate, the enzymes in our body, including the digestive enzymes, form chemical reactions with greater ease. If cells are working slowly and producing minimal energy, they don't give off a large amount of heat and body temperature remains low. Intolerance to cold is a typical complaint in cases of low thyroid.[23] It is not uncommon to have male patients reporting that they feel warm when, in fact, their body temperature measures are clearly low. Some people may have

fluctuant temperatures where they feel warm at times yet are cold at other times; this inability to adapt to temperature (decreased heat tolerance) is indicative of low adrenal function which, is typically associated with low thyroid function.[50]

Note that 'hypothyroidism' is a problem with the gland itself and more specifically, with its inability to produce adequate thyroid hormone. In classic hypothyroidism, blood tests reveal that there is low output of thyroid hormone (T4 or T3) and/or elevated thyroid stimulating hormone (TSH) levels. However, low thyroid function cases may have normal blood test measures, low body temperature, and obvious low thyroid symptomology. It is not uncommon to see hypothyroid patients on thyroid hormone treatment with normal test measures and low thyroid symptoms. This can happen if adequate levels of circulating thyroid hormone (T4) are not readily converted peripherally into active thyroid hormone (T3).[29,30,51]Currently, there is no conventionally accepted diagnostic agreement on physiological states that account for normal test measures and poor peripheral conversion. Wilson's Temperature Syndrome however has emerged as a syndrome that fits that criterion. Orthomolecular interventions can help support the thyroid gland directly and also help support peripheral conversion. Orthomolecular thyroid treatment can be done safely as an adjunct to thyroid hormone medication. Blood testing can help rule out immune involvement typical of Hashimoto's thyroiditis. Hashimoto's is seen in 80% of hypothyroid cases and it responds well to low thyroid treatment. Blood testing can also help to rule out the thyroid hyper-functioning state typical in Grave's Disease. Grave's, in its active phase, is a state of thyroid hyperfunction and requires orthomolecular treatment to calm thyroid function. In mood and behaviour disorders, thyroid support has global benefits because it improves the cellular physiology of the brain, liver, gastrointestinal tract, kidney, immune system, and musculoskeletal system.

B6 and Zinc Deficient Mood & Behavior Dysfunction

Zinc and B6 are involved at a basic biochemical level in the manufacture of protein complexes, including neurotransmitters, out of simple amino acid building blocks.[52,53] B6 and zinc deficiency are clearly associated with mood and behaviour disorders and optimal doses of B6 and zinc are required to treat this condition.[54,55]

Zinc is important to several biochemical pathways as over 200 enzymes are zinc dependant. Zinc and iron are the most concentrated metals in the human brain. Insufficient levels of zinc are associated with depression, dementia, mental retardation, learning disabilities, lethargy, and apathy.[56] Zinc is essential for the synthesis of serotonin and melatonin.[57] It is crucial to brain development as it plays a major role in protein synthesis.[56,57] 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 averting oxidative damage.[57] 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.[58] Zinc has a role in biogenic amine storage 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. Zinc is involved in limbic system metabolism which regulates emotions. Hormonal metabolism of the hypophysis and hypothalamus are dependant on zinc as well.

B6 is involved in the decarboxylation of tyrosine, tryptophan, and histadine into the neurotransmitters nor-epinephrine, serotonin, and histamine.[55] It is a cofactor in homocysteine re-methylation.[59] B6 has been found useful in memory acquisition, with just a 20mg dose.[60] B6 is essential for the synthesis of antioxidants such as metallothionein, glutathione, and CoQ10 which help to prevent neuronal oxidative stress. B6 (and zinc) are involved in the synthesis of glutamic acid decarboxylase (GAD) which blocks excitotoxicity which causes secondary oxidative damage. B6 is essential for glutathione peroxidase and glutathione reductase which help prevent mitochondrial decay.

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 which is readily excreted.[61-65]

Hypoglycemic Mood & Behavior Dysfunction

Hypoglycemia is the term that describes low sugar in the blood. 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.[66]The brain has a great demand for sugar and doesn't like to be starved for long. Neurons function poorly in sugar deficient states. 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. Irritability, poor memory, "late afternoon blues", poor concentration, tiredness, cold hands, muscle cramping, and "feeling better when fighting" are typical hypoglycemic symptoms.[61]

Mono-croping of grains and resultant 'saccharine diseases' have lead to serious problems in society today including depression and carbohydrate neuroses.[67]

Diabetic or pre-diabetic cases also exhibit hypoglycemic symptoms. Mood and behaviour disorder patients with hyperglycemia, much like diabetics, present with hypoglycemic mental symptoms because glucose doesn't get into the brain neurons. Brain neurons starved for energy behave differently resulting in mood and cognitive dysfunction.[68,69] It is not clear if dysglycemia has a causative role in mood and behaviour dysfunction 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 mood and behaviour disorder patient requires three solid meals (of 40% protein) a day and sometimes additional protein-containing snacks. Many patients need to be educated about 'complex' versus 'fast' carbohydrates (e.g. avoiding junk food and sugar). When they increase 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.

Essential Fatty Acid Deficient Mood & Behavior Dysfunction

Depression, anxiety, bipolar disorder, ADHD, and behavior disorders are benefited by EFA supplementation.[70] EFA's, including omega-3 (DHA & EPA) and omega-6, are good fats, not saturated with hydrogen, and unfortunately not readily provided in the American diet. 60% of the dry weight of the brain is fat. EFA's are important components of nerve cell walls and are involved in neurotransmitter electrical activity and post-receptor phospholipid mediated signal transduction. DHA and EPA have proven the most useful in the clinical treatment of mood and behavior disorders.[71-73]

Inadequate Nutriture, Digestive Compromise, and Mal-absorption in Mood & Behavior Dysfunction

Neurotransmitter production is dependant on amino acid protein building blocks (phenylalanine, tyrosine, tryptophan, 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 mood and behaviour disorder and, general mental well-being. I have seen many mood and behaviour disorder patients 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 many patients.

Many mood and behaviour disorder patients 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. Such patients do well to avoid high glycemic load foods including junk food, white sugar, white rice, and white bread. If they have poor appetite, this can lead to inadequate nutriture. Poor appetite may be associated with zinc or iron loss.

Fat nutriture is important in mood and behaviour disorders. Cold water fish with teeth have a fat profile suitable for these patients. 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. I constantly see gastrointestinal problems in mood and behaviour disorders; symptoms include 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 medication. 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 for the average adult is about two litres per day. This is essential to keep toxins moving out and bowel contents hydrated. Orthomolecular 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 mood and behaviour dysfunction.

Food Intolerant Mood & Behavior Dysfunction

Mood and behaviour disorder patients have the potential to exhibit mild to severe food intolerance symptoms and we see this commonly in the general population.[74-77] 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.[78,79] I have several clients who have an increased severity and frequency of depression, anxiety, irritability, and insomnia when they eat intolerant foods. We see mood and behaviour disorder patients that experience a wide range of food related physical symptoms such as headaches, skin eruptions, palpitations, weakness, painful digestion, constipation, diarrhea, and arthralgia. Common food intolerances include gluten, dairy, eggs, tree nuts, citrus, soy, fish, legumes and crustaceans (high in copper). It is helpful to survey patient responses with a seven-day diet diary. Often mood and behaviour disorder patients 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.[74,80] 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 mood and behaviour disorder patients experience profound improvements after removing intolerant foods.

Vitamin B3 and C Deficient Mood & Behavior Dysfunction

B3 and C are anti-stress vitamins and optimal dosing is indicated for these two nutrients.[67,81]A good portion of mood and behaviour dysfunction patients do better with moderate orthomolecular doses of vitamin B3 and C.

Copper is involved in dopamine production and vitamin B3 and C are physiologically antagonistic to copper and as such, can help to moderate the overstimulation of dopamine pathways typical in mood and behaviour dysfunction. When dopamine pathways are overstimulated, serotonin (the opposing 'feel good' master neurotransmitter system) can become depleted.

Vitamin B3 and vitamin C (ascorbic acid) are centrally active in the brain as "niacinamide in the brain acts on the diazepine receptors, while ascorbic acid acts on the dopamine receptors".[67] Vitamin B3 has an anti-anxiety effect.[82]

Mood disorder and perhaps more specifically, psychotic depression, may have a sub-clinical pellagra associated vitamin B3 deficiency component as classic pellagra symptoms include depression, anxiety, confusion, memory loss, fatigue, and psychosis.[82-84]

References

1. Delgado PL, Moreno, FA: Role of norepinephrine in depression. *J Clin Psychiatry*. 2000; 61(Suppl 1): 5-12.

2. Shelton RC: The molecular neurobiology of depression. Psychiatr Clin North Am. 2007 Mar; 30(1): 1-11.

3. Herrmann W, Lorenzl S, Obeid R: [Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders--current evidence and preliminary recommendations]. Fortschr Neurol Psychiatr. 2007 Sep; 75(9): 515-27. (abstract only)

4. Herrmann W, Obeid R. Review: Biomarkers of folate and vitamin B(12) status in cerebrospinal fluid. Clin Chem Lab Med. 2007 Sep 24. (abstract only)

5. Bottiglieri T: Homocysteine and folate metabolism in depression. Prog Neuropsychopharmacol Biol Psychiatry. 2005 Sep; 29(7): 1103-12.

6. Gilbody S, Lewis S, Lightfoot T: Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review. *Am J Epidemiol*. 2007 Jan 1; 165(1): 1-13.

7. Coppen A, Bolander-Gouaille C: Treatment of depression: time to consider folic acid and vitamin B12. *J Psychopharmacol.* 2005 Jan; 19(1): 59-65.

8. Parnetti L, Bottiglieri T, Lowenthal D: Role of homocysteine in age-related vascular and non-vascular diseases. *Aging* (Milan, Italy). 1997 Aug; 9(4): 241-257.

9. Kelly G: Peripheral Metabolism of Thyroid Hormones: A Review. *Alternative Medicine Review*, 2000; 5(4): 306-333.

10. Aschner M, Cherian MG, Klaassen CD, et al: Metallothioneins in brain--the role in physiology and pathology. *Toxicol Appl Pharmacol*, 1997; 142(2): 229-242.

11. Stanley PC, Wakwe VC: Toxic trace metals in the mentally ill patients. *Niger Postgrad Med J.* 2002 Dec; 9(4): 199-204.

12. Jones CE, Underwood CK, Coulson EJ, et al: Copper induced oxidation of serotonin: analysis of products and toxicity. *J Neurochem*, 2007 Aug; 102(4): 1035-1043.

13. Kitchen I: Lead toxicity and alterations in opioid systems. *Neurotoxicology*, 1993 Summer-Fall; 14(2-3): 115-124.

14. Cai L, Li XK, Song Y, Cherian MG: Essentiality, toxicology and chelation therapy of zinc and copper. *Curr Med Chem*, 2005; 12(23): 2753-2763.

15. Goyer RA: Nutrition and metal toxicity. *Am J Clin Nutr*, 1995 Mar; 61(3 Suppl): 646S-650S.

16. Wenzel KG, Pataracchia RJ: *The earth's gift to Medicine: Minerals in health and Disease*. Alton, Ontario. KOS Publishing. 2005.

17. Pasternak G, Becker CE, Lash A, et al: Cross-sectional neurotoxicology study of lead-exposed cohort. *J Toxicol Clin Toxicol*, 1989; 27(1-2): 37-51.

18. Rajanna B; Hobson M: Influence of mercury on uptake of [3H]dopamine and [3H]norepinephrine by rat brain synaptosomes. *Toxicol Lett*, 1985 Sep; 27(1-3): 7-14.

19. Foster HD: *What really causes Alzheimer's Disease?* 2004. (A pdf of the book is available at www.hdfoster.com.)

20. Pfeiffer CC: Excess copper as a factor in human diseases. *J Ortho Med*, 1987; 2(3): 171-182.

21. Pfeiffer CC, Iliev V: Pyrroluria, urinary mauve factor, causes double deficiency of B6 and zinc in schizophrenics. *Fed Proc*, 1973; 32: 276.

22. Gittleman AL: *Why am I always so tired?* New York, NY. HarperSanFrancisco. 1999.

23. Heinrich TW, Grahm G: Hypothyroidism Presenting as Psychosis: Myxedema Madness Revisited. *Prim Care Companion J Clin Psychiatry*, 2003 Dec; 5(6): 260-266.

24. Mello AA, Mello MF, Carpenter LL, et al: Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis.*Rev Bras Psiquiatr*, 2003 Oct; 25(4): 231-238.

25. Abdullatif HD, Ashraf AP: Reversible subclinical hypothyroidism in the presence of adrenal insufficiency. *Endocr Pract*, 2006 Sep-Oct; 12(5): 572.

26. Candrina R, Giustina G: Addison's disease and corticosteroid-reversible hypothyroidism. *J Endocrinol Invest*, 1987 Oct; 10(5): 523-526.

27. Contreras F, Menchon JM, Urretavizcaya M, et al: Hormonal differences between psychotic and non-psychotic melancholic depression.*J Affect Disord*, 2007 Jun; 100(1-3): 65-73.

28. Bauer M, London ED, Silverman DH, et al: Thyroid, brain and mood modulation in affective disorder: insights from molecular research and functional brain imaging. *Pharmacopsychiatry*, 2003 Nov; 36 Suppl 3: S215-S221.

29. Jackson IM: The thyroid axis and depression. *Thyroid*, 1998 Oct; 8(10): 951-956.

30. Haggerty JJ, Stern RA, Mason GA, et al: Subclinical hypothyroidism: a modifiable risk factor for depression? *American Journal of Psychiatry*, 1993; 150: 508-510.

31. Monzani F, Del Guerra P, Caraccio N, et al: Subclinical hypothyroidism: neurobehavioral features and beneficial effect of l-thyroxine treatment. *Clinical Investigator*, 1993; 71: 367-371.

32. Toffe RJ, Levitt AJ: Major depression and subclinical (grade 2) hypothyroidism. *Psychoneuroendocrinology*, 1992; 17: 215-221.

33. McGaffee J, Barnes MA, Lippmann S: Psychiatric presentations of hypothyroidism. *Am Fam Physician*, 1981 May; 23(5): 129-133.

34. Haddow JE, Palomaki GE, Allan WC, et al: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*, 1999 Aug 19; 341(8): 549-555.

35. Brouwer A, Morse DC, Lans MC, et al: Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. *Toxicol Ind Health*, 1998 Jan-Apr; 14(1-2): 59-84.

36. Westphal SA: Unusual presentations of hypothyroidism. *Am J Med Sci*, 1997 Nov; 314(5): 333-337.

37. Heitman B, Irizarry A: Hypothyroidism: common complaints, perplexing diagnosis. *Nurse Pract*, 1995 Mar; 20(3): 54-60.

38. Shafer RB, Prentiss RA, Bond JH: Gastrointestinal transit in thyroid disease. *Gastroenterology*, 1984 May; 86(5 Pt 1): 852-855.

39. Oppenheimer JH, Braverman LE, Toft A, et al: A therapeutic controversy. Thyroid hormone treatment: when and what? *J Clin Endocrinol Metab*, 1995; 80(10): 2873-2883.

40. Hatterer JA, Herbert J, Hidaka C, et al: CSF transthyretin in patients with depression. *Am J Psychiatry*, 1993; 150(5): 813-815.

41. Schreiber G: The evolutionary and integrative roles of transthyretin in thyroid hormone homeostasis. *J Endocrinol*, 2002; 175(1): 61-73.

42. Sullivan GM, Mann JJ, Oquendo MA, et al: Low cerebrospinal fluid transthyretin levels in depression: correlations with suicidal ideation and low serotonin function. *Biol Psychiatry*, 2006; 60(5): 500-506.

43. Sullivan GM, Hatterer JA, Herbert J, et al: Low levels of transthyretin in the CSF of depressed patients. *Am J Psychiatry*, 1999; 156(5): 710-715.

44. Wan C, Yang Y, Li H, et al: Dysregulation of retinoid transporters expression in body fluids of schizophrenia patients. *J Proteome Res*, 2006; 5(11): 3213-3216.

45. Huang JT, Leweke FM, Oxley D, et al: Disease biomarkers in cerebrospinal fluid of patients with first-onset psychosis. *PLoS Med*, 2006; 3(11): e428.

46. Zheng W, Lu YM, Lu GY, et al: Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: effect of lead exposure. *Toxicol Sci*, 2001; 61(1): 107-114.

47. Zheng W, Blaner WS, Zhao Q: Inhibition by lead of production and secretion of transthyretin in the choroid plexus: its relation to thyroxine transport at blood-CSF barrier. *Toxicol Appl Pharmacol*, 1999; 155(1): 24-31.

48. Visser TJ, Leonard JL, Kaplan MM, et al: Kinetic evidence suggesting two mechanisms for iodothyronine 5'-deiodination in rat cerebral cortex. *Proc Natl Acad Sci USA*, 1982; 79(16): 5080-5084.

49. Barnes BO, Galton L: *Hypothyroidism: The Unsuspected Illness*. New York, NY. Harper & Row. 1976.

50. Michel V, Peinnequin A, Alonso A, et al: Decreased heat tolerance is associated with hypothalamo-pituitary-adrenocortical axis impairment. *Neuroscience*, 2007 Jun 29; 147(2): 522-531.

51. Lum SM, Nicoloff JT, Spencer CA, et al: Peripheral tissue mechanism for maintenance of serum triiodothyronine values in a thyroxine-deficient state in man. *J Clin Invest*, 1984 Feb; 73(2): 570-575.

52. Bourre JM: Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. *J Nutr Health Aging*, 2006 Sep-Oct; 10(5): 377-385.

53. Cuajungco MP, Lees GJ: Zinc metabolism in the brain: relevance to human neurodegenerative disorders. *Neurobiol Dis*, 1997; 4(3-4): 137-169.

54. Sahley, BJ. Nutrition and Mental Illness. *MMRC Health Educator Reports*, 2006: 1-2.

55. Marz RB: *Medical Nutrition from Marz*. Portland, OR. Omni-Press. 1997.

56. Pfeiffer CC, Braverman ER: Zinc, the brain and behavior. *Biol Psychiatry*, 1982; 17(4): 513-532.

57. Johnson S: Micronutrient accumulation and depletion in schizophrenia, epilepsy, autism and Parkinson's disease? *Med Hypotheses*, 2001; 56(5): 641-645.
58. Noseworthy MD, Bray TM: Zinc deficiency exacerbates loss in blood-brain barrier integrity induced by hyperoxia measured by dynamic MRI. *Proc Soc Exp Biol Med*, 2000; 223(2): 175-182.
59. Levine J, Stahl Z, Sela BA, et al: Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biol Psychiatry*, 2006; 60 (3): 265-269.
60. Deijen JB, van der Beek EJ, Orlebeke JF, et al: Vitamin B-6 supplementation in elderly men: effects on mood, memory, performance and mental effort. Psychopharmacology (Berl), 1992; 109(4): 489-496.
61. Wenzel K-G: Orthomolecular Treatment for Mental Health: The Roles of Hypoglycemia, Pyrroluria and Histamine Disturbances. 2000 Apr. Nutritional Medicine Today 29th Annual Conference. Vancouver, BC.
62. Jackson JA, Riordan HD, Neathery S, et al: Case from the Center: Urinary Pyrrole in Health and Disease. *J Orthomol Med*, 1997; 12(2): 96-98.
63. Edelman E: *Natural Healing for Schizophrenia: A Compendium of Nutritional Methods*. Eugene, OR. Borage Books. 1996.
64. Pfeiffer CC: *Mental and Elemental Nutrients*. New Canaan, CN. Keats Publishing. 1975.
65. Sohler A, Beck R, Noval JJ: Mauve factor re-identified as 2,4-dimethyl-3-ethylpyrrole and its sedative effect on the CNS. *Nature*, 1970; 228(278): 1318-1320.
66. Rao J, Oz G, Seaquist ER: Regulation of cerebral glucose metabolism. *Minerva Endocrinol*, 2006 Jun; 31(2): 149-158.
67. Hoffer A: *Orthomolecular Medicine for Physicians*. New Canaan, CT. Keats Publishing. 1989.
68. Cox D, Gonder-Frederick L, McCall A, et al: The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes. *Int J Clin Pract Suppl*, 2002 Jul; 129: 20-26.
69. Mitrakou A, Ryan C, Veneman T, et al: Hierarchy of glycemic thresholds for counter regulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol*, 1991 Jan; 260(1 Pt 1): E67-E74.
70. Greenwood CE, Young SN: Dietary fat intake and the brain: a developing frontier in biological psychiatry. *J Psychiatry Neurosci*, 2001 May; 26(3): 182–184.
71. McNamara RK, Carlson SE: Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukot Essent Fatty Acids*, 2006 Oct-Nov; 75(4-5): 329-349.
72. Kidd PM: Bipolar disorder and cell membrane dysfunction. Progress toward integrative management. *Altern Med Rev*, 2004 Jun; 9(2): 107-135.
73. Ranjekar PK, Hinge A, Hegde MV, et al: Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res*, 2003 Dec 1; 121(2): 109-122.
74. Hardman G, Hart G: Dietary advice based on food-specific IgG results. *Nutrition & Food Science*, 2007; 37(1): 16-23.
75. Jackson JA, Neathery S, Kirby R: Hidden Food Sensitivities: A Common Cause of Many Illnesses. *J Orthomol Med*, 2007; 22(1): 27-30.
76. Crowe SE, Perdue MH: Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. *Gastroenterology*, 1992 Sep; 103(3): 1075-1095.
77. Hall K: Allergy of the nervous system: a review. *Annals of Allergy*, 1976 Jan; 36(1): 49-64.
78. Takahashi M, Fukunaga H, Kaneto H, et al: Behavioral and pharmacological studies on gluten exorphin A5, a newly isolated bioactive food protein fragment, in mice. *Jpn J Pharmacol*, 2000 Nov; 84(3): 259-265.
79. King DS: Psychological and behavioral effects of food and chemical exposure in sensitive individuals. *Nutr Health*, 1984; 3(3): 137-151.
80. Atkinson W, Sheldon TA, Shaath N, et al: Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut*, 2004 Oct; 53(10): 1459-1464.

81. Stone, I: *The healing factor: vitamin C against disease*. New York. Grosset and Dunlap. 1972.

82. Prousky, JE: Supplemental niacinamide mitigates anxiety symptoms: three case reports. *J Orthomol Med*, 2005; 20(3): 167-178.

83. Pitche PT: Service de dermatologie. *Sante*, 2005 Jul-Sep; 15(3): 205-208. (abstract only)

84. Hoffer A: Vitamin B-3 Dependency: Chronic Pellagra. *Townsend Letter for Doctors & Patients*. 2000 Oct; 207: 66-73.