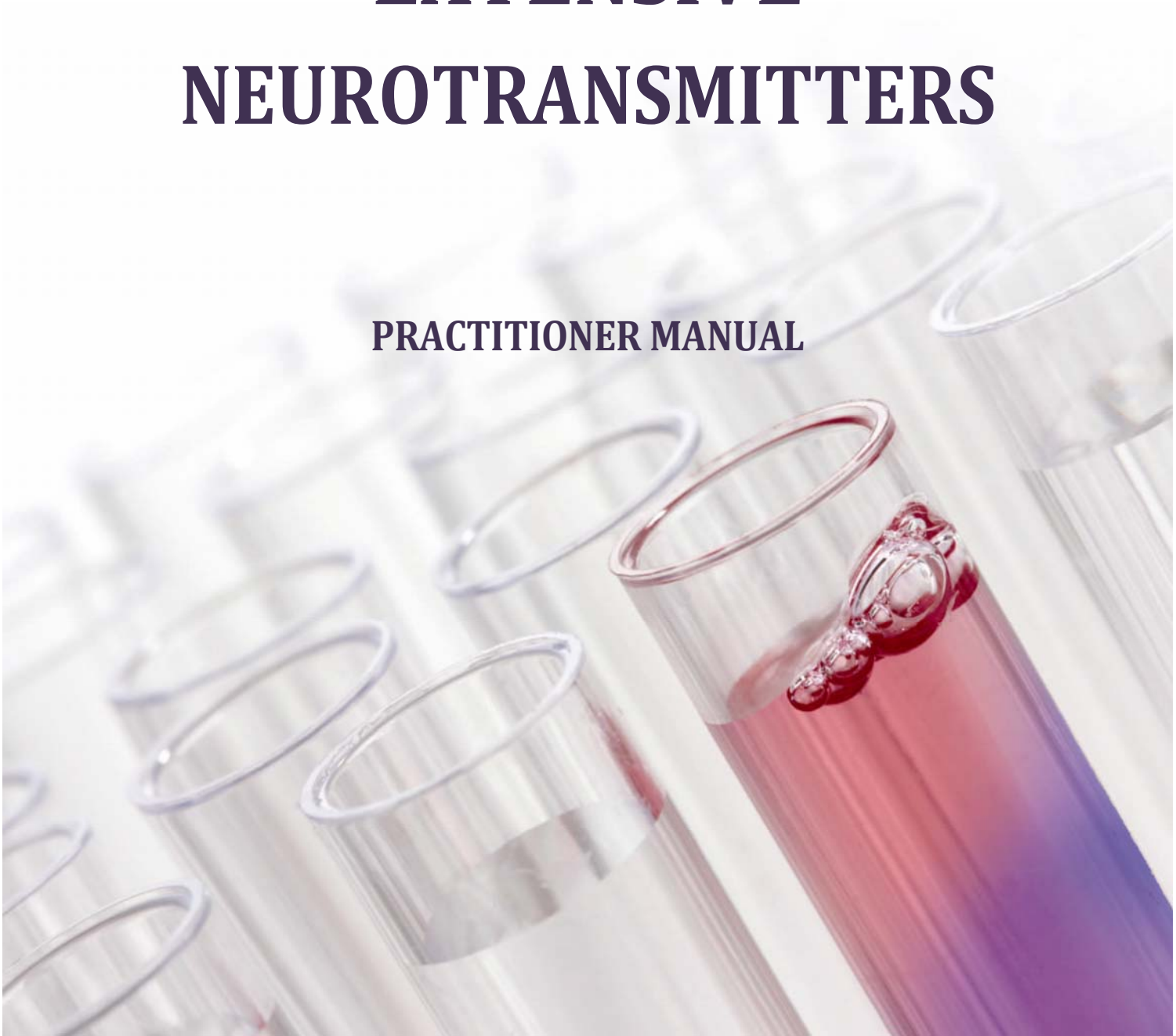
NutriPATH

INTEGRATIVE PATHOLOGY SERVICES

EXTENSIVE NEUROTRANSMITTERS

PRACTITIONER MANUAL



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V2.0

Contents

EXTENSIVE NEUROTRANSMITTERS

We are in a Sad Mood Epidemic

Does any one or more of these statements describe your patients?

- They feel irritable, anxious, depressed and isolated;
- They have tried anti-depressants and they are not working properly;
- The anti-depressants they're on is causing them to have side effects;
- Their depression/anxiety is affecting their relationships and/or work performance;
- They no longer take pleasure in activities they once enjoyed;
- Their libido, appetite and sleep patterns are disturbed;
- They worry more than they should and have problems concentrating or staying focused on conversations or tasks at hand;
- They are losing or gaining weight faster than usual.

If the answer is **YES** to any one or combination of these, your patients may be suffering from one or a combination of mood disorders including anxiety and/or depression.

With life becoming more pressured and fast paced, the development of mood disorders and associated mental health decline are on the increase. It has been recognised that around 1 in 5 Australians aged 16–85 years suffer from some form of mental illness.

The rates for medically diagnosed anxiety and depression have tripled in the last 10-15 years. Mental health disorders are also recognised as a disability legally upheld under the Mental Health Act. If left untreated, the effects of chronic stress, anxiety or depression may become quite debilitating, often leading to progressive cognitive decline and physical or mental disability.

Like many other disease processes, there are commonly multiple underlying factors involved in the development of mood disorders. Some of these may include:

- Hormonal imbalances involving thyroid, adrenal and sex hormones;
- Disturbed neurotransmitter biochemistry, particularly affecting GABA, glutamate, dopamine, noradrenaline and serotonin pathways;
- Nutritional impairment – either by poor food choices, gut dysbiosis or malabsorption;
- Environmental factors including both heavy metal and environmental chemical poisoning;
- Genetic factors involving polymorphisms in key genes regulating neurotransmission pathways.

All of the following chemicals may affect our moods, memory and cognitive processes:

- Neurotransmitters – GABA, glutamate, dopamine, serotonin, adrenaline and noradrenaline;
- Thyroid, sex and adrenal hormones, including Cortisol and DHEA(s);
- MTHFR and methylation co-factors e.g. Formiminoglutamic acid (FIGLU), Methylmalonic acid (MMA) - folate and B12 metabolites;
- Amino acids – especially tryptophan, tyrosine and phenylalanine;
- Antioxidants, vitamins and minerals;
- C-reactive protein, interleukins and various inflammatory biomarkers;
- Histamine;
- Kryptopyrroles (Mauve factor);
- Heavy metals and/or environmental pollutants.

DSM Model

Depression and anxiety is currently diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) recognised rating scales and primarily involves symptomatic treatment, the current screening assessment criteria for manic, bipolar, cognition, schizophrenia, ADD, ADHD, delusional disorder, suicidal ideation, etc.

DSM	YEAR	DIAGNOSIS SYMPTOMS- BASED	NUMBER OF PAGES
I	1952	107	132
II	1968	180	180
III	1989	226	226
IV	1994	365	886
V	2007	10 levels	On-line

Conventional western pharmacological therapies have an extensive variety of options available for the treatment of individuals diagnosed with mood disorders. All of these involve treatment with drugs that modulate neurotransmitter pathways. As with all medications, the response to a given agent is highly individualised, with the net result that some patients will improve, some may get worse whilst others may be unchanged. Also, there may be possible side effects which can result directly from the pharmaceuticals themselves or from interactions with other medicines that the individual may be taking concurrently.

So, what other options are there for these individuals, particularly for those whom do not improve with conventional pharmacotherapy? Are we able to uncover some of the underlying biological causes of their illness and treat the symptoms of anxiety and depression more effectively?

THE MOST COMMON DISORDERS

A detailed description of mental health disorders is expansive and continually changing. However, these are some of the commonest disorders encountered in clinical practice.

Depression

Depression is ranked as one of the top five disease burdens for men and women in Australia. Whilst drugs such as SSRIs and tricyclic antidepressants have established evidence for efficacy in adults in moderately severe depression, they have limited efficacy in milder forms of the illness. Additionally, they exhibit a significant range of toxic side effects that limit patient acceptance and/or compliance with regular dosing of these pharmaceutical preparations.

Depression is typically characterised by a persistently lowered mood state over a period of several months or more.

Common symptoms of depression include lack of motivation, low self-esteem, feeling blue, inordinate guilt, shame, worthlessness, hopelessness and despair.

Physical symptoms can include loss of weight and physical conditioning, loss of appetite, sleep disturbances, decreased libido and persistent fatigue. Whilst genetic, biological, psychological, environmental and social factors are all believed to play various roles in depression, the contribution of each factor varies from individual to individual.

Depression isn't an illness with a one cause or one treatment. For some the problem may be primarily psychological or social, for others largely biochemical. Most people experience a mixture of both.

Common biochemical imbalances that may induce a depressive illness include:

- Deficiencies of nutrients (vitamin B3, B6, methylfolate, B12, C, zinc, magnesium, copper, essential amino and fatty acids);
- Neurotransmitter imbalances (serotonin, dopamine, noradrenaline, GABA, glutamate and histamine);
- Blood sugar imbalances (often associated with excessive sugar, sugar substitutes and stimulants);
- Food allergies and sensitivities in susceptible individuals.

The presence of one or more of these factors may worsen a person's ability to cope with stress and thus be an underlying contributor to what might otherwise be considered depression of a psychological origin. Conversely, many depressed people fail to gain proper nourishment, particular in the form of necessary proteins, essential fatty acids and micronutrients required for normal neurotransmitter functioning.

Anxiety

Whilst for many people, anxiety develops in response to an imminent danger or threat (real or imagined). For some it can generate seemingly inappropriate and exaggerated responses that may result in intensely frightening attacks that can severely impact on an individual's ability to perform daily functions and sabotage their enjoyment of life.

One common form of anxiety is agoraphobia which literally means 'fear of the marketplace'. Agoraphobia often develops after an individual experiences a panic attack in a certain place or situation. The individual then develops a fear of that place or situation such that they will avoid it in the future for fear of having another episode. This avoidance can then become generalised to certain types of public place and not uncommonly, may result in sufferers becoming housebound.

One's capability to handle anxiety has as much to do with one's genetic and biochemical makeup as with one's psychological resources and stress management skills. The ratio of the major inhibitory neurotransmitter GABA to the major excitatory transmitter glutamate is most significant in this regard. Additionally, the levels of urinary noradrenaline generally reflect CNS levels, as the body's primary source of this amine is the locus coeruleus in the brainstem, located in close proximity to the fourth ventricle.

By comparison, adrenal synthesis of noradrenaline is approximately one quarter that of adrenaline, and is primarily concerned with the maintenance of vascular tone and haemodynamic stability. Excessive cortical signalling to the locus coeruleus leads to an increased output of noradrenaline, which may then influence the functioning of the amygdala and other parts of the limbic system, to generate a fear response.

Neurotransmitter testing can assist in defining these relationships and provide a rational basis for therapeutic intervention.

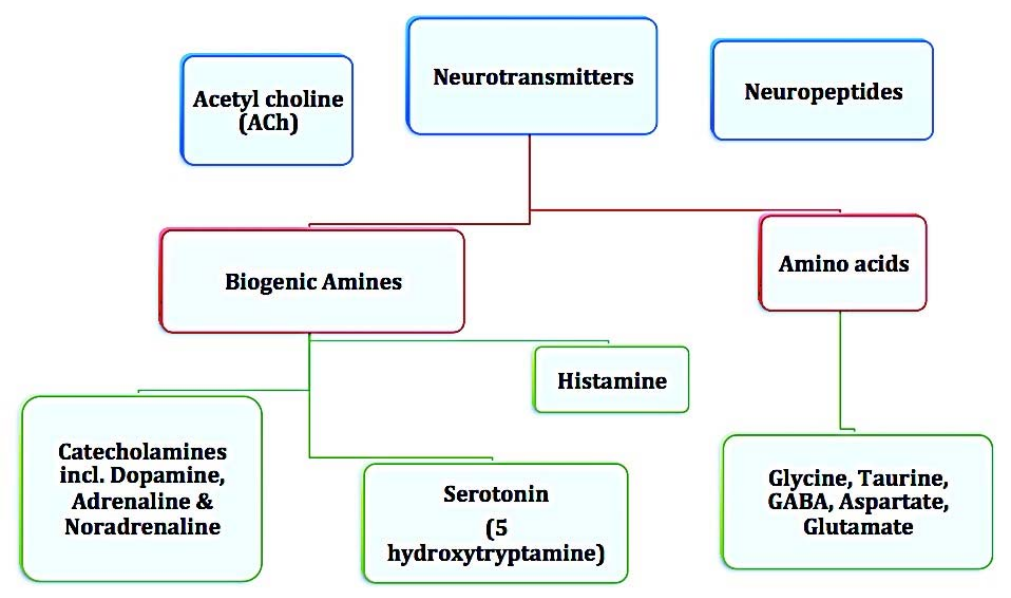
CLASSIFICATION OF NEUROTRANSMITTERS

Broadly speaking, neurotransmitters may be classified into four main groups:

1. **Amino acids** – aspartic acid (aspartate), GABA, glutamic acid (glutamate), glycine and taurine.
2. **Biogenic amines** - includes the three main catecholamines (dopamine, noradrenaline and adrenaline), histamine, 5-hydroxytryptamine (serotonin) and acetylcholine.
3. **Peptides** – includes MSH, ACTH, β-endorphin, enkephalins and related opioid peptides, Substance P, neurokinin A, neuropeptide K, neuropeptide γ and many others.
4. **Acetylcholine** – a carboxylic acid derivative and the first neurotransmitter to be identified.

These chemical messengers are distributed throughout the central nervous system (CNS), peripheral nervous system (PNS), the autonomic nervous system (ANS) and the enteric nervous system of the gut.

Furthermore, some of the peptide molecules are released at the same time as inhibitory neurotransmitters such as GABA and glycine, thereby combining both anxiolytic and analgesic effects simultaneously.



NEUROTRANSMITTER IMBALANCES

There are many biochemical neurotransmitter imbalances that result in mental health symptoms such as:

- Adrenal dysfunction
- Blood sugar imbalance
- Food and chemical allergies / sensitivities
- Heavy metal toxicity
- Hormone imbalance
- Nutritional deficiency
- Serotonin / dopamine / noradrenaline imbalances
- Stimulant and drug intoxication
- Under or overactive thyroid

Disrupted communication between the brain and the body can have deleterious effects upon one's physical and mental health. Depression, anxiety and other mood disorders are thought to be directly related to neurotransmitter imbalances. The four major neurotransmitters that regulate mood are serotonin, dopamine, GABA and noradrenaline and these are normally kept in balance with all the other neurotransmitters and neuropeptides within the central nervous system.

The Excitatory System is the dominant regulatory network. It ensures that the machinery of the brain executes all the sensory and motor functions for which it was originally designed. Glutamate (or glutamic acid) is the most widespread of all neurotransmitters in the CNS, and it is assisted by the three catecholamines: **dopamine, noradrenaline and adrenaline**.

The Inhibitory System is the brain's 'braking system'; it prevents electrical signals from continuing along their pathways unchecked. The inhibitory system therefore slows things down, acting in a regulatory manner. Glycine, **GABA and serotonin** are all examples of inhibitory neurotransmitters. The normal ratio of glutaminergic to GABAergic neurones throughout the CNS is approximately 4:1.

INHIBITORY NEUROTRANSMITTERS

GABA

GABA (*Gamma amino butyric acid*) is the major inhibitory (calming) neurotransmitter in the central nervous system and, as such, is important for balancing excitatory action of other neurotransmitters. It helps the neurons recover after transmission, reduces anxiety and stress. It regulates noradrenaline, adrenaline, dopamine and serotonin; it is a significant mood modulator.

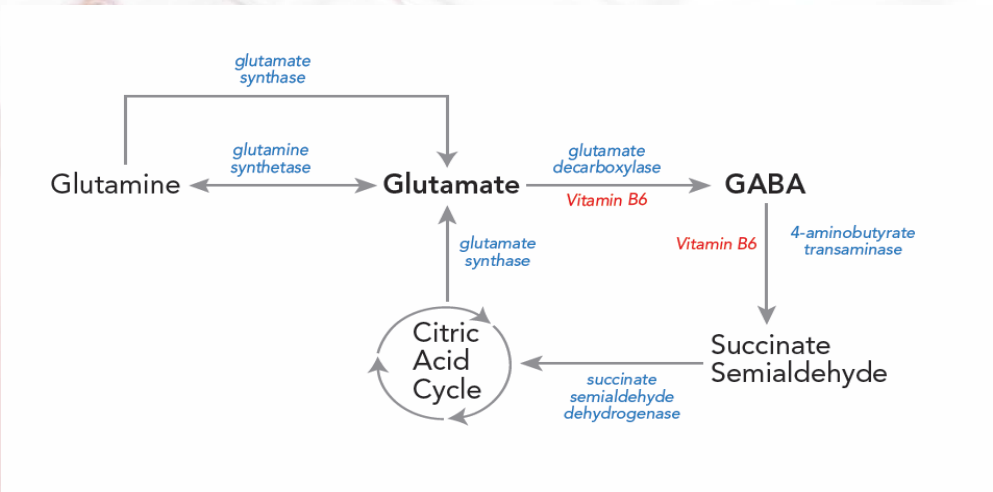
Inhibitory neurotransmitters act via their receptors to reduce excitability in neuronal transmission and modulate the size of the electrical impulse thus generated. For optimal functioning, the brain must balance the excitatory and inhibitory influences: Excessive excitation can lead to anxiety, sleep disturbances, seizures and other clinical conditions, whereas excessive neuronal inhibition can result in drowsiness, sedation and anaesthesia. This situation is most commonly seen when someone has overdosed on benzodiazepines such as diazepam or has simply consumed far too much alcohol.

GABA filters out irrelevant messages (static) by terminating signals from the excitatory neurotransmitters: glutamate, and its positive modulators adrenaline, noradrenaline and PEA. GABA can be viewed as the 'braking system' in the realm of neurotransmitters and acts via interneurones, interposed into excitatory pathways.

High levels of GABA may be a result of excitatory overload, or a compensatory mechanism to balance the surplus excitatory neurotransmitter activity. These high levels result in a 'calming' action that may contribute to sluggish energy, feelings of sedation and foggy thinking.

Low GABA levels are associated with dysregulation of the adrenal stress response.

Without the inhibiting function of GABA, impulsive behaviours are often poorly controlled, contributing to a range of anxious and/or reactive symptoms that extend from poor impulse control to seizure disorders.



GABA effects:

- Has a calming influence upon the mind;
- May reduce symptoms of anxiety and depression;
- May reduce symptoms of alcohol withdrawal;
- May reduce anxiety disturbances in schizophrenics;
- May suppress appetite or reduce elevated blood pressure;
- May increase insulin sensitivity;
- May help relieve premenstrual symptoms;
- May alleviate the frequency or severity of epileptic fits.

Low GABA levels have been found in alcoholism, bipolar and panic disorders, chronic anxiety disorders, major depression, epilepsy and heavy metal poisoning.

Causes of GABA deficiency

GABA receptor function may be reduced because of a genetic polymorphism in the GABA receptor that reduces the efficiency of GABA neurotransmission, the presence of GABA receptor inhibitors or low serotonin levels. Serotonin is a positive regulator of GABA-GABA receptor interaction.

Alcohol as well as benzodiazepine drugs act on GABA receptors and imitate the effects of GABA. Though these substances don't cause an increase in GABA levels, understanding their mechanism can give us additional insight into the effects of GABA.

Deficient GABA levels may be caused by:

- Inhibition of glutamate decarboxylase by heavy metals or environmental chemicals;
- Prolonged stress;
- Genetic polymorphisms in either the GABA receptor or the genes for the manufacture of glutamate decarboxylase.

SEROTONIN

Serotonin is a key neurotransmitter that is involved in the regulation of sleep, appetite and aggression. Serotonin imbalance is a common contributor to mood problems, and pharmacologic agents that alter serotonin levels are among the most commonly used class of drugs prescribed for anxiety and depression.

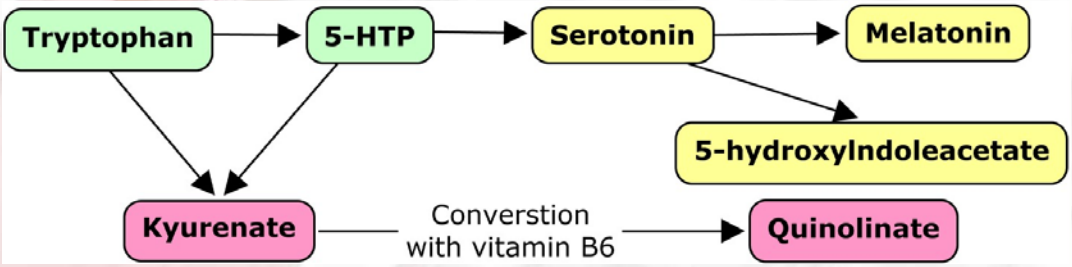
Serotonin is key to our feelings of happiness and very important for our emotions because it helps defend against both anxiety and depression. You may be experiencing a shortage of serotonin if you have a persistently sad or depressed mood, anxiety, panic attacks, low energy, migraines, sleeping problems, obsession or compulsions, feeling tense and irritable, crave sweets and have a lowered sex drive. Additionally, your hormones and oestrogen levels can affect serotonin levels and this may explain why some women have pre-menstrual and menopausal mood problems. Moreover, daily stress can greatly reduce your serotonin production.

Causes and contributors of low serotonin levels and deficiency

High stress, insufficient nutrients, fluctuating hormones and the use of stimulant medications or caffeine can all contribute to the depletion of serotonin over time. When serotonin is out of range, depression, anxiety, worry, obsessive thoughts and behaviors, carbohydrate cravings, PMS, difficulty with pain control and sleep cycle disturbances can result.

Serotonin is synthesised in the brain and body from the amino acid tryptophan. This is just one of a number of essential amino acids that we must obtain from our diet. Tryptophan has to compete with other neutral amino acids for transport across the blood brain barrier. Dietary tryptophan is converted to 5HT (5-hydroxytryptophan) and then into serotonin (5-hydroxytryptamine), provided that all of the cofactors are present in sufficient quantities and the two intermediary enzymes are functioning appropriately.

A shortage of tryptophan is believed to be a major factor leading to depression. Increased levels of tryptophan directly result in increased serotonin production and subsequent melatonin synthesis.



EXCITATORY NEUROTRANSMITTERS

This system can be likened to your car's accelerator. It allows the signal to go. When the excitatory neurotransmitter system is in overdrive your system gets all revved up for action. Without a functioning inhibitory system to put on the brakes, things (like your mood) can get out of control.

DOPAMINE – the modulatory neurotransmitter

Dopamine is largely responsible for regulating the pleasure reward pathway, memory and motor control. It is responsible for motivation, interest and drive. It is associated with positive experiences such as being in love, exercising, listening to music and enjoying sexual relationships.

Its function creates both inhibitory and excitatory action depending on the dopaminergic receptor it binds to. When we don't have enough of it we may lack motivation, we have difficulty initiating or completing tasks, poor concentration, no energy and gain little pleasure from daily activity.

Memory issues are common with both elevations and depressions in dopamine levels. Caffeine and other stimulants, such as medications for ADD/ADHD, often improve focus by increasing dopamine release, although continual stimulation of this release can deplete dopamine over time.

Common symptoms associated with low dopamine levels include loss of motor control, cravings, compulsions, loss of satisfaction and addictive behaviors including: drug and alcohol use, smoking cigarettes, gambling, and overeating. These actions often result from an unconscious attempt to self-medicate, looking for the satisfaction that is not occurring naturally in the body. Low dopamine levels can cause us to self medicate using either prescription or illicit drugs, consume excessive amounts of alcohol, smoke cigarettes, gamble and/or overeat.

Common symptoms associated with low dopamine levels include loss of motor control, cravings, compulsions, loss of satisfaction and addictive behaviors including: drug and alcohol use, smoking cigarettes, gambling, and overeating. These actions often result from an unconscious attempt to self-medicate, looking for the satisfaction that is not occurring naturally in the body. High dopamine levels have been observed in patients with poor GI function, mood swings, psychosis as well as in children with autism or various attention disorders.

Symptoms of elevated dopamine

Elevated dopamine levels may contribute to hyperactivity or anxiety and have been observed in patients with schizophrenia. High dopamine may also be related to autism, mood swings, psychosis and attention disorders.

L-dopa is a precursor to dopamine, and is used therapeutically for low dopamine conditions such as Parkinson's disease. These medications can cause elevations in dopamine.

Symptoms of dopamine deficiency

Low dopamine levels can result in depression, impaired fine motor control, loss of satisfaction, addictions, cravings, compulsions, low sex drive, poor attention and focus. When dopamine levels are elevated symptoms may manifest in the form of anxiety, paranoia, or hyperactivity. Comments by your patients that may alert you to the presence of a dopamine deficiency:

- Do they often feel depressed, flat, bored and apathetic?
- Are they low on physical or mental energy? Do they feel tired a lot?
- Are their drive, enthusiasm, and motivation on the low side?
- Do they have difficulty focusing or concentrating?
- Do they tend to put on weight too easily?
- Do they feel the need to get more alert and motivated by consuming a lot of coffee or other 'uppers' like sugar, diet soda or recreational drugs such as cocaine?

What causes low dopamine levels?

Dopamine levels are depleted by stress, certain antidepressants, drug use, poor nutrition or poor sleep. Alcohol, caffeine and sugar all seem to decrease dopaminergic activity in the brain. Dopamine is a catecholamine and serves as the precursor to noradrenaline. However, it is an immensely important neurotransmitter in its own right. Dopamine systems modulate the activity of large areas of brain tissue that regulate mood, motivation and reward. It is dopamine that is responsible for salience, our ability to experience positive reward from our endeavours. Dopamine activity is what we are all after. It is indeed the basis of the pleasurable sensations that accompany behaviours like sexual activity, eating and most recreational drug use. Dopamine is thus the core of motivation and of addiction, and without it we experience anhedonia, the inability to feel pleasure.

The ability to restore dopamine balance will help treat motor dysfunctions such as restless leg syndrome and Parkinson's disease, as well as the delusional thinking typically found in psychoses and bipolar disorder.

NORADRENALINE

Noradrenaline, also called norepinephrine, is produced by the adrenal medulla or made from dopamine in the locus coeruleus. It is involved in a wide variety of actions including attention, focus, regulating heart rate, affecting blood flow and suppressing inflammation. Involved in arousal, it prepares the body for action by relaying messages in the sympathetic nervous system as part of the autonomic nervous system's fight-or-flight response.

High levels of noradrenaline are linked to anxiety, stress, high blood pressure and hyperactivity.

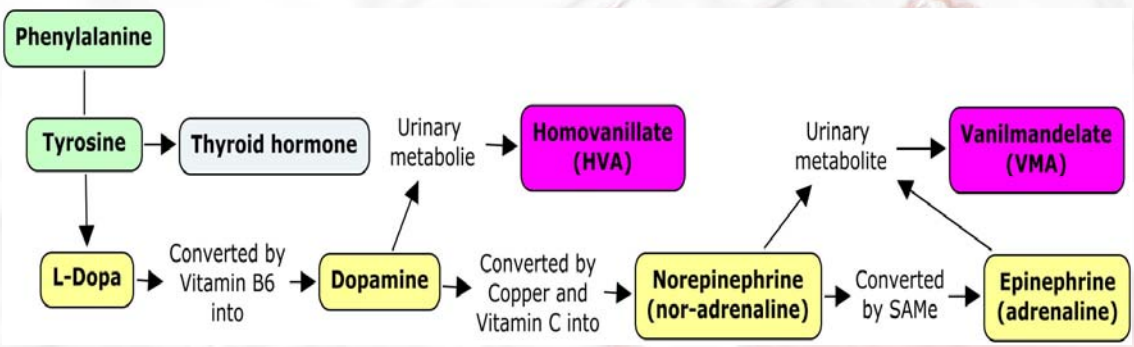
Low levels are linked to lack of energy, focus and motivation.

ADRENALINE

Adrenaline, also known as epinephrine, is synthesised from noradrenaline both in the adrenal glands and central nervous system. In the adrenal medulla, adrenaline synthesis predominates, whilst in the CNS, the reverse is true.

Adrenaline helps regulate muscle contraction, heart rate, glycogen breakdown, blood pressure and more, and is heavily involved in a stress response. It regulates attention, mental focus, arousal and cognition. It also inhibits insulin excretion and raises the amounts of fatty acids in the blood.

Elevated levels are often associated with hyperactivity, ADHD, anxiety, sleep disturbances and low adrenal function. Over time, chronic stress and stimulation can deplete adrenaline stores leading to difficulty concentrating, fatigue, depression, difficulty losing weight, insufficient cortisol production, chronic stress, poor recovery from illness, dizziness and more.



GLUTAMATE

Glutamate is the major excitatory neurotransmitter throughout the central nervous system. It is required for learning and memory, particularly in the hippocampus and temporal lobes. It is involved in most aspects of normal brain function including cognition, memory and learning, although high levels of glutamate can cause excitotoxicity, a process where nerve cells are damaged by excessive stimulation.

Elevated glutamate levels are commonly associated with panic attacks, anxiety, difficulty concentrating, and may contribute to OCD, autism and depression. Excessive glutamate levels can cause neuronal loss by activating intracellular caspase pathways that result in cell death.

Disordered glutamate function and lowered GABA/glutamate ratios may be found in various neurodegenerative diseases such as Alzheimer's disease, Parkinson's, Huntington's and Tourette's Syndromes.

Low glutamate levels may result in agitation, memory loss, sleeplessness, low energy levels and depression.

Other Neurotransmitters

GLYCINE

Glycine accomplishes two major functions as a transmitter in the central nervous system (CNS). It is primarily distributed throughout the brain stem, grey matter of the spinal cord, and to a lesser extent, the cerebellum where its activity is principally associated with the modulatory function of GABAergic interneurones. As an inhibitory neurotransmitter, it participates in the processing of motor and sensory information that permits movement, vision and audition. This action of glycine is mediated by the strychnine-sensitive glycine receptor, whose activation produces inhibitory post-synaptic potentials. In its second major role, glycine modulates excitatory neurotransmission by potentiating the action of glutamate at N-methyl-D-aspartate (NMDA) receptors. These functions may be determined by the relative synaptic concentrations of glycine at both inhibitory and excitatory neurones.

PHENYLETHYLAMINE (PEA)

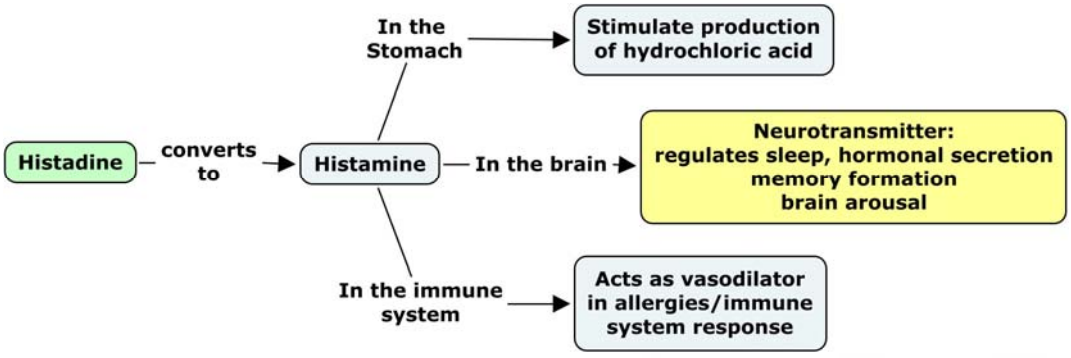
PEA is an excitatory neurotransmitter made from phenylalanine. It is important in focus and concentration.

High levels are observed in individuals experiencing ‘mind racing’, sleep problems, anxiety and schizophrenia. Low PEA is associated with difficulty paying attention or thinking clearly, and in depression.

HISTAMINE

Histamine is most commonly known for its role in allergic reactions but it is also involved in neurotransmission and can affect your emotions and behaviour as well. Histamine helps control the sleep-wake cycle and promotes the release of adrenaline and noradrenaline.

High histamine levels have been linked to obsessive compulsive tendencies, depression and headaches. Low histamine levels can contribute to paranoia, low libido, fatigue and medication sensitivities.



TAURINE

Although taurine is the second most abundant amino acid within brain tissue, it is not a neurotransmitter in its own right. Rather, it acts to modulate glutaminergic neurotransmission by reducing the excitatory influence of calcium on NMDA and kainate receptors in glutaminergic neurones and enhancing GABAergic activity. It therefore acts in an auxiliary, but nonetheless important, inhibitory role throughout the central nervous system. The concentration(s) of taurine may be measured in both plasma and 24hr urinary amino acid screens.

SYMPTOMS OF MAJOR NEUROTRANSMITTERS

NEUROTRANSMITTER	LOW LEVELS	HIGH LEVELS
GABA **(γ-amino butyric acid)**	Muscle tension Stressed, burned out Depression Irritability Unable to relax, overwhelmed Anxiety, Panic attacks Seizures	Sedation Impaired recent memory
Serotonin (5HT) **(5-hydroxytryptamine)**	Depression Worry, anxiety, low self esteem, Obsessive thoughts/behaviours Irritability, aggression Panic disorder, phobias, suicidal thoughts Fibromyalgia Carbohydrate craving, evening cravings; Eating disorders	Sedation, increased sleep Decreased anxiety Decreased sex drive; decreased orgasms Indecision Craving for sweets and carbohydrates May have hallucinations (if greatly increased levels)
Dopamine	Depression, no joy or pleasure Lack of energy, lack of drive Cravings for caffeine, other stimulants Lack of focus and concentration, A.D.D. Cognitive decline/inattention Addictive behaviour Severe: Parkinson's disease, movement disorders	Developmental issues Schizophrenia Psychosis Mild: Enhanced creativity and problem solving; good spatial ability; premature ejaculation Severe: Disorganised thinking; disabling compulsions; tics
Glutamate	Excitotoxicity Anxiety disorders Cognitive impairment Poor memory	Stress Anxiety Neurotoxicity Decreased mood
Adrenaline	Long term stress Fatigue, lack of energy Lack of focus Poor blood sugar control Poor methylation	Stress Anxiety Insomnia Blood sugar issues, insulin resistance
Noradrenaline	Depression (with apathy) Decreased attention and focus Lack of motivation Lack of energy, exhaustion	Stress Anxiety Hyperactivity Increased BP

Symptoms of other neurotransmitters

NEUROTRANSMITTERS	COMMON DEFICIENCY SYMPTOMS
Acetylcholine (Ach)	Cognitive decline Autonomic nervous system dysfunction Digestive dysfunction
Endorphins / Encephalins (endogenous opioids)	Very sensitive to emotional or physical pain; Cry easily Crave comfort, reward or numbness Addictive behaviour Chronic pain Depression
Histamine	Anxiety Schizophrenic illness Seizures
Melatonin	'Night owl' Insomnia, hard to get to sleep, disturbed sleep maintenance
Phenylethylamine (PEA)	Depression Poor attention Migraine

HORMONES AND NEUROTRANSMITTERS

Sex hormone imbalances create many symptoms in the peri-menopausal and menopausal woman and ageing man. These symptoms can also stem from neurotransmitters, adrenal and thyroid imbalances. For example:

- Oestrogen reduces level of inhibitory enzyme of serotonin and dopamine, thereby increases their effects. Progesterone decreases their effects.
- Progesterone increases GABA effects and reduces neurotransmitter activity. Cortisol increases GABA effects (by inhibiting catecholamine release).
- DHEA enhances noradrenaline and serotonin effects (enhances cognitive function and reduces depression).

Throughout a woman's lifetime they experience the fluctuating hormones and attribute mood swings, hot flushes, cravings, anxiety, depression, fatigue, joint pain, weight gain, low libido, brain fog, memory loss or insomnia to the imbalance of female hormones.

Frequently this is only one piece of the puzzle. How we feel and respond involve the interaction and integration of the endocrine (hormones), immune, enteric (gut) and nervous system. Neurotransmitters carry messages to every organ, muscle and gland. Poor nutrition, drugs, heavy metal toxicity and over-stimulation deplete and imbalance the neurotransmitters which impairs the function of all systems. Often when a woman experiences PMS, peri-menopause or menopause, they are usually prescribed the contraceptive pill or HRT. When these are not effective or symptoms remain, the hormones are changed or dosages increased. Looking at only one hormone system is not adequate.

Successful treatment of women requires proper diagnosis and treatment of adrenal function. When adrenals are stressed, oestradiol (E2) and testosterone can be shunted to DHEA, while progesterone goes to cortisol (via 'pregnenolone steal pathway').

In women, the adrenal glands are the only source of DHEA. In the menopausal female, the adrenals are the source of testosterone, oestrogen and progesterone. If the adrenals are exhausted and cortisol is low, menopausal and PMS symptoms intensify. Therefore adrenal normalisation would precede hormone modulation.

Neurotransmitter evaluation and support is also very important. The inhibitory neurotransmitters are interlinked with hormones. The hormones and their interactions are responding not only to each other but are modulated by our lifestyles and significantly impacted by stress. The complicated balance of our hormones and our brain chemistry challenges our stress adaptation mechanisms and fatigue can result. The fluctuating levels in hormones such as oestrogen, progesterone, testosterone, cortisol and thyroid interact with brain neurotransmitters that affect our emotional and physical responses to life.

NEUROTRANSMITTER EFFECTS ON HORMONES

NEUROTRANSMITTER EFFECTS ON HORMONES	
Serotonin	Increase Thyroid function Needed to increase TSH for feedback stimulation of fT4 & fT3
GABA (excess)	Inhibits Thyroid function
Dopamine (excess)	Increases Growth hormone Decreases Prolactin
Noradrenaline (excess)	Increases Cortisol (when acute) Decreases Cortisol (if chronic)
Adrenaline (excess)	Increases insulin (insulin resistance)

HORMONE EFFECTS ON NEUROTRANSMITTERS

HORMONE EFFECTS ON NEUROTRANMSITTERS	
Oestrogen	Serotonin agonist Dopamine modulator
Progesterone	GABA agonist
Testosterone	Serotonin / Dopamine agonist
DHEA	Serotonin / Dopamine / Noradrenaline agonist
Cortisol (excess)	Blocks Tryptophan metabolism into Serotonin
Cortisol (insufficiency)	Increases Noradrenaline Increases Glutamate Decreases Adrenaline
Thyroid	Serotonin agonist
Insulin (excess)	Decreases Serotonin
Insulin resistance	Increases Dopamine / Noradrenaline

IMBALANCES THAT MAY BE ASSOCIATED WITH HORMONAL CHANGES/SYMPTOMS

Symptoms	LOW LEVELS	HIGH LEVELS
Anxiety	Low Serotonin Low GABA	High Noradrenaline High Adrenaline High Glutamate High cortisol
Carbohydrate cravings	Low Serotonin Low Dopamine	Insulin resistance
Depression	Low Serotonin Low Noradrenaline Low thyroid	High Glutamate
Fatigue	Low Dopamine Low Noradrenaline Low Adrenaline Low Glutamate Low adrenals Low thyroid	
Hot flushes	Low Serotonin	High cortisol
Insomnia	Low adrenals Low Serotonin Low GABA Low blood sugar	High Noradrenaline High Adrenaline High cortisol
Memory loss / Lack of focus	Low Dopamine Low Noradrenaline Low Adrenaline Low Glutamate Low cortisol Low thyroid	
Mood swings	Low Serotonin Low GABA Low adrenals Low thyroid	High Dopamine
Motivation, lack of	Low Serotonin Low Dopamine	
Pain	Low Serotonin Low cortisol	High Noradrenaline
Weight gain	Low thyroid	High cortisol Insulin resistance

PATHOLOGY ASSESSMENTS

Neurotransmitter Levels

Neurotransmitter levels can now be determined by the **Extensive Neurotransmitter profile [4026]** a simple and convenient urine test collected at home. Knowing your patients' neurotransmitter levels can help you correct a problem today or prevent potential problems from occurring in the future.

Functional neurotransmitter testing is a useful clinical tool for the assessment of chemical and metabolic markers in the brain. The total picture of the patient's mental health status can only be achieved with proper consideration of the patient's medical history, supplements, medications, lifestyle and diet.

The Art of Interpretation

We strongly recommend that all patients undertake a **24hr Urinary Amino Acid profile** [**5004]** in conjunction with the Extensive Neurotransmitter profile. This test provides vital information on the status of tryptophan, tyrosine, taurine, glycine and phenylalanine as represented by their urinary excretion over a 24 hour period.

Conversely, one may order a **Plasma Amino Acid profile [5003]**, and whilst useful, this test only provides a snapshot of nutrient values at any one given point in time. (A thorough workup would include both urinary and plasma amino acid profiles).

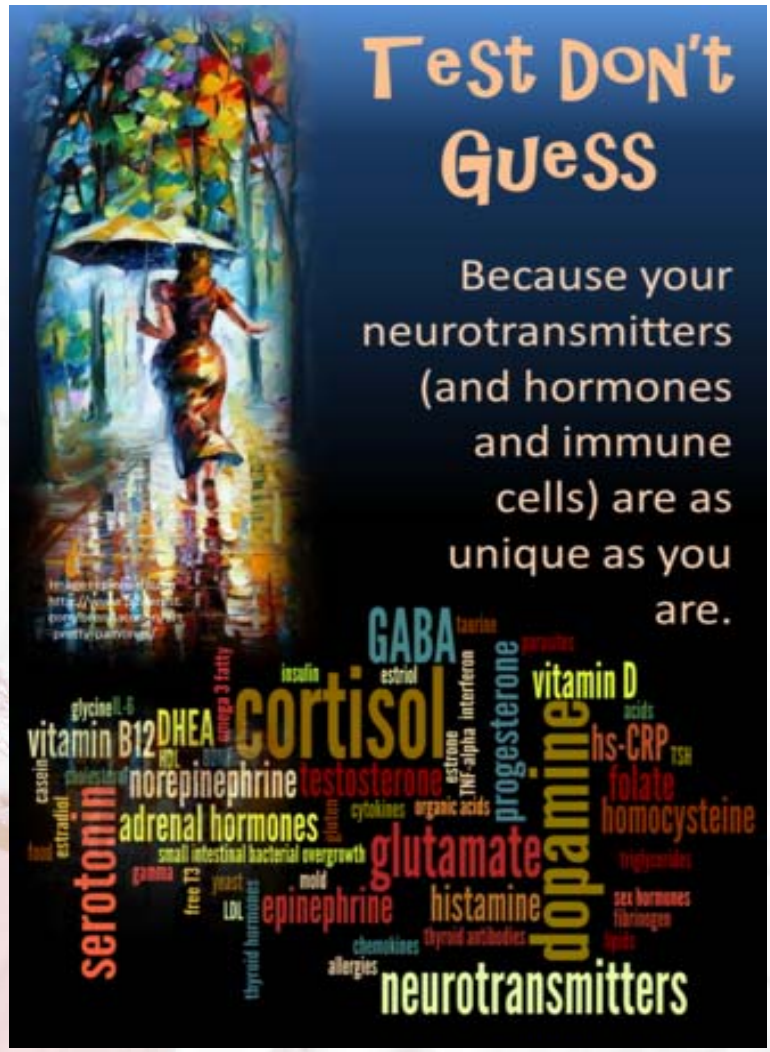
The ability of the stomach to generate sufficient quantities of hydrochloric acid (HCl) and pepsin for protein digestion is a key factor determining the availability of these nutrients for optimal neurosynthesis and neurotransmission.

Once the test results have been collated, we may recommend further testing such as:

- ***Salivary Adrenocortex Stress profiles*** *including DHEA status*
- ***Urinary Adrenal Hormone profiles*** *– Levels 1, 2 or 3*
- ***Organic Acid profiles*** *including environmental toxin analysis*
- ***Serum gastrin*** *– to assess gastric HCl production*
- ***Sex hormones, thyroid, or insulin/glucose panels*** *may also provide further information*
- ***Individual co-factor analyses*** *- incl.* ***red cell magnesium, serum copper, ferritin etc.***

Rarely does one single test provide all the answers you need. Usually, the information obtained from one test will lead you to discover the adjacent pieces of the jigsaw puzzle. Often we discover that it is only when one joins together all the pathology work that a patient has had done, and then relate these test results to their presenting symptoms and clinical findings, that one is able to make the connections that finally solve the puzzle.

A detailed interpretive guideline based both upon the patient's questionnaire and test results are provided with each report.



RESULTS INTERPRETATION

If GABA is ELEVATED, consider:

- **Appropriate response to elevated excitatory neurotransmitters**

Elevations of the catecholamines (dopamine, noradrenaline and adrenaline) and/or glutamate will normally cause induction of GABA activity. It is common to see the chronic elevation of noradrenaline +/- glutamate being countered by a GABA response. In these cases, it is important to support the GABAergic system to prevent depletion. Glutamate elevations, without GABA inhibitory control are dangerous to the central nervous system due to the excitotoxic nature of excessive glutamate, can result in either neuronal death or neurodegeneration.

If GABA is LOW, consider:

- **Depleted neuron stores due to high demand (i.e. high excitation)**

Chronic stress will elevate (and ultimately deplete) the catecholamines. Over time, this can deplete GABA stores, as output rises in order to inhibit excess excitation. It is generally necessary to support the GABA system to prevent depletion of GABA and the resultant anxiety, insomnia or panic that will inevitably ensue.

- **Deficient Vitamin B6**

The concentration of GABA in the brain is controlled by two P5P (pyridoxal 5'-phosphate)-dependent enzymes, glutamate decarboxylase (GAD) and GABA transaminase. A decrease in the levels of GABA in the brain secondary to decreased levels of P5P can lead to seizures. Using P5P can help rule out B6 deficiency as a cause of low GABA.

If GABA is NORMAL, but anxiety, insomnia (high excitation) symptoms still present:

Consider that the normal reference range is not optimal for this individual. Biochemical individuality is no more evident than in the CNS. For this reason, clinical observation must be valued as a primary aspect of treatment.

High noradrenaline levels may mimic some of the symptoms associated with low GABA levels, so even if GABA lies somewhere within the normal range and noradrenaline levels are high, anxiety-type symptoms are likely to persist. Note that the ratio between glutamate and GABA is more important than the individual neurotransmitter levels alone.

If SEROTONIN is ELEVATED, consider:

- **Appropriate stores**

If a patient has adequate neuronal stores of serotonin upon entering a stressful situation, serotonin activity should rise in response to the elevation in excitatory neurotransmitter activity. The resulting increase in urinary serotonin is indicative of an appropriate response to the circumstances. Giving serotonin precursors in this case may elevate urinary measures even further.

- **Precursor supplement use (5-HTP or tryptophan)**

Use of either 5-HTP or L-tryptophan can elevate urinary serotonin in as little as two weeks. When urinary serotonin is elevated, it is necessary to rule out supplementary precursor use. When stressors result in elevated inflammation or cortisol levels, 5-HTP is a much more effective way to raise serotonin than is supplemental tryptophan. Elevated cortisol, our body's response to increased inflammation, directs tryptophan down an alternative route (kynurenine/ quinolinate pathway), rendering tryptophan less effective as serotonin support. It is therefore important in assessing serotonin, to also assess adrenal corticosteroid levels as high cortisol levels inhibit 5HTP synthesis.

If SEROTONIN is LOW, consider:

- **Depleted neuronal stores (poor nutrition +/- high demand)**

Protein deficient diets may not supply tryptophan adequate for sufficient serotonin production. Poor diets may also be deficient in B vitamins and other necessary nutrients. Good tryptophan sources include cottage cheese, fish, seafood, meats, poultry (especially turkey), peanuts and lentils.

Tetrahydrobiopterin (BH4): a folic acid metabolite, vitamin B6 as pyridoxal-5-phosphate and magnesium are all required in the process of serotonin synthesis.

- **Low carbohydrate diet**

Different types of amino acids compete for available transport mechanisms in the body. Because tryptophan is not abundant in the diet relative to other amino acids, it often loses out when competition is heavy (e.g. after a high protein meal). However, a dietary trick can overcome this difficulty. If a carbohydrate is eaten, insulin is induced. Insulin not only delivers glucose to the cells, it also delivers amino acids to muscle cells all the essential amino acids except tryptophan. Tryptophan travels in the bloodstream bound to albumin whence it then crosses the blood-brain barrier without competition. In summary, carbohydrate is necessary to deliver adequate tryptophan to the brain for Serotonin production. This is one of the reasons why a low carbohydrate diet may be associated with symptoms of fatigue and depression.

- **High protein competition**

Large neutral amino acids including phenylalanine, compete for transport across the blood-brain barrier (BBB) via the L-type amino acid carrier. This transporter also carries the three essential branched-chain amino acids: valine, leucine and isoleucine, along with methionine, histidine, tyrosine and tryptophan. The rate of transport for each individual amino acid is directly related to its plasma concentration. As it generally is the least abundant of dietary amino acids, an excess consumption of these other nutrients can limit the transport of tryptophan into brain tissue. High protein/low carbohydrate diets are a twofold problem - insufficient insulin synthesis and excessive amino acid competition.

NOTES:

If DOPAMINE is ELEVATED, consider:

- Alcohol or nicotine use
- Cocaine / amphetamine / heroin use
- Pharmaceutical dopamine agonist use
- Use of ADD/ADHD drugs, cortisol and L-dopa
- Hyperthyroidism; Metabolic Syndrome
- Diets high in sucrose induce dopamine, hence their addictive properties in some people

Note that raised cortisol, however, has an inhibitory effect on dopaminergic neurones in the meso-cortical area of the brain, where dopamine is essential for normal cognitive function.

If DOPAMINE is LOW, consider:

- **Damage (chronic) to dopamine neurons, receptors, transporter**

Damage to dopaminergic neurotransmission has been shown to occur from chronic exposures such as methamphetamine use in ADHD (damage to dopaminergic nerve endings), mercury accumulation (cortical D2 receptor damage), the pesticide rotenone (nigrostriatal nerve degeneration), the herbicides atrazine (neurotoxicity to several Dopamine pathways) and paraquat (microglia mediated oxidative damage to nigrostriatal pathway). The widespread exposure to such chemicals predisposes to depletion of dopaminergic neurotransmission.

- **Chronic use of neuro-active pharmaceutical drugs**

Excess serotonin can reduce dopamine function in important brain areas. This situation may accompany the well recognised serotonergic syndrome.

If GLUTAMATE is ELEVATED, consider:

- **Deficient GABA**

GABA, the most important inhibitory neurotransmitter in the brain, is the main 'brake' on excitatory neurotransmission. When enough GABA is present, glutamate cannot overexcite its neurons. GABA is therefore extremely important in preventing excitotoxicity (neuronal destruction from excessive glutamate activity).

- **Elevated Catecholamines (Dopamine, Noradrenaline, Adrenaline)**

Elevated noradrenaline is known to enhance glutamate NMDA receptor activity. The most common reasons for elevated catecholamines are depleted inhibitory serotonin/GABA and any stressor or perceived stressor, including, blood sugar instability (hypoglycaemia, Metabolic Syndrome/Insulin Resistance), environmental toxins/toxicity, infections, allergies, physical trauma, inflammation or emotional upset. Stress then upregulates both the catecholamines and glutamate resulting in a vicious cycle of depleted inhibitory and excess excitatory neurotransmitters.

- **Glutamine supplementation**

Glutamine is a common ingredient in many functional foods and is frequently supplemented in various protocols for gastrointestinal and other healing. The brain and body can easily metabolise glutamine into glutamate and vice versa. In the brain, released glutamate is taken up by astrocytes (astroglia), specialised support cells for brain neurons, where it is converted to glutamine, transported back to the presynaptic neuron and re-converted to glutamate.

Persons sensitive to monosodium glutamate (MSG) may want to avoid glutamine supplements. For this same reason, people with epilepsy, bipolar disorder or any neurodegenerative condition should avoid using glutamine supplements. It is clinically observed that excitatory reactions to glutamine, though not common, are seen and may be due to the dose given and/or cofactor availability for the conversion. Higher amounts may be reserved for those without neurological conditions.

- **Functional oestradiol deficiency**

Oestradiol (E2) increases glutamate uptake capacity by astrocytes. Oestradiol is thus part of the homeostatic balance in the cycle of glutamate. E2 deficiency leaves more glutamate in the synapse, elevating this excitatory neurotransmitter. This may be one of the ways using bio-identical oestrogen replacement is neuroprotective.

If GLUTAMATE is LOW, consider:

- **Malabsorption**

The supply of glutamate depends upon the absorption of glutamic acid from the GI tract. Anything that impairs gastric HCl and pepsin synthesis may reduce absorption. This includes the usual proton pump inhibitors (PPIs), atrophic gastritis, heavy metal toxicity (esp. arsenic and mercury), copper toxicity, antacid abuse etc. The older H2 antagonists such as cimetidine and ranitidine are not as potent as the newer drugs but reduce gastric HCl production nonetheless. Therefore, it is imperative to order both a **Hair Mineral Analysis** together with a urinary **Amino Acid profile** if there is no pharmacological reason for these findings. Glutamate is the most plentiful of all neurotransmitters in the CNS; hence this situation must be investigated thoroughly.

- **Iron deficiency**

In animal models, the binding of Glutamate to its receptors in iron-deficient animals was reduced by 63%. Iron thus plays an important functional role in receptor binding in both GABA and glutamate.

NOTES:

NATURAL TREATMENTS FOR NEUROTRANSMITTER IMBALANCES

Once a deficiency such as depression develops, correcting it may not be as simple as eating the right foods. It usually requires specialised supplementation at higher levels than can be obtained from your diet. Nutrient therapies greatly increase the levels of neurotransmitters in which a patient has been found to be deficient. Studies have shown that it is both safe and effective and most patients experience symptom reduction within a few weeks. These pharmaceutical grade nutrients cross the blood brain barrier where they become synthesised into new neurotransmitter molecules, thereby restoring normal neural transmission. They are prescribed individually according to need, thus giving the patient a more personal treatment plan than would otherwise be possible.

Amino acids are referred to as the building blocks of life; they make up proteins in every tissue of the body and contribute to the formation of hormones, immunoglobulins, haemoglobin, collagen, muscles, neurotransmitters, enzymes, antibodies and receptors and are involved in cellular energy production. They play a major role in nearly every chemical process that affects physical and mental function. Amino acid deficiencies may manifest as fatigue, allergic sensitivities, arthritis, digestive disorders, cognitive dysfunction, cardiovascular complaints, reduced athletic performance and neurological disturbances. Taking supplements such as 5HTP, GABA, taurine and acetyl L-tyrosine may help reduce anxiety and enhance neurotransmitter function.

Serotonin Treatments

Once your natural serotonin levels are sufficiently low to cause symptoms, it is difficult to significantly raise serotonin levels enough by diet alone.

SSRIs and SNRIs do not actually increase the quantities of serotonin molecules in the brain. SSRIs are thought to block the reabsorption (reuptake) of serotonin into pre-synaptic neurones. They act to prolong the length of time that a transmitter remains in contact with its dedicated 5HT receptor. This theoretically leaves more serotonin available to facilitate neurotransmission. However, if you have impaired synthesis of serotonin to begin with, then these medications will generally be of limited benefit in relieving the full spectrum of symptoms associated with the depressive illness.

Natural serotonin supplements are likely to be the most effective means to raise serotonin levels in the brain while being safe and without the potential side effects of antidepressant medications. Derived from seeds of Griffonia simplicifolia, a native African plant, 5-hydroxy tryptophan (5HPT) is generally regarded as a safe dietary alternative to conventional pharmaceutical treatments.

Dietary Therapies

Foods that may increase Serotonin:

- Complex carbohydrates
- Chicken, turkey
- Tuna, salmon
- Rolled oats
- Chickpeas, lentils, kidney beans
- Sunflower seeds, pumpkin seeds
- Baked potato with skin
- Avocado, walnuts
- Almond butter, sesame seed butter (tahini)

Foods that may increase Dopamine:

- Almonds, pumpkin seeds and sesame seeds
- Avocados, bananas
- Dairy products

Dopamine is easily oxidised. Foods that are rich in antioxidants such as fruits and vegetables may help protect dopamine-using neurons from free radical damage. Many healthcare professionals recommend supplementing with vitamins C, vitamin E and other antioxidants.

Synergistic combination of nutrients: Phosphatidylserine is one of the key building blocks of cellular membranes, concentrating particularly in the myelin sheaths of neurons. **Phosphatidylserine** has been shown to counteract the exaggerated release of adrenocorticotropic hormone and cortisol that may occur. **NADH** has been shown to play a role in dopamine and noradrenaline production, whilst **tyrosine** is a precursor of noradrenaline and dopamine.

Foods that may increase Glutamate:

Contain free GLUTAMIC ACID [Additive number]	May contain or produce free GLUTAMIC ACID	Suspected of containing or creating sufficient free GLUTAMIC ACID as MSG-reactions in highly sensitive people
Glutamic acid / Glutamate [620]	Carrageenan [407]	Corn starch
Monosodium glutamate (MSG) [621]	Bouillon and broth	Corn syrup
Monopotassium glutamate [622]	Stock	Modified food starch
Calcium glutamate [623]	Any flavours or flavouring	Dextrose
Monoammonium glutamate [624]	Maltodextrin	Rice syrup
Magnesium glutamate [625]	Citric acid, citrate [330]	Milk powder
Natrium glutamate	Barley malt	Reduced fat milk (skim, 1%, 2%)
Yeast extract	Pectin [440]	Many low fat / no fat foods
Anything 'hydrolysed'	Protease	Anything 'enriched'
Hydrolysed protein (any)	Malt extract	Anything 'vitamin-enriched'
Calcium caseinate, Sodium caseinate	Soy sauce	
Yeast food, yeast nutrient	Anything 'protein fortified', 'enzyme modified', 'fermented'	
Autolysed yeast		
Gelatine		
Textured protein (TVP)		
Soy protein, soy proteína concentrate		
Whey protein, whey protein concentrate		
Whey protein isolate		

Herbal Therapies

1. Adaptogens

Adaptogens are a class of naturally occurring metabolic regulators, which enable the organism to withstand stresses of a physical, biological or psychological nature. Such substances:

- Increase one's capacity to respond to acutely stressful situations;
- Have a normalising influence on disturbed physiological parameters, thereby enhancing the body's homeostatic mechanisms;
- Increase one's resistance to the deleterious biological effects engendered by prolonged, excessive exposure to noxious stimuli.

Such stimuli may be of singular or diverse origins, however, one's capacity to deal with such stimuli may be compromised by chronic illness, the expectations and demands of family, one's nutritional status (both macronutrient and micronutrient), demands of employment, travel or study, reduced quality or duration of restful sleep etc.

Adaptogens produce changes in the body as a result of the balancing (amphoteric) effects on humoral and neuroendocrine functions. They are capable of alternatively 'toning down' or restoring the proper functioning of the sympathetic/parasympathetic nervous systems, and respective components of the HPA axis.

In TCM, such herbs are referred to as chi tonics or as rasayanas in Ayurvedic tradition.

2. Nervine Relaxants

Nervine relaxants have a relaxing/calming effect on nerve and muscle tissue without the overtly suppressant effects of sedatives. This type of herb helps restore emotional balance and reduce anxiety, irritability, sleeplessness and other psychosomatic symptoms. They are most beneficial when used in conjunction with one or more adaptogens because of their complementary therapeutic effects.

3. Nootropics

The word nootropic derives from two Greek words, literally interpreted as 'bending the mind'. These herbs are used to enhance memory, improve cognitive functioning, improve the cerebral circulation and inhibit degenerative brain processes. Such herbs are often given in combination with the adaptogens with which they exhibit synergistic effects.

4. Sedatives and Hypnotics

While hypnotics induce sleep, it is to some extent dose-dependent and therefore the boundaries between sedatives and hypnotics can be blurred. Thus the same herbs are frequently used as sedatives are also used as a hypnotic in higher doses. A number of these herbs exhibit a spectrum of therapeutic activity. For example, many of these herbs are trophorestorative, relaxant and sedative, thereby having the potential to treat a variety of nervous system disorders. Generally speaking, these herbs do not have a 'hangover' effect, unless combined with alcohol or prescription medication.

They are also known to:

- Diminish nervous tension
- Decrease neuromuscular spasm
- Decrease pain
- Induce sleep
- Non habit-forming/non-dependent forming (unlike many allopathic alternatives)

Nutritional Therapies

SEROTONIN	Fe, Ca, Tryptophan, B6/P5P, Zn, Mg, Vit C
GABA	Taurine, Glutamine, B5, B6; L-theanine
DOPAMINE	Tyrosine, B6/P5P, Fe, Mg, Zn, activated B3
NORADRENALINE	Vit C, Cu; tyrosine, B6, B3, Fe, Zn, Mg, folate
ADRENALINE	SAMe, cortisol; Vit C, Cu; tyrosine, B6, B3, Fe, Zn, Mg, folate
GLUTAMATE	Mg, Zn, Vit E, Vit C, CoQ10, ALA; L-theanine

PRESCRIPTION MEDICATIONS FOR MENTAL HEALTH CONDITIONS

The National Institute of Mental Health (USA) has classified the various types of psychotropic medications. These include:

1. Antipsychotic medications

Used to treat both schizophrenia and schizophrenia-like disorders. These include the older 'typical' antipsychotics as well as the newer 'atypical' varieties. The older types are renowned for inducing serious extra-pyramidal side effects that may become disabling. Such drugs include:

- Chlorpromazine (THORAZINE)
- Fluphenazine (generic only)
- Haloperidol (HALDOL)
- Perphenazine (generic only)

The newer agents that psychiatrists routinely prescribe for schizophrenia include:

- Aripiprazole (ABILIFY)
- Clozapine (CLOZARIL)
- Olanzapine (ZYPREXA)
- Quetiapine (SEROQUEL)
- Risperidone (RISPERDAL)
- Ziprasidone hydrochloride (ZELDOX)

Atypical antipsychotic medications are sometimes used to treat bipolar disorder. Specifically these include:

- Aripiprazole (ABILIFY) - which can be taken as a tablet or as an injection.
- Clozapine (CLORAZIL) - which is often used for people who do not respond to lithium or anticonvulsants.
- Olanzapine (ZYPREXA) - which is used to treat people with severe or psychotic depression, typically accompanied by hallucinations and/or delusional thinking
- Risperidone (RISPERDAL)

2. Antidepressants

Subdivided into various classes, depending on their mode of pharmacological activity. Selective serotonin reuptake inhibitors (SSRIs) are currently the most commonly prescribed and include each of the following:

- Citalopram (CELEXA)
- Escitalopram (LEXAPRO)
- Fluoxetine (PROZAC)
- Paroxetine (PAXIL)
- Sertraline (ZOLOFT)

These drugs all differ in their pharmacokinetics, receptor binding affinities and toxicological profiles.

SSRIs and SNRIs typically do not cause as many side effects as older classes of antidepressants. Such medications include tricyclics, tetracyclics and monoamine oxidase inhibitors (MAOIs). For some people, however, these medications may be the most suitable in particular circumstances.

Bipolar disorder is commonly treated with mood stabilisers such as lithium carbonate or sodium valproate +/- anti-depressants in specific circumstances.

3. Anticonvulsant medications

May be either prescribed for their anticonvulsant or mood stabilising effects. Such drugs include:

- Sodium valproate (EPILIM)
- Carbamazepine (TEGRETOL)
- Lamotrigine (LAMICTAL)
- Oxcarbazepine (TRILEPTAL)

Newer agents such as Gabapentin, Tiagabine and Vigabatrin act either as GABA agonists or GABA transaminase inhibitors thereby enhancing GABAergic neurotransmission.

4. Anxiolytics

Antidepressants, benzodiazepines and beta-blockers are the most common medications used for anxiety disorders. These disorders include:

- Generalised anxiety disorder (GAD)
- Obsessive compulsive disorder (OCD)
- Panic disorder
- Post-traumatic stress disorder (PTSD)
- Social phobia

Benzodiazepines act primarily on the benzodiazepine subunit of the $GABA_A$ receptor thereby inducing both relaxation +/- sedation. The ones specifically designed for the treatment of anxiety disorders include:

- Alprazolam (XANAX) - used for panic disorder and GAD.
- Clonazepam (KLONOPIN) - used for social phobia and GAD
- Lorazepam (ATIVAN) - used for panic disorder

Antidepressants such as fluoxetine (PROZAC), sertraline (ZOLOFT), escitalopram (LEXAPRO), paroxetine (PAXIL) and citalopram (CELEXA) may be prescribed for panic disorder, OCD, PTSD and social phobia. The SNRI venlafaxine (EFFEXOR) is also commonly used to treat GAD.

Low doses of some tricyclic antidepressants work well for anxiety. For example, imipramine (TOFRANIL) may be prescribed for panic disorder and GAD. Clomipramine (ANAFRANIL) is used to treat OCD. Tricyclics are generally started at low doses and increased over time.

MAOIs are occasionally used for anxiety disorders. Doctors sometimes prescribe moclobemide, a selective MAO-A inhibitor for its anxiolytic effects. Patients who take older types of non-selective MAOIs must avoid particular foods and medicines that may cause potential interactions and induce sustained elevations in blood pressure. For these reasons, they are now rarely prescribed.

5. CNS Stimulants

These drugs are principally prescribed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), which occurs in both children and adults. ADHD is commonly treated with stimulants, such as:

- Amphetamine (ADDERALL)
- Dextroamphetamine (DEXEDRINE, DEXTROSTAT)
- Methylphenidate (RITALIN, METADATE, CONCERTA, DAYTRANA)

Side Effects of Medication

All pharmaceutical medications have their limitations due to a plethora of side effects which may include:

- Agitation (feeling jittery)
- Bladder disturbances. It may be difficult to empty the bladder or the urine stream may not be as strong as usual. Older men with enlarged prostate conditions may be more commonly affected.
- Blurred vision
- Constipation or diarrhoea
- Drowsiness
- Dry mouth
- Headache
- Menstrual problems for women
- Postural dizziness when changing positions such as from lying down to standing up
- Rapid heartbeat (tachycardia)
- Sensitivity to the sun (photosensitivity)
- Sexual problems, which can affect both men and women and may include both reduced sex drive and problems having and/or enjoying sex
- Skin rashes
- Sleeplessness (insomnia)

Communication System Management™ Evidential Brief, Sanesco Health (June 2012)

Statistical analysis indicates strong negative correlation between epinepherine levels and severity of fatigue. Patients with low levels of epinepherine are significantly more likely to report moderate to severe fatigue. Patients indicating severe decreased stamina are 71.4 % more likely to have low epinepherine levels

Statistical analysis indicates strong correlations between deficient dopamine levels and low libido. Patients reporting decreased libido are almost 15% more likely to have low dopamine levels than patients reporting normal libido.

Patients reporting severe agitated depression are 31.73% more likely to have low serotonin levels than those reporting no symptoms. Patients reporting no agitated depression are 2.8 times more likely to be within reference range than those reporting severe symptoms. Patients reporting no vegetative depression are 71.92% more likely to be within reference range than those with severe vegetative depression.

Statistical analysis indicates a negative relationship between GABA levels and anxiety. The 99% confidence interval for patients reporting no anxiety falls completely within reference range, while there is almost no overlap with the 99% confidence intervals for patients reporting anxiety. Of male patients with low GABA on Test 1 who increase GABA levels by Test 2 following TNT™ treatment protocols, 75% improve their symptom of anxiety, while no patients in this group worsen their symptom of anxiety.

Statistical analysis indicates strong correlations between low levels of dopamine and depression. Of all patients reporting less severe or no depression by Test 2 following TNT™ treatment, almost 30% also had higher dopamine levels. Women are far more likely, statistically, to have low levels of dopamine than men. Women are also 65.49% more likely to report severe agitated depression.

Analysis of Test 1 levels for serotonin reveal 69.41% of females and 73.71% of males have low levels of serotonin. For the combined group of males and females, mean serotonin levels increased by 89% given treatment with the CSM™ clinical model from Test 1 to Test 2. 47.62% fewer women have low serotonin in Test 2 than in Test 1. For males, 56.66% fewer have low serotonin in Test 2 than in Test 1. The percentage of female and male patients testing low for serotonin on Test 1 who raised their serotonin by Test 2 are 80.52% and 88.89% respectively.

FREQUENTLY ASKED QUESTIONS

Do neurotransmitters cross the blood-brain barrier and as such, does urinary neurotransmitter testing provide adequate assessment of brain neurotransmitter levels?

The raw materials, e.g. 5HTP, cross the blood-brain barrier where the neurotransmitters are produced in the neurons, e.g. serotonin. As the pre-synaptic neuron fires, serotonin attaches to the receptor on the postsynaptic neuron. What is left in the synapse is taken back up into the pre-synaptic neuron. If there is too much (excess) in the synapse, MAO enzymes 'gobble them up'.

The postsynaptic neurons feed into the HP axis and stimulates the hypothalamus, which generates a down stream effect on hormone production in the periphery as the hypothalamus meets the pituitary. As the endocrine system begins at the pituitary, this is the beginning of the neuroendocrine system.

If there is too much (excess) in the synapse that is not taken up because reuptake is blocked or there is insufficient MAO enzymes to break them down, this creates 'overflow' in that the circulatory system carries them through the blood and if there are insufficient receptors or receptors are damaged and cannot bind the neurotransmitters (in the case of serotonin, it could be receptors in the platelets or the gut), then it is cleared from the blood by the kidneys or through the urine.

Therefore, put simply, neurotransmitters do not have to cross the blood-brain barrier but the raw materials do since the neurotransmitters are made in the neurons of the brain.

I have a male patient who is 52 years of age and had his Adrenocortex Stress profile assessed in which his morning and midday results were very low. His histamine levels are within normal range. Clinical symptoms: broken sleep, anxiety and slightly depressed….

Sleep issues are often a result of high cortisol levels but that is not his case. We would expect to see low inhibitory levels with sleep and anxiety and possibly high glutamate and/or other excitatory levels that may be disruptive.

After initiating inhibitory support (and possibly some time-released melatonin) to help with his immediate sleep concerns it would be recommended to add in adrenal support. If his DHEA was also low, it may need support.

How is his diet? Some patients will use caffeine or sugar for energy when adrenal function is low so dietary counselling may prove helpful with eating more protein and more often throughout the day, especially if he has symptoms of hypoglycaemia. When sugar is low or fluctuating, it can disturb cortisol levels.

If serotonin and dopamine are low, begin with supporting those levels. Assess adrenal and thyroid hormones to determine if they are contributing to depression.

If, after measuring all hormones and neurotransmitters, levels are normal, some patients with exhaustive depression do well with methylation support: SAMe and folinic acid.

I have a patient with high serotonin, GABA and noradrenaline levels. Patient is currently on SAME 100mg per day, 5HTP 50mg (3-4 times a day), P5P and zinc. This patient is a very anxious and nervous person showing symptoms of severe depression.

The high noradrenaline may be the main contributor to her nervousness, however, SAMe should be helping it to convert. Is she taking any excitatory support that might contribute to her noradrenaline level?

Otherwise, we have noticed in a small percent of the population that when serotonin is supported, the patient experiences a nervous rather than a calming reaction, which is possibly due to excitatory noradrenaline or cortisol rising to counter the increase in serotonin. If that is the case, consider decreasing her 5HTP support to lower serotonin, allowing the noradrenaline reaction to dissipate.

It would be good to check her cortisol levels to determine if cortisol is also up-regulated and consider a cortisol modulator, if that is the case.

For those people who experience this response to serotonin support, we suspect they may be missing a co-factor for the pathway; as she is taking P5P, consider the use of a multivitamin and mineral and/or whether she is anaemic as iron is required for the pathway.

For those who respond well to inositol, the addition of inositol alone can improve anxiety. 1-2 grams a day would be suggested, split between 2 daily doses.

When we identify a patient who is extremely sensitive to 5HTP in even small amounts, we suggest 'stepping back up the pathway' and using tryptophan rather than 5HTP.

Glutamate is the immediate precursor to GABA; therefore, if both are elevated, I would look to the use of precursors: glutamine, glutamic acid, MCG, theanine, etc. Also, GABA rises in response to excess excitatory function since it is the main inhibitory neurotransmitter including: glutamate, adrenal hormones, catecholamines and thyroid, e.g. we often see it high in patients on thyroid hormones.

High glutamate can drive up GABA so, was she on anything that would increase glutamate or GABA? Another thought: if GABA receptors are not functioning correctly, they cannot bind it and it is released into the system, ending up in the urine as it passes out of the body

Therefore, identify and remove any precursors that may increase levels; if cortisol is high, lower with the use of a cortisol modulator; use a receptor product like inositol to help with binding and to reduce the amount of urinary loss; determine if she is on thyroid support and reduce.

What studies are there on autism and neurotransmitters?

Neuropathological studies in autistic brains have shown small neuronal size and increased cell packing density in a variety of limbic system structures including the hippocampus, a change consistent with curtailment of normal development. Data from these single concentration ligand binding studies indicate that the GABAergic receptor system is significantly reduced in high binding regions, marking for the first time an abnormality in the GABA system in autism. In contrast, the density and distribution of the other six receptors studied (various serotonin, glutamate and acetylcholine receptors) in the hippocampus did not demonstrate any statistically significant differences in binding.

G.J. Blatt, C.M. Fitzgerald, J.T. Guptill, A.B. Booker, T.L. Kemper & M.L. Bauman. *Density and Distribution of Hippocampal Neurotransmitter Receptors in Autism.* Journal of Autism and Developmental Disorders. Volume 31, Number 6, December, 2001.

Studies examining the brains of individuals with autism have identified anatomic and pathologic changes in regions such as the cerebellum and hippocampus. Abnormalities in the protein or mRNA levels of several additional molecules in the glutamate system were identified on further analysis, including glutamate receptor binding proteins. AMPA-type glutamate receptor density was decreased in the cerebellum of individuals with autism. Subjects with autism may have specific abnormalities in the AMPA-type glutamate receptors and glutamate transporters in the cerebellum. These abnormalities may be directly involved in the pathogenesis of the disorder.

A.E. Purcell, O.H. Jeon, A.W. Zimmerman, M.E. Blue & J. Pevsner. *Postmortem brain abnormalities of the glutamate neurotransmitter system in autism.* Neurology, 57:1618-1628. 2001.

Some forms of autism are caused by an increased ratio of excitation/inhibition in sensory, mnemonic, social and emotional systems. The model further postulates that the increased ratio of excitation/inhibition can be caused by combinatorial effects of genetic and environmental variables that impinge upon a given neural system.

J.L.R. Rubenstein & M.M. Merzenich. *Model of autism: increased ratio of excitation/inhibition in key neural systems* Genes, Brain and Behavior, Volume 2 Issue 5, 255 – 267. 2010.

The severe disruptions observed in autism may be linked to suppression of GABAergic inhibition, resulting in excessive stimulation of glutamate-specialised neurons and loss of sensory gating… Neuroanatomically, autistic individuals have been found to demonstrate loss of pyramidal neurons in the frontal cortex, limbic system abnormalities, and significant loss of Purkinje cells in the cerebellar hemispheres. These brain areas have specialised responses to glutamate, or are selectively vulnerable to stress from high glutamate levels… In vitro evidence suggests that excessive glutamate activation of non-NMDA receptors reduces the number of synapses and the extent of dendrite growth in the pyramidal neurons of the hippocampus. This finding is mirrored in neuroanatomic evidence which demonstrates decreased complexity and dendritic arborization in the pyramidal cells of autistic individuals.

J.P. Hussman. *Suppressed GABAergic Inhibition as a Common Factor in Suspected Etiologies of Autism.* Journal of Autism and Developmental Disorders, Vol. 31. No. 2, 2001.