

Neurotransmitter Testing in Dried Urine

Neurotransmitter Testing – Giving a Diagnostic Edge in Treating Mood Disorders

Mental health disorders affect millions of people in the United States and profoundly contribute to the burden of disease in society. The National Alliance of Mental Illness reports that nearly 7% of American adults live with major depression and approximately 18% live with anxiety disorders such as panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and phobias¹. Mood disorders are the third most common cause of hospitalization in the U.S. for individuals aged 18 to 44¹. The top-prescribed and top-selling prescription drugs in the U.S. in 2014 included antipsychotics, antidepressants, and attention-deficit disorder drugs².

The current treatment paradigm in addressing poor brain health relies on diagnostic tools that encompass the evaluation of clinical signs and symptoms. Despite the lack of testable biomarkers for mood disorders, for many patients, treatments can generally be effective. However, even after treatment frequent relapse episodes can still occur. Furthermore, a large number of patients suffer from treatment-resistant depression³. Therefore, selection of the best therapeutic regimen for each patient remains a challenge, and is often discovered through a time-consuming process of trial and error. Also, no single approach works for everyone with any one disorder.

Targeted neurotransmitter testing can help health care practitioners achieve a diagnostic edge beyond the traditional psychological inventory by identifying specific imbalances in neurotransmitter levels. Based on neurotransmitter test results, practitioners can identify specific biochemical heterogeneities for each particular patient, and objectively monitor therapeutic responses during and after intervention. Neurotransmitter testing objectively enhances medical assessment and represents a major advance in the personalization of the treatment of mood disorders.

Available Tests

NeuroAdvanced Profile

Tests: GABA, Glu, Gly, DA, Epi, NE, HIST, 5-HT, PEA, DOPAC, HVA, 5-HIAA, NMN, VMA, Crtn (dried urine)

Testing neurotransmitters in patients with a suspected neurochemical imbalance can help assess individual biochemistry and get to the root of persistent issues such as mood/affective disorders, adrenal dysfunction, addictive behaviors, ADD or OCD, or PMS or PMDD.

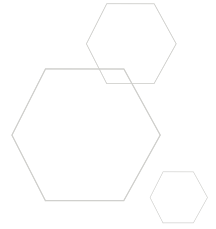
Add-On Options (dried urine, unless noted)

- ▶ Saliva Hormones: E2, Pg, T, DS, C
- ▶ Urine Hormones: E2, Pregnanediol, Allopregnanolone, Androstenedione, T, Epi-T, DHT, DHEA, 5 α ,3 α -Androstenediol
- ▶ Diurnal Cortisol: Free Cortisol x 4, Free Cortisone x 4
- ▶ Diurnal Cortisol & Melatonin: Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4
- ▶ Diurnal Cortisol, Norepinephrine & Epinephrine: Free Cortisol x 4, Free Cortisone x 4, NE x 4, Epi x 4
- ▶ Diurnal Cortisol, Melatonin, Norepinephrine & Epinephrine: Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4, NE x 4, Epi x 4
- ▶ Urine Elements: Iodine, Selenium, Bromine, Lithium, Arsenic, Cadmium, Mercury



Neurotransmitter Testing

Non-invasive home test kit



How Neurotransmitters Relay Information within the Body

The brain orchestrates the delicate interplay between the body and the mind. Structural brain units, the neurons, discharge neurotransmitters. These neurotransmitters provide a communication platform for the brain to fuel internal systems with information. Anything the body senses, feels, hears, smells, touches, or ingests serves as an input that prompts an astoundingly fast response. In the central and peripheral nervous system, neurotransmitters operate as chemical messengers that relay the signal and receive feedback via electrochemical impulses to regulate cognition, memory, emotions, respiration, heart rate and contractility, digestion, metabolism, blood flow and pressure, and hormonal responses. When released from peripheral organs, neurotransmitters can also behave as hormones by diffusing to distant sites via the circulation.

Clinical Utility of Urinary Neurotransmitter Analysis

The etiology of mood disorders is profoundly complex and likely encompasses many different types of neurotransmitters, how they achieve balance in the brain and in the gut axis, and how they each interplay with other hormone systems throughout the body. Appropriate balancing of neurotransmitter signals allows the body to maintain equilibrium. When brain and peripheral neurochemistry become unbalanced, the body will struggle to re-establish physiological integrity, which may present in the form of suboptimal psychological well-being. Excessive or deficient levels of certain neurotransmitters in both the brain and in the periphery are associated with a spectrum of neurobiological disorders, such as depression and anxiety. The measurement of specific imbalances may be a very effective neurobiological tool in guiding targeted intervention, aimed at addressing the individual excess or deficiency in question.

Clinical Validity of Urinary Neurotransmitter Assessment

The importance of effectively assessing and treating mood disorders cannot be overstated. Objectivity is a key element to the therapeutic approach to mood disorders. Currently, the standard of care dictates a trial and error pharmaceutical approach is taken with each patient based on both self and clinician assessments. However, without information yielded from objective clinical testing, selection of the most effective treatment for each particular patient with a mood disorder continues to be a challenge. While this may prove effective for some patients, the potential for harm during those interim treatment failures is a real concern for clinicians and patients alike.

Urinary neurotransmitter testing is performed with the goal that therapeutic interventions may be introduced to address, alleviate, and improve a patient's well-being and has a breadth of data to support the efficacy of the test in clinical practice (see Table on next page). Evaluation of neurotransmitter levels in urine provides valuable information about the heterogeneity of patient biochemistry, epigenetics, and how the body functions as a whole.

Although the urine test is not a direct measure of brain neurotransmitter levels, it provides relevant information with respect to neurotransmitter regulation in the brain, which can be altered by treatment. The levels in urine often parallel levels in the central nervous system, and the test may therefore assist in the selection of patients with mood issues who might respond to specific pharmaceutical or over-the-counter treatment interventions^{58,59}. In other words, the test provides a means to glean a functional systemic perspective regarding each neurotransmitter in the periphery, which ultimately operates under the control of the brain.

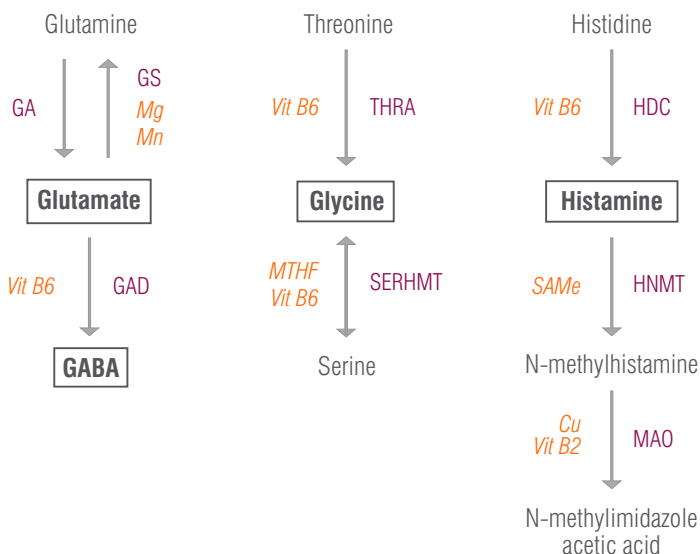
How do neurotransmitters end up in urine? Some neurotransmitters are produced in the brain and transported

NEUROTRANSMITTER FUNCTIONS & IMBALANCES

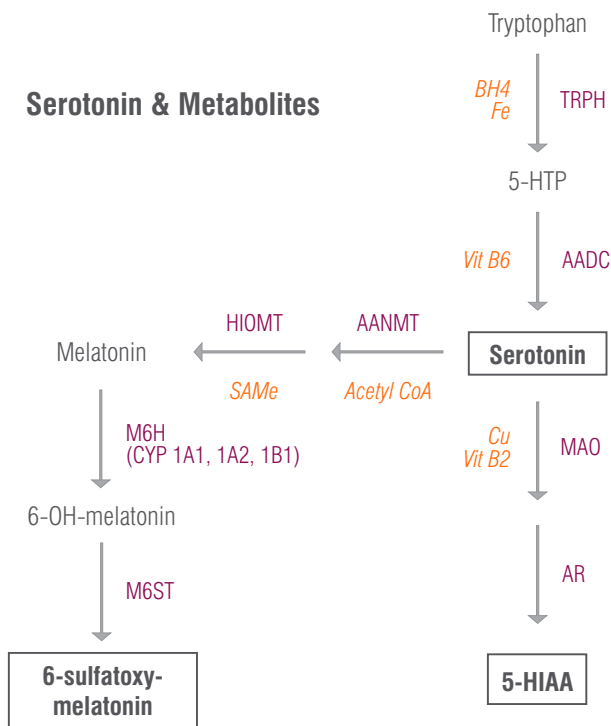
Neurotransmitter	High Levels in Urine	Low Levels in Urine
Serotonin is the “housekeeping” molecule – promotes healthy sleep, regulates appetite, improves mood, supports healthy digestive function and so much more. 5-HIAA is a metabolite.	Serotonin is high in depression ^{4,5} and with 5HTP use ⁶ , and is implicated in anxiety, dysbiosis, irritability, and low libido.	Serotonin is decreased in autism spectrum disorder ⁷ , depression ⁸ , with oral contraceptives ^{9,10} and may be associated with anxiety, low mood, irritability, and sleep disturbances.
GABA functions as the major inhibitory neurotransmitter, induces relaxation and reduces anxiety.	GABA is elevated in sleep apnea ¹¹ , ovarian cancer ¹² , and is suspected in anxiety, excessive need for sleep, foggy thinking, and lethargy.	Low GABA is implicated in anxiety, sleep difficulties, adrenal distress and hypothalamic pituitary adrenal axis feedback dysfunction. Low GABA levels are associated with disorders like ADHD and Tourette syndrome ¹³ .
Glycine plays a dual role as a neurotransmitter and an amino acid that serves as a building block to proteins.	Clinically, high glycine levels are suspected in anxiety and may be associated with insufficient vitamin B status and/or methylation events.	Glycine levels are low in diabetes ¹⁴ , hypothyroidism ¹⁵ , obesity ¹⁶ , and after intense exercise ¹⁷ . Clinically, low glycine levels are suspected in depression.
Glutamate functions as the major excitatory neurotransmitter and metabolic fuel throughout the body.	Glutamate is high in celiac disease ¹⁸ and hyperthyroidism ¹⁹ . Clinically, high glutamate is suspected in anxiety, autism spectrum disorder, depression and sleep issues.	Glutamate is low in patients with migraines ²⁰ . Clinically, low glutamate is implicated in depression, chronic fatigue, lack of concentration, low energy levels, and sleep disturbances.
Histamine is a neurotransmitter and immuno-modulator.	Histamine is high in cystitis ²¹ , flushing disorder ²² , food allergies ²³ , polycythemia ²⁴ and pregnancy ²⁵ . High histamine may implicate allergies, depression, headaches, migraines, OCD, and sleep difficulties.	Low histamine is associated with fatigue, low libido, low productivity, mild depression, tension headaches, and weight gain.
PEA serves as a biomarker for ADHD.	PEA is elevated in individuals with bipolar major affective disorder ²⁶ , anxiety and insomnia ²⁷ , phenylketonuria ²⁸ and with methylphenidate treatment ²⁹ .	PEA is low in patients with autistic spectrum disorder ³⁰ , ADHD ^{29,31,32} , depression ³³ , and inattentiveness ^{34,35} .
Dopamine serves as the reward and pleasure center in the brain, and messenger of the sympathetic nervous system in the periphery. DOPAC and HVA are metabolites.	High dopamine is reported in patients with high in anxiety ³⁶ , stress ³⁷ , paroxysmal hypertension ³⁸ , primary aldosteronism ³⁹ , PTSD ⁴⁰ , and mercury toxicity ⁴¹ .	Dopamine is low in Alzheimer’s disease ⁴² , anorexia nervosa ⁴³ , fibromyalgia ⁴⁴ , hypertension ⁴⁵ , periodic limb movement disorder ⁴⁶ , sleep disturbances ⁴⁷ , hypoadrenergic orthostatic hypotension ⁴⁸ .
Epinephrine and norepinephrine regulate the “fight or flight” response. Normetanephrine is a norepinephrine metabolite, and VMA is a norepinephrine and epinephrine metabolite.	Epinephrine and norepinephrine levels are high in patients with anxiety ^{49,50} , ADHD ^{34,35} , bipolar disorder ⁵¹ , depression ⁵² , hyperglycemia ⁵³ , sleep apnea ¹¹ , PTSD ⁴⁰ , and stress ^{54,55} .	Epinephrine and norepinephrine levels are low in Alzheimer’s disease ⁴² , metabolic syndrome ⁵⁶ , and obesity ⁵⁷ .

NEUROTRANSMITTER CASCADE

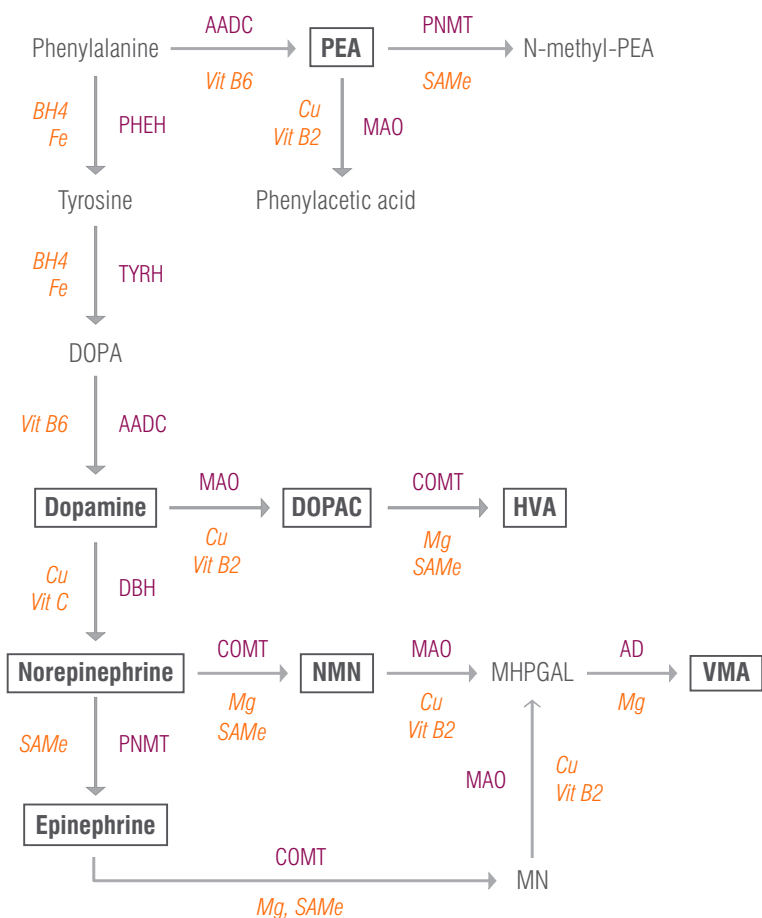
Glutamate/GABA, Glycine & Histamine



Serotonin & Melatonin



Catecholamines & Metabolites



Neurotransmitters & Metabolites:

HVA	homovanillic acid
NMN	normetanephrine
PEA	phenethylamine
VMA	vanillylmandelic acid
5-HIAA	5-hydroxyindole 3-acetic acid

Enzymes:

AADC	aromatic L-amino acid decarboxylase
AANMT	arylalkylamine N-methyltransferase
AD	aldehyde dehydrogenase
AR	aldehyde reductase
COMT	catechol-O-methyltransferase
DBH	dopamine beta hydroxylase
GA	glutaminase
GAD	glutamate decarboxylase
GS	glutamine synthetase
HDC	histidine decarboxylase
HIOMT	hydroxyindole-O-methyltransferase
HNMT	histamine N-methyltransferase
MAO	monoamine oxidase
M6H	melatonin 6 hydroxylase
M6ST	melatonin 6 sulfotransferase
PHEH	phenylalanine hydroxylase
PNMT	phenylethanolamine N-methyltransferase
SERHMT	serine hydroxymethyltransferase
THRA	threonine aldolase
TRPH	tryptophan hydroxylase
TYRH	tyrosine hydroxylase

Cofactors:

BH4	tetrahydrobiopterin
Cu	copper
Fe	iron
Mg	magnesium
Mn	manganese
MTHF	methyltetrahydrofolate
SAMe	S-adenosyl methionine

across the blood-brain barrier into blood, and others are produced in the periphery (e.g., norepinephrine and epinephrine). Nephrons, the functional units of the kidney, filter circulating neurotransmitters or their precursors from the blood into urine⁶⁰. For some neurotransmitters, urinary measurements correlate with levels in the central nervous system (e.g., glutamate, PEA), and for others, what ends up in urine is only reflective of peripheral biosynthesis (e. g., serotonin, GABA, dopamine, norepinephrine, epinephrine). Regardless of production origin, neurotransmitter excretion reflects the overall systemic neurotransmitter tone, dysregulation of which may contribute to disease states. The ability to identify abnormality across specific areas of the catecholamine and PEA, GABA/ glutamate, serotonin, histamine, and glycine pathways allows healthcare providers to develop a tailored treatment plan to the specific areas associated with imbalance.

Dried Urine – A Convenient Testing Option

The nature of urine collection is non-invasive and preferable over the traditional invasive collection approaches such as measurement of cerebrospinal fluid. Even with liquid urine collection the patient experiences the enormous hassle of collecting all urine voids over a 24-hour period into a large jug. To circumvent this inconvenience some labs have settled for collecting only the 2nd void, limiting neurotransmitter results to a single morning time point snapshot. ZRT Laboratory offers an alternative to the liquid

urine collection method by offering a simple and convenient collection of four separate urine samples at specific time points throughout the day – 1st morning, 2nd morning (approximately 2 hours after the first collection), early evening, and bedtime. Urine is collected onto filter strips by urinating directly on the strip, or by dipping the filter card in a cup containing the collected urine. The urine cards are then allowed to dry overnight, and sent to ZRT for testing. The convenience of the collection method warrants patient compliance and ease of incorporation into clinical practice.

Considerations

- ▶ The neurotransmitter test assumes proper kidney function. Neurotransmitter levels are reported in µg/g creatinine, where creatinine is measured from the same sample. This test should not be used in individuals with compromised renal function.
- ▶ The sample can become very dilute due to increased fluid consumption during the day. Therefore, on the day of testing, individuals should restrict their liquid intake to normal consumption.
- ▶ On the day of testing, individuals are advised to refrain from consuming alcohol, nicotine, bananas, pineapple, and walnuts as they may interfere with testing.

HORMONE ADD-ON OPTIONS

Both hormones and neurotransmitters serve as key modulators of psychological wellbeing. The targeted neuroendocrine assessment including hormones as well as neurotransmitters provides clinicians with a focused individualized biochemical platform to guide treatment interventions.

Saliva Hormones

The saliva hormones add-on includes estradiol, progesterone, testosterone, DHEA-S, and cortisol, and is an excellent way to assess the initial “big picture” of overall sex and adrenal hormone status in female and male patients. The test provides clinical information regarding the bioavailable fraction of hormones. For those Individuals who produce very little saliva or who use supplementary troche/sublingual hormones, this test is not suitable. It can be used with oral, topical, vaginal, patch, injectable, and pellet forms of hormone administration.

Urine Hormones

The hormonal profile in dried urine features 2 main progesterone metabolites and 6 major androgens, along with estradiol. Assessment of these hormones in dried urine is a convenient option for those patients who are unable to collect sufficient saliva for the salivary test. While the salivary hormones add-on provides an overall glance at the major hormones, the metabolites add-on expands the evaluation to the major sex steroid metabolites and is specifically geared to those patients who present with low or high androgen symptoms or symptoms of estrogen dominance. Urine hormone testing is only suitable for oral, topical, patch, injectable, and pellet forms of hormone administration, but not for vaginal supplementation as vaginal hormones can contaminate the sample.

When to Test Neurotransmitters Alone	When to Combine Neurotransmitters with Diurnal Urinary Hormones	When to Combine Neurotransmitters with Saliva Hormones	When to Combine Neurotransmitters with Urine Hormone Metabolites
<ul style="list-style-type: none"> Managing psychiatric interventions Establish a baseline Patients unable to use HRT Children and Adolescents Hormone levels recently tested 	<ul style="list-style-type: none"> Suspected HPA axis dysfunction Sleep problems PCOS Pre-menopause & menopause Andropause ADHD 	<ul style="list-style-type: none"> PMS/PMDD Symptoms of estrogen dominance High or low androgen symptoms Pre-menopause & menopause Irregular cycles PCOS Suspected HPA axis dysfunction 	<ul style="list-style-type: none"> Low androgen symptoms: fatigue, foggy thinking, decreased stamina High androgen symptoms: acne, scalp hair loss, facial hair growth PCOS Symptoms of estrogen dominance Suspected HPA axis dysfunction

Diurnal Urinary Hormones

Diurnal rhythms of cortisol, cortisone, norepinephrine, and epinephrine reflect HPA axis function; the addition of diurnal melatonin provides a useful measure of circadian rhythm regulation. Detailed characterization of these biochemical parameters may aid in identifying specific imbalances in an individual's response to stress.

Elements Add-on Option

We are exposed to both nutritional and toxic elements through diet, drinking water, supplements, and even the air we breathe. Elements have a variety of effects on brain health. Seven elements are tested in the urine elements profile to give an assessment of deficiencies in essential elements or excessive exposure to toxic heavy metals.

Iodine is essential for healthy thyroid function, and a healthy thyroid is essential to a healthy brain. Thyroid hormone is neuroprotective and plays an important role in regulating the major enzyme involved in methylation in the brain and the body.

Selenium combats mercury and cadmium toxicity. Selenium's effects are antioxidant, anti-inflammatory and neuroprotective in nature through its integration with selenoproteins. Selenoproteins play an essential role in the activation of thyroid hormones as well as integration with glutathione production.

Bromine, in high amounts through exposure to environmental pollutants (e.g., brominated flame retardants), can induce neurotoxicity by inappropriately modifying glycine, glutamate and GABA signaling. Neurological abnormalities from

excessive bromine exposure can include detrimental changes in cognition and mood.

Lithium, in trace amounts, has been shown to improve mood and slow the progression of dementia. Overall, lithium's effects on the brain are neuroprotective, antioxidant and regenerative. Lithium can modulate monoamine oxidase activity to appropriately break down serotonin, dopamine, and phenethylamine.

Arsenic disrupts serotonin and dopamine metabolism, thus compromising neuronal health. Even at low-level exposure, arsenic predisposes to cognitive dysfunction and susceptibility to mood disorders. Additionally, arsenic can induce neuronal death by stimulating processes implicated in Alzheimer's disease.

Cadmium upsets the delicate balance between glycine, glutamate and GABA to negatively impact memory and cognition by being especially destructive to white matter in the brain. Cadmium exposure has detrimental effects on neurocognitive development in children, and is associated with learning disabilities, lower IQ, attention deficits, behavioral problems, and hearing loss.

Mercury is a potent neurotoxin, which increases oxidative stress by permanently inhibiting glutathione function, thereby stripping neurons of their defensive mechanisms. Mercury radically skews neurotransmission – it stimulates excitatory signaling (e.g., glutamate, dopamine) and decreases inhibitory signaling (e.g., GABA). Mercury exposure can cause a variety of neurological symptoms, including irritability, concentration and memory difficulties, and sleep disturbances.

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