

# Urinary Neurotransmitter Testing: Myths and Misconceptions

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## Summary

Urinary neurotransmitter testing has a long history as a means to non-invasively assess neurotransmitter excretion from the body. With the advent of clinical applications of this technology come questions surrounding its feasibility and utility. This review first examines documented mechanisms of neurotransmitter transport across the blood-brain barrier. Further studies examine the effects of renal stimulation on neurotransmitter levels in the urine. Beyond the mechanisms of how neurotransmitters come to be in the urine, numerous studies have demonstrated the utility of urinary measurements. These studies examine potential correlations between urinary levels and various psychological conditions, as well as pharmaceutical drug effects on urinary values. Lastly, data supporting the accurate measurement of neurotransmitter levels in urine is necessary to solidify this technology as a reliable tool for the assessment of nervous system function. This paper will summarize the available literature and provide a compelling perspective about how non-clinical models can assist clinicians in explaining how and why clinical measures of urinary neurotransmitters are a useful indicator of central nervous system activity.

## Introduction

In 1902, Ernest Starling and William Bayliss introduced the world to the existence of an internal communication system with their discovery of the hormone, secretin<sup>1</sup>. Subsequently, scientists have identified countless other chemical messengers within the body. Further research provided clinical relevance to the function of these messengers, many becoming useful biomarkers for various conditions and disease states. This rapidly growing field has expanded to include biomarkers of the nervous system.

Neurotransmitters are the chemical messengers of the nervous system, essential for relaying signals within the brain and communicating with all organ systems of the body. Disruptions in neurotransmission have been implicated in a long list of clinical conditions, ranging from Alzheimer's Disease to Tourette's Syndrome. Urinary neurotransmitter measurements, serving as predictive or correlative biomarkers of nervous system function, are an exciting prospect with a broad spectrum of potential clinical applications.

Neurotransmitters are present in many body fluids, including serum, cerebral spinal fluid (CSF), saliva, and urine. Urinary neurotransmitter assessments have a long, albeit somewhat unknown, history in academic research. For nearly 60 years, scientists have been measuring neurotransmitters and their metabolites as markers for a myriad of applications. Recent developments in this field have taken this technology from an academic to a clinical setting, where neurotransmitter testing can be used by clinicians as a non-invasive tool to address nervous system function. The following review focuses on the evidence regarding the feasibility and utility of urinary neurotransmitter testing and addresses many of the common misconceptions held regarding this technology.

## Neurotransmitters and the Blood-Brain Barrier

Although present throughout the body, neurotransmitters exert primary functions within the central nervous system (CNS). Here, neurotransmitters are synthesized, stored, and released from specialized cells called neurons. Neurons are the workhorses

of the CNS, relaying messages through an electro-chemical process known as neurotransmission. This delicate and highly regulated system is closed off from the rest of the body by the blood-brain barrier (BBB) (see Figure 1.). Located within the capillaries that deliver blood to the brain, the BBB is single layer of specialized endothelial cells referred to as BCEC's (brain capillary endothelial cells). These cells play a protective role, selectively allowing molecules into the CNS while preventing disruptive or harmful molecules from entering. For this reason, it is a commonly held misconception that neurotransmitters from the CNS cannot move to the periphery. In fact, BCEC's possess transporters whose function is to regulate the passage of neurotransmitters in and out of the CNS.

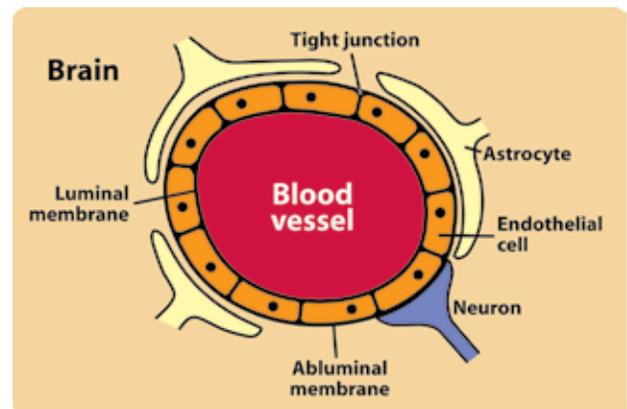


Figure 1. The blood-brain barrier

The majority of the CNS's key neurotransmitters are synthesized from amino acids obtained from the diet. As such, the blood-brain barrier has facilitative and gradient-dependent transporters that shuttle precursors into the CNS for neurotransmitter synthesis. Likewise, the BBB also has transporters that shuttle neurotransmitters and their metabolites out of the CNS (see Figure 2.). Studies have documented the presence of a number of major neurotransmitter transporters, some of which are described below. Other studies have demonstrated the ability

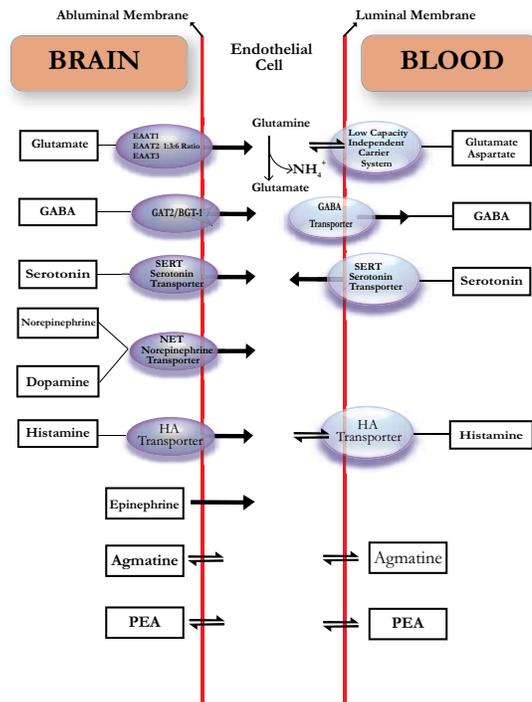
of neurotransmitters to cross cerebral endothelial membranes, further supporting intact CNS neurotransmitter efflux.

- GABA transport from the brain to the blood has been shown to occur on the abluminal membrane via GAT2/BGT-1 transporters<sup>2</sup>. GABA transport across the luminal membrane is thought to occur, however, the transporter has not been identified yet<sup>3</sup>.
- Dopamine and Norepinephrine have been found to cross the abluminal membrane via the NET (Norepinephrine transporter)<sup>4,5</sup>.
- Serotonin has been found to cross both the luminal and abluminal membranes via the SERT (Serotonin transporter)<sup>6</sup>.
- Agmatine crosses the blood-brain barrier. When injected intraperitoneally in mice, an increase in whole-brain agmatine levels was apparent. Additionally, increased CSF agmatine levels were measured following intravenous injection in monkeys<sup>7</sup>.
- Glutamate crosses the abluminal membrane into the endothelial cell via excitatory amino acid transporters (EAAT) EAAT1, EAAT2, and EAAT3<sup>8</sup>. Facilitative glutamine and glutamate transporters are located in the luminal membranes, transporting glutamate from the brain and restricting entry of glutamate into the extracellular fluid of the brain<sup>9</sup>.
- Aspartic acid is transported out of the brain across the abluminal membrane via the EAAT and ASCT2<sup>10</sup>. Luminal transport is facilitated by XG<sup>-11</sup>.
- Phenylethylamine (PEA) is a lipid-soluble neurotransmitter that freely crosses the blood-brain barrier<sup>12</sup>.
- Histamine has been shown to cross both abluminal and luminal cerebral endothelial membranes, with primary action being luminal release<sup>13</sup>.
- Epinephrine uptake in human endothelial cells has been demonstrated in vitro<sup>14</sup>.

The CNS employs a number of mechanisms to clear neurotransmitters from extracellular spaces. The majority of neurotransmitter molecules are taken back up into neurons and repackaged for future use. A percentage of the neurotransmitter pool is degraded into non-signaling metabolites through enzymatic conversion. Based on the evidence cited above, it is clear that intact neurotransmitters are directly transported out of the CNS and into the periphery.

## Neurotransmitters and the Kidneys

Neurotransmitters circulating in the blood are filtered by the kidneys and subsequently excreted in the urine. The existence of intact neurotransmitters in urine is not disputed, as evidenced by studies demonstrating renal transporters capable of filtering neurotransmitters from the blood to the urine. Researchers have identified renal polyspecific cation transporters, hOCT1, hOCT2, hOCT3, as well as the SLC6 family of transporters, which are responsible for monoamine elimination<sup>15-16</sup>. However, questions regarding the potential influence of renal neurotransmitter metabolism on urinary values are raised. Human kidneys contain the enzymes necessary to synthesize and metabolize the major neurotrans-



**Figure 2.** Neurotransmitter transport across the blood-brain barrier

mitters, as well as receiving neural inputs, thus potentially influencing urinary neurotransmitter levels. The degree to which renal neurotransmitter output influences urinary neurotransmitter levels must be considered, as this may affect how urinary data are interpreted. A study examining renal catecholamine (dopamine, norepinephrine, and epinephrine) excretion demonstrated that kidney nerve stimulation led to increased urinary catecholamine output. Based on the data collected, the researchers demonstrated renal nerve catecholamine release. In addition, it was concluded that urinary catecholamine excretion is a poor indicator of renal nerve catecholamine release<sup>17</sup>. This finding suggests neural renal catecholamine contribution to the total pool of urine catecholamines is not a major factor.

Additionally, alterations in neurotransmitter metabolism are not tissue-specific processes. Deficiencies in amino acid neurotransmitter precursors would limit both central neurotransmitter synthesis and renal neurotransmitter synthesis, or any other organ for that matter. In this regard, urinary values are a representation of whole body neurotransmitter metabolism.

Conclusive information comparing the contribution of renal neurotransmitter output to central and peripheral output is scant. However, this consideration may not be an issue if sufficient evidence exists that correlates urinary neurotransmitter levels to various clinical conditions.

## Urinary Neurotransmitters and the CNS

Studies have demonstrated a link between central nervous system neurotransmitter activity and urinary transmitter output. A study in rats examined the effects of oral ingestion of the serotonin precursor, 5-hydroxytryptophan (5-HTP), on specific brain regions<sup>18</sup>. Serotonin levels were measured using brain tissue immunoreactivity and urinalysis. The researchers noted

maximum serotonin immunoreactivity in the serotonergic dorsal raphe nucleus within 2 hours of administration. Urinary analysis of serotonin, 5-HTP, and 5-hydroxyindolacetic acid (the major metabolite of serotonin) mirrored the changes observed in immunoreactivity, suggesting a positive correlation between CNS and urinary serotonin levels.

Another study in rats investigated the effect of induced hemiparkinsonism on the metabolism of catecholamines, as well as the relationship between cerebral catecholamine content and urinary catecholamine excretion. A positive correlation between urinary and striatal dopamine concentrations was demonstrated. Interestingly, the researchers concluded that measurement of urinary catecholamines and their metabolites is a prospective test for evaluating the status of the dopaminergic nigrostriatal system of the brain in experimental parkinsonism<sup>19</sup>.

The studies described above suggest a relationship between urinary neurotransmitter measurements and CNS levels. However, a limitation consistent in these types of studies is the use of animal models. Studies comparing urinary neurotransmitter excretion and neurotransmitter levels in CNS tissue samples are performed in non-human subjects for ethical reasons; consequently, human studies making similar comparisons do not exist. Post-mortem studies investigating correlations in urinary neurotransmitter concentrations and various conditions may offer further insight, however, studies of these type are rare.

A commonly held misconception suggests that cerebral spinal fluid (CSF) serves as the ideal body fluid for assessing CNS activity. While there are many studies correlating CSF to various conditions, a review of the literature did not reveal any studies demonstrating CSF neurotransmitters as diagnostic biomarkers for any psychological condition. Nor is there conclusive evidence that suggests CSF may be a superior clinical correlate to urine. In terms of clinical utility, this realization places urinary and CSF measures on a level playing field. However, a primary drawback using CSF is the invasive nature of the procedure itself. The stressors accompanied with a spinal tap, including mental, physical, and emotional, are likely to activate neurological stress pathways, which utilize neurotransmitters to modulate the response. The resulting stress response could potentially skew the results obtained.

Data correlating urinary to CSF neurotransmitter levels as they relate to various conditions is scarce. However, when considering the practical application of urinary assessments, the argument surrounding the urinary/CSF relationship may be inconsequential. The value in urinary neurotransmitter assessments is not derived from their correlation to CSF or CNS levels, rather from their correlation to various clinical conditions.

### **Urinary Neurotransmitters as Markers for Clinical Conditions**

Research documenting the excretion of urinary neurotransmitters and their metabolites in humans dates back to 1951, when von Euler published a number of papers on this subject<sup>20-22</sup>. The results of this pioneering research led to the first clinical application of neurotransmitter testing, the role of norepinephrine and its metab-

olites as biomarkers of an adrenal tumor known as pheochromocytoma<sup>22-23</sup>. The condition is characterized by the excessive urinary output of norepinephrine, and urinary measurements have been a recommended means of diagnosis for the condition<sup>24</sup>.

In the years since this pioneering work, a compelling number of studies examining psychological disorders have employed urinary neurotransmitter testing. These studies provide evidence supporting three key points: *changes in urinary neurotransmitter excretion correlate with disease states, changes in neurotransmitter excretion correlate with therapeutic effectiveness, and urinary neurotransmitter assessments can assist the healthcare practitioner make more informed decisions regarding the choice of a particular intervention.*

Researchers have demonstrated significant differences between children diagnosed with autism and normal children in the urinary excretion of dopamine, norepinephrine, and their respective metabolites. Autistic children were found to have high levels of urinary dopamine excretion and low levels of urinary norepinephrine excretion relative to non-autistic controls. The results of this study support previous findings suggesting a potential role for altered monoamine metabolism in autistic children. The researchers also noted the prospect of urinary assays in pediatric research<sup>25</sup>.

Investigators examining the effects of trauma on urinary markers and their potential relation to posttraumatic stress disorder found significantly elevated levels of epinephrine following a traumatic event. These results correlated highly with the onset of acute posttraumatic stress disorder symptoms<sup>26</sup>. The findings suggest a predicative role for urinary assessments.

Another study examined the relationship between depression and anxiety symptoms and urinary norepinephrine excretion. The researchers compared urinary data to a psychological assessment evaluating depression and anxiety, the Beck Depression Inventory, and the anxiety portion of the Spielberger State-Trait Anxiety Inventory, respectively. There were significant positive correlations between scores on the inventories and levels of urinary norepinephrine excretion<sup>27</sup>. This study highlights the importance of interpreting urinary neurotransmitter results in tandem with accurate patient history information, due to the number of roles neurotransmitters play within the body.

Researchers have established a link between urinary epinephrine and norepinephrine excretion and obesity. A study in 577 Chinese subjects found that increased body mass index (BMI) was associated with increased norepinephrine but decreased epinephrine output. Additionally, subjects with an increased number of components of metabolic syndrome also had increased norepinephrine but decreased epinephrine output<sup>28</sup>. It was postulated that interactions between the insulin and sympathoadrenal systems could lead to the development of obesity. As such, urinary assessments may offer healthcare providers insight into the mechanisms underlying obesity.

### **Urinary Neurotransmitter Excretion Correlates with Therapeutic Effectiveness**

Another aspect of the clinical utility of urinary assessments is the

ability to monitor therapeutic effectiveness. Because many of the modalities employed to treat psychological disorders influence neurotransmission, neurotransmitter testing can be used to assess the impact of various interventions under certain circumstances.

A study performed by researchers at Texas Christian University explored the efficacy of nutritional interventions enhancing neurotransmitter synthesis on a population of adopted children with high risk for the development of serious behavior disorders. Baseline and follow-up urine samples were collected from a group of 78 subjects, who were randomly assigned to a control group or a treatment group. Achenbach's Child Behavior Checklist (CBCL) was also performed at baseline and follow-up. The treatment group showed significant improvements on four of eight neurotransmitter assays: epinephrine, serotonin, GABA and PEA. Improvements on six of the eleven CBCL subscales were also reported: Anxiety/Depression, Thought Problems, Attention Problems, Aggressive Behavior, Other Problems, and Externalizing Behaviors (see Figure 3). The research focused on the efficacy of the nutritional intervention, which was demonstrated by both the CBCL subscale changes and improvements in urinary neurotransmitter levels<sup>29</sup>.

Changes in Behavior Problems		
Child Behavior Checklist Subscale:	Percent Change	
	Experimental	Control
Attention Problems	-18	-1
Thought Problems	-33	+13
Other Problems	-23	1
Anxiety/Depression	-29	-3
Externalizing Problems	-22	-6
Aggression	-21	-5

Changes in Neurotransmitter Levels		
Morning Urine Levels of:	Percent Change	
	Experimental	Control
Serotonin	+148	+9
GABA	+21	-19
PEA	+8	+40
Epinephrine	-2	-53

**Figure 3.** Changes in neurotransmitter levels and behavior problems in at-risk children. Green boxes indicate a positive change. Red boxes indicate a negative change. Adapted with permission from Purvis et al.

A study examining PEA excretion provided evidence that urinary assessments may be useful in determining therapeutic effectiveness. Twenty-two children diagnosed with attention deficit hyperactivity disorder (ADHD) were treated with methylphenidate, a CNS stimulant. The subjects were divided into two groups, those that responded to treatment and those that did not. Urinary PEA levels in the eighteen subjects who responded were significantly elevated by methylphenidate over baseline values. Conversely, treatment with methylphenidate did not increase PEA in non-responders<sup>30</sup>.

Further supporting the use of urinary measurements for the assessment of neurological interventions is a publication focusing on the use of L-DOPA in Parkinson's Disease patients. Here, the researchers investigated urinary and plasma measurements

of L-DOPA, dopamine, and DOPAC in patients using L-DOPA therapy. It was concluded that both urine and plasma measurements are an effective means to assess patient compliance and avoid over-dosage<sup>31</sup>.

### Urinary Neurotransmitter Testing Guides Therapeutic Decisions

Urinary neurotransmitter testing can be used to assist the clinician in making more informed decisions regarding therapeutic interventions. Psychological conditions are complex, often involving numerous neurotransmitter systems. As such, many are labeled as "spectrum" disorders, others are broken into various subgroups. Recognizing the biochemical diversity within a particular condition implies the need for interventions that are tailored to those differences. Neurotransmitter testing can help the clinician identify the unique biochemical pattern within a disorder, and offer insight into the modality that would best address the issue.

Drugs labeled for use in individuals diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) work on various transmitter systems via differing proposed mechanisms of action. A study in children diagnosed with ADHD demonstrated, via urinary neurotransmitter testing, the differences between common treatments for ADHD. Subjects were given either methylphenidate hydrochloride or dextroamphetamine to compare the effects on excretion of urinary catecholamines and PEA. Methylphenidate led to a significant increase in norepinephrine excretion and no change in PEA excretion. Conversely, dextroamphetamine showed no change in norepinephrine excretion and a 1600% increase in PEA excretion. Currently, there are no definitive means of selecting a drug or other intervention that leads to the best possible outcome<sup>32</sup>.

A study on subjects diagnosed with Tourette's Syndrome (TS) examined differences in urinary PEA excretion. TS subjects with low PEA excretion performed worse than TS subjects with normal PEA excretion on a battery of neuropsychological measures<sup>33</sup>. This study suggests neurotransmitter testing may be useful in characterizing subgroups within a condition. Defining subgroups for a condition may allow clinicians to preferentially target therapeutic interventions to this particular biochemical imbalance.

### Limitations of Urinary Assessments

Urinary assessments do carry certain limitations. A primary limitation is that, with the exception of pheochromocytoma, neurotransmitter testing, in any medium, is not diagnostic for any particular disease or condition. However, urinary neurotransmitter testing can be considered a functional assessment, requiring interpretation of results in the context of a detailed patient history. Likely the most obvious limitation is the argument that urine is not an ideal indicator of CNS activity. Most of the organs within the body are capable of synthesizing, as well as degrading, one or more of the neurotransmitters. This is especially true of the gastro-intestinal system, where enterochromaffin cells serve as the primary site of serotonin synthesis, storage, and release in the body. Here, serotonin plays a pivotal role in the enteric nervous system, activating reflexes associated with intestinal secretion and

motility<sup>34</sup>. As mentioned earlier, the kidneys contain the enzymes necessary to synthesize most neurotransmitters, likewise, serotonin receptors have been located in the skin, suggestive of additional peripheral roles. Therefore, urine neurotransmitter levels are representative of both peripheral and central activity. Regardless, neurotransmitters play essential roles outside of the CNS. Imbalances in urinary neurotransmitter levels are likely indicative of altered neurotransmitter metabolism throughout the body, reinforcing the importance of interpretation of values in tandem with patient history.

## Conclusion

The current body of literature provides evidence that urinary neurotransmitter testing has a place in clinical practice as a biomarker of nervous system function. Studies have demonstrated intact neurotransmitter transport out of the CNS, into the periphery, via blood-brain barrier transporters. Renal filtration of neurotransmitters via specific transporters is well-documented. Researchers have provided examples of urinary neurotransmitter measurements that correlate with CNS tissue concentrations. Lastly, a growing body of evidence exists that associates urinary neurotransmitter output with various clinical conditions, correlates values with therapeutic effectiveness, and allows clinicians to make more informed decisions.

Questions surrounding the source of neurotransmitters in the urine become irrelevant in light of the correlations between urinary excretion and various conditions. The studies cited offer a compelling argument that urinary neurotransmitter testing improves the ability of a clinician to make an informed decision, based on empirical evidence, in first line therapeutic choices that will improve outcomes.

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