

# The Clinical Utility of Urinary Neurotransmitter Analysis: An Overview

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## ABSTRACT

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Neurotransmitters are recognized as the primary biochemical messengers of the central and peripheral nervous systems. Studies have demonstrated that urinary neurotransmitter measures are reflective of circulating levels as evidenced by renal neurotransmitter clearance mechanisms. Laboratory methodology for the accurate assessment of urinary neurotransmitter levels has been established. Urinary measures are not recognized as a direct reflection of central activity, however definite associations exist. The ability to measure neurotransmitters has led to the generation of scientific literature that demonstrates urinary neurotransmitter measurements have clinical value as representative biomarkers of various neurological, immunological, and endocrinological conditions.

Urinary neurotransmitter assessment carries a long history as a means to assess nervous system activity. Early investigations date back to the 1950s when von Euler, et al, first described the measurement of urinary catecholamines as biomarkers for pheochromocytoma, a rare tumor of the adrenal gland. Since then, many studies have been published regarding neurotransmitter excretion and its relevance to neurological, endocrinological, and immunological function. While urinary neurotransmitter measures are not considered direct reflections of central nervous system activity, various disease states stemming from central nervous system imbalances have been associated with urinary neurotransmitter alterations. There is a definite association between urinary and central neurotransmitter concentrations and many studies have examined that association through various neuro-immune communication mechanisms. Controlled studies have shown that after intervention with centrally-acting medications, symptoms resolve with changes in corresponding urinary biomarkers. Below are eight summaries chosen from the literature that discuss the validity and utility of urinary neurotransmitter measurement.

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### URINARY NEUROTRANSMITTER MEASUREMENT METHODOLOGY

Westermann, Hubl, Kaiser & Salewski (2002) established the accuracy and reproducibility of an enzyme linked immunoassay (ELISA) methodology as compared to previously validated high pressure liquid chromatography (HPLC) methodology. The authors concluded that ELISA measures for urinary epinephrine and norepinephrine are appropriate for clinical applications where rapid, accurate, and reproducible measures were desired.

- Design: ELISA methodology validated against established HPLC methodology.
- Biomarker analysis: urinary & plasma epinephrine and norepinephrine.
- Conclusion: ELISA-based laboratory methodology was validated as a reproducible and accurate means to assess urinary epinephrine and norepinephrine.
- Clinical Correlation: ELISA-based measures for urinary epinephrine and norepinephrine are accurate, cost effective, and efficient measures in clinical settings.

### URINARY NEUROTRANSMITTER LEVELS REFLECT CIRCULATING LEVELS

Eisenhofer, McCarty, Pacak, Russ, & Schomig (1996) explored the effects of Disprocynium24 (D24), a renal monoamine transporter inhibitor, on catecholamine clearance in a rat model. Upon administration of D24, plasma catecholamines increased significantly, while a significant decrease in urinary catecholamine levels was observed. The data suggest that urinary catecholamine measures are reflective of circulating catecholamine levels.

- Design: Renal catecholamine clearance in rat was investigated through administration of a monoamine transporter inhibitor
- Biomarker analysis: urinary & plasma epinephrine and norepinephrine.

- Conclusion: Administration of a renal monoamine transporter inhibitor led to significant increases in plasma catecholamine levels and significant decreases in urinary catecholamine levels.
- Clinical Correlation: Urinary catecholamine measures are reflective of circulating catecholamine levels.

### **URINARY NEUROTRANSMITTERS AS BIOMARKERS FOR CLINICAL CONDITIONS**

Vgontzas, Tsigos, Bixler, Stratakis, Zachman Kales, et al (1998) assessed the activity of the adrenal stress system and its association with chronic insomnia. Fifteen adults were tested over 3 consecutive nights for 24 hour levels of cortisol and catecholamines (epinephrine, norepinephrine and dopamine). Findings indicated a positive correlation between total wake time and urinary free cortisol and catecholamine levels. The authors concluded that, based on biomarker analysis, chronic insomnia was correlated with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system.

- Design: 15 Chronic insomniacs studied for 3 consecutive nights
- Biomarker analysis: urinary cortisol & catecholamines
- Conclusion #1: In chronic insomnia, an up-regulated HPA axis and sympathetic nervous system was correlated to the degree of sleep disturbance, as indicated by urinary cortisol and catecholamine excretion
- Conclusion #2: Urinary biomarkers correlated with sleep, a central nervous system function.
- Clinical Correlation: Sleep disturbances associated with HPA axis dysfunction may be evaluated by urinary neurotransmitter and adrenal hormone measurements.

Hughes, Watkins, Blumenthal, Kuhn, & Sherwood (2004) studied the involvement of the autonomic nervous system in depression and anxiety. Urinary catecholamine excretion was measured in 91 women who were also evaluated for depression and anxiety. Higher degrees of depression and anxiety symptoms were associated with increased norepinephrine excretion. These results suggest that depression and anxiety may be associated with increased sympathetic nervous system activity and may be a contributing factor to increased morbidity associated with depressive disorders.

- Design: 91 depressed & anxious women
- Biomarker analysis: urinary cortisol, norepinephrine, & epinephrine
- Conclusion #1: Depression and anxiety, issues related to central nervous system dysfunction, correlated with increased sympathetic nervous system activity as indicated by urinary cortisol & norepinephrine excretion.
- Clinical correlation: Urinary neurotransmitter and adrenal hormone assessments may be useful to effectively address depression and anxiety due to autonomic nervous system dysfunction.

Kusaga, Yamashita, Koeda, Hiratani, Kaneko, Yamada, et al (2002) explored baseline and treatment levels of urinary phenylethylamine (PEA) in 37 children diagnosed with attention deficit hyperactivity disorder (ADHD) who were treated with methylphenidate. Urinary PEA levels were found to be significantly lower in the ADHD individuals compared to controls. In the treatment group, urinary PEA levels significantly increased in those children who responded symptomatically to the medication, whereas PEA levels did not increase in non-responders.

- Design: 37 children diagnosed with ADHD, administered methylphenidate
- Biomarker analysis: urinary PEA
- Conclusion #1: Urinary PEA levels were significantly greater in children who responded to methylphenidate. PEA levels did not significantly change in those who did not respond to treatment.
- Conclusion #2: Urinary measures of the neurotransmitter PEA correlated with the positive response to a centrally-acting medication.
- Conclusion #3: Urinary PEA correlated with ADHD, an issue associated with central nervous system imbalance.
- Clinical correlation: Urinary measurements of PEA may provide valuable insight into intervention effectiveness in patients with ADHD.

Cohrs, Zhenghua, Pohlman, Jordan, Pilz, Ruther, et al (2004) measured urinary dopamine and DOPAC levels in a cohort who experienced nighttime periodic leg movements (PLMs). Nocturnal measures demonstrated significantly lower levels of dopamine and DOPAC in those with PLMs vs. Non-PLM controls. The authors concluded that this and other studies suggest low urinary dopamine measures are indicative of low central dopaminergic activity.

- Design: Comparative study, 4 with periodic leg movement disorder vs 11 controls
- Biomarker analysis: urinary dopamine, DOPAC
- Conclusion: Urinary dopamine and DOPAC levels were significantly lower in subjects who experienced PLMs during the night. A significant negative correlation between dopamine levels and PLMs per hour existed. The findings suggest reduced urinary dopamine excretion is indicative of decreased central dopaminergic activity.
- Clinical correlation: Urinary measurements of dopamine and DOPAC may provide valuable insight into central dopamine activity as it relates to PLMs.

Delahanty, Nugent, Christopher, & Walsh (2004) examined the role of urinary epinephrine and cortisol as biological correlates of chronic post traumatic stress disorder (PTSD) in children. Samples were collected from 82 children immediately following a traumatic event. PTSD and depressive symptoms were reassessed 6 weeks following the event. Urinary epinephrine and cortisol levels immediately following a traumatic event correlated with the risk for development of subsequent PTSD symptoms.

- Design: 82 children aged 8-18 admitted to trauma center
- Biomarker analysis: Urinary epinephrine, cortisol
- Conclusion: Increased urinary epinephrine and cortisol excretion immediately following a traumatic experience was correlated with increased risk of development of PTSD symptoms 6 weeks following the event.
- Clinical correlation: Urinary epinephrine and cortisol measures may predict the development of PTSD symptoms in children following traumatic events.

#### **URINARY NEUROTRANSMITTERS AS INDICATORS OF INTERVENTION EFFICACY**

Kotzailias, Marker, & Gilma, (2004) administered the selective serotonin reuptake inhibitor paroxetine (20mg/day) to twenty male volunteers for 18 days. This was a double-blind, placebo-controlled, block-randomized, 2-way crossover study designed to characterize the effects of paroxetine on urinary and plasma serotonin levels. After 24 hours, there was a slight transient rise in plasma serotonin concentration while urinary serotonin excretion increased by 89%. No significant change in urinary serotonin excretion was observed in non-treatment controls. Evidence suggests that urinary serotonin can monitor the effectiveness of paroxetine.

- Design: 20 males administered paroxetine at 20mg/day for 18 days
- Biomarker analysis: Urinary & plasma serotonin
- Conclusion: Urinary serotonin levels significantly increased following paroxetine administration
- Clinical correlation: Urinary serotonin measures are an effective way to objectively measure the effectiveness of the centrally-acting antidepressant SSRI, paroxetine.

#### **SUMMARY**

A review of the literature concerning the clinical validity and relevance of urinary neurotransmitter analysis has revealed numerous publications exploring these topics. Data prove that neurotransmitters can be accurately and reproducibly measured via ELISA-based laboratory methodologies. Studies show that neurotransmitter transporters are present in renal tissue and that urinary measures of neurotransmitters reflect circulating levels. While urinary measures are not a direct assessment of central activity, studies have characterized urinary neurotransmitters as biomarkers of various conditions linked to the disruptions within the central nervous system. Interventions targeting the CNS illustrate definite changes in symptomology along with corresponding changes in urinary neurotransmitter levels. In conclusion, urinary neurotransmitter measurements are effective tools which can assist clinicians choose the optimal interventions for therapeutic success.

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