

# Urinary Neurotransmitter Analysis as a Biomarker for Psychiatric Disorders

by Amnon Kahane, MD

A biomarker is a measurement used as an indicator of biological actions. Biomarkers are prevalent in most branches of medicine. Measurement of specific biological features allows practitioners to determine diagnoses and prognoses and predict treatment outcomes by providing objective measurements to target. Significant strides have been made to understand complex disorders like diabetes and heart disease with the measurement of a limited number of biomarkers, such as measures of lipoproteins and triglycerides (Gotto, Jr. 1998). Currently, there are no biomarkers available for psychiatric disorders; therefore, diagnostic tools and treatment decisions are restricted to the evaluation of clinical signs and symptoms that lack objectivity. That said, treatments for managing psychiatric symptoms are relatively effective. However, no single treatment works for everyone with a given disorder, and selection of the best treatment in mainstream psychiatry remains a challenge.

As in any other disease state, a primary goal in psychiatry is the identification of specific biomarkers that would permit a more precise definition of specific disorders and, in turn, enhance the ability to develop targeted patient treatments. In fact, research has highlighted a need for

biomarkers in psychiatry to enhance patient management and ensure treatment success (Holsboer 2008; Keshavan et al. 2005; Peedicayil 2008).

In a recent article by Cook (2008), an outline of desirable characteristics of biomarkers in psychiatry was described. Cook (2008) stated that certain criteria must be met for a biomarker to be considered for psychiatric management. First, the biomarker must be timely, clinically useful, and cost-effective. Second, the technology needed to assess the biomarker must be well tolerated by the target patient population. Third, methods that can be easily integrated into the practitioner's current practice patterns are more likely to be accepted than those that require a major change in the delivery of care. These criteria are mentioned here as a prelude for an innovative technology that both satisfies psychiatric biomarker requirements and significantly enhances initial treatment regimens for patients with psychiatric symptoms. In addition, this technology provides ongoing analysis of existing treatment strategies, thereby supplying valuable and relevant biological feedback to the psychiatric practitioner. This technology is urinary neurotransmitter analysis and has become an integral component of my psychiatric practice.

Urinary neurotransmitter analysis has a breadth of data to support its usefulness in clinical practice. In the late 1950s, publications revealed correlations of urinary catecholamine measures to various psychiatric symptoms (Bergsman 1959; Carlsson et al. 1959; Sulkowitch et al. 1957). Since then, research on urinary neurotransmitter analysis has expanded to encompass methodological improvements (Seegal et al. 1986; Westermann et al. 2002) and further development on clinical utility for psychiatric disorders. Specifically, research has focused on categorizing subsets of depression and anxiety through urinary neurotransmitter analysis, as well as determining biochemical changes with pharmaceutical intervention.

Roy and colleagues (1986) examined subsets of unipolar depressed patients and compared these subjects to non-depressed controls. Overall, depressed patients had high urinary norepinephrine and its metabolite normetanephrine, but lower urinary output of the dopamine metabolite dihydroxyphenylacetic acid (DOPAC) compared to controls. Subjects that met DSM-III criteria for a major depressive episode with melancholia, characterized by irrational fears, guilt, and apathy, exhibited significantly higher urinary outputs of normetanephrine than

controls. Subjects with a major depressive episode but without melancholia or subjects with dysthymic disorder had levels comparable with controls. It was concluded that high urinary output of norepinephrine and its metabolite, normetanephrine, reflected abnormal sympathetic nervous system activity and thus, may be helpful in determining subsets of depression (Roy et al. 1986). Later studies confirmed these findings, which reported elevations in urinary norepinephrine output in depressed and anxious individuals (Grossman and Potter 1999; Hughes et al. 2004; Otte et al. 2005).

Although research shows significant correlations between depression and urinary neurotransmitter levels, its clinical application is not validated unless changes in urinary values and symptoms can be observed with treatment. Mooney and colleagues (1988) conducted a study in which depressed patients who had favorable antidepressant responses to alprazolam, a benzodiazepine, had significantly higher pretreatment urinary catecholamine levels than control subjects. In addition, non-responders to alprazolam did not have significant elevations in urinary neurotransmitters output compared to control subjects. After only eight days of treatment with alprazolam, urinary catecholamine levels declined significantly, which contributed to the improvement in depressive symptoms (Mooney et al. 1988). Additionally, a double-blind, placebo-controlled, block-randomized, two-way crossover study revealed that after administration of 20 mg/d of paroxetine, urinary serotonin excretion significantly increased when compared to placebo, and correlated with an improved symptom profile (Kotzailias et al. 2004). Lastly, fear and anxiety were analyzed in patients who underwent outpatient surgery, by examination of urinary catecholamines. Duggan and colleagues (2002) examined the effect of the benzodiazepine diazepam on the stress response in patients after outpatient anesthesia and surgery,

by the measurement of urinary catecholamines. The study showed significant reductions in urinary norepinephrine levels in the group that received diazepam compared to placebo (Duggan et al. 2002). These findings, along with earlier studies, illustrate the importance of urinary neurotransmitter measurements in the determination of treatment effectiveness.

Attention-Deficit-Hyperactivity Disorder (ADHD) has also been a primary target for the utilization of urinary neurotransmitter analysis. Research has shown that subjects with ADHD tend to have decreased urinary beta-phenylethylamine (PEA) levels (Kusaga et al. 2002a). Beta-PEA is a monoamine neurotransmitter that has amphetamine-like functions that can alter mood and attention, and decreased beta-PEA levels may contribute to symptoms of inattentiveness (Berry 2004). After treatment with methylphenidate, those that responded to medication had significantly elevated urinary beta-PEA levels (Kusaga et al. 2002b). Other studies have reported decreased urinary epinephrine levels in ADHD children compared to controls (Anderson et al. 2000). These findings are consistent with prior studies that demonstrated an inverse relationship between epinephrine excretion and inattentive, restless behavior (Hanna et al. 1996). Urinary norepinephrine levels were found to be positively correlated with the degree of hyperactivity in ADHD children. The same study showed that after one month of Pycnogenol treatment, a bioflavonoid extract from pine bark, norepinephrine levels decreased significantly and correlated with improvement in ADHD symptoms (Dvorakova et al. 2007).

Overall, urinary neurotransmitter analysis can be a useful tool in any clinical practice dealing with psychiatric disorders. Clearly, research supports the clinical relevance of urinary monoamine measurements, and with the advent of improved laboratory techniques, the cost of the

testing has significantly decreased along with the time it takes to run the laboratory analysis. In addition, other neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), histamine, glycine, and taurine are being measured with high specificity and selectivity. If we consider the established criteria required for a biomarker to correspond to or indicate psychiatric symptoms, urinary neurotransmitter analysis meets these necessary requirements. It is cost-effective, timely, non-invasive (to ensure patient compliance), and can easily be incorporated into any clinical practice. Objectivity is essential to treating patients with psychiatric disorders. Medical history and DSM-IV criteria may suffice for the diagnosis of psychiatric disorders (Maj et al. 1999; Maj et al. 2000), however, the heterogeneity of patient biochemistry can decrease successful treatment outcome (Schwarz and Bahn 2008). Neuropsychiatric biomarkers may aid in determining successful treatment regimens based on patient biochemistry rather than simply relying on standard diagnostic protocols.

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### Amnon Kahane, MD

Dr. Kahane was born in Tel Aviv, Israel, and graduated from Hadassah Medical School (Hebrew University of Jerusalem, Israel). Dr. Kahane was trained in General Psychiatry at New York University and Bellevue in New York City and conducted his fellowship in child psychiatry at The University of Texas Medical Branch at Galveston, Texas. Following his training, Dr. Kahane did a four-year post fellowship at Yale University at New Haven, Connecticut. Dr. Kahane currently practices psychiatry at Northlight Counseling Associates in Phoenix, Arizona.