

Monitoring Substance Abuse Recovery with Urinary Neurotransmitter Analysis

Judith Miller, PhD; David Marc, BS^a; Corena McManus, MS; Mike Bull, BS; Kelly Olson, PhD; Gottfried Kellermann, PhD

^a NeuroScience, Inc., 373 280th St., Osceola, WI 54020, United States
david.marc@neurorelief.com

ABSTRACT

Evidence-based practices are becoming more prevalent for the treatment of substance abuse disorders. Substance abuse causes a substantial burden to society due to certain substances causing potential adverse health effects and leading to increases in crime. Traditional treatment for substance abuse relies on pharmacological and spiritual guidance, yet new strategies are being explored. Of interest is the use of complementary and alternative medicine (CAM) approaches that target neurological functioning. Amino acid supplementation is one modality that may show promise as an adjunctive therapy in substance abuse programs. The purpose of this study was to examine the use of amino acid supplementation in substance abuse patients and also introduce a novel method that may aid in detecting responders and non-responders prior to beginning treatment. Patients at a residential rehabilitation facility provided urine specimens before and three weeks following amino acid supplementation to monitor neurotransmitter levels. The amino acids were shown to increase serotonin, taurine, and decrease phenylethylamine (PEA) following three weeks of treatment. This study also demonstrated significantly higher baseline norepinephrine, serotonin, and PEA levels in the patients that remained sober following amino acid supplementation. Overall, results demonstrated that amino acid supplementation may be a promising addition to current substance abuse programs and that urinary neurotransmitters may serve as biomarkers to predict treatment responses in substance abuse patients.

INTRODUCTION

The abuse of alcohol and illegal substances poses a substantial burden to society. Research suggests that substance abuse leads to extensive economic costs due to increases in crime, violence, and institutionalization/hospitalization, (Conover et al., 2006; Miller et al., 2006). Financially, the abuse of alcohol cost between 210-665 billion US dollars in 2002 in medical and legal fees (Baumberg, 2006). Due to the tremendous economic burden, evidence-based practices in traditional and complementary and alternative medicine (CAM) are being explored as a means to improve treatment regimens for addiction (O'Brien, 2008).

Traditionally, pharmacological and spiritual guidance have been the primary treatments for substance abuse, however, non-traditional methods are being explored. For instance, acupuncture has been examined as an adjunctive therapy to existing treatments for cocaine addiction (Kim et al., 2005). Other CAM modalities, such as herbal therapy, continue to appear more frequently in psychiatric settings. A study found that 63% of respondents to a recent survey, of which 26% had a diagnosed substance abuse disorder, used at least one CAM modality in the previous 12 months (Elkins et al., 2005). The most frequently used CAM modality was herbal therapy, followed by mind-body therapies such as relaxation or mental imagery, hypnosis, meditation, and biofeedback (Elkins et al., 2005).

Research has shown that amino acid supplementation can alter levels of neurotransmitters that may be related to addiction making it a promising CAM approach in substance abuse programs (Kiefer & Mann, 2005). Specifically, intravenous administration of L-tryptophan has been found to attenuate the cocaine-induced increase in forebrain dopamine and decrease the

cocaine-induced locomotor activity in rats (Molina et al., 2001). Similarly, the administration of 5-hydroxytryptophan (5-HTP), the direct precursor to serotonin, with co-administration of phentermine, a dopamine agonist, reduced alcohol intake and suppressed alcohol withdrawal seizures in rats (Molina et al., 2001). These therapeutic actions may be related to elevations in synaptic dopamine and serotonin in critical brain regions such as the nucleus accumbens (Molina et al., 2001).

The nucleus accumbens is a forebrain region that plays an important role in reward, laughter, pleasure, addiction, and fear (Schwienbacher et al., 2006). Human studies have found that N-acetylcysteine administration can reduce the desire for and interest in an abused substance in the presence of drug cues (LaRowe et al., 2007). Additionally, N-acetylcysteine has been shown to prevent cocaine-induced changes in cystine transport (LaRowe et al., 2007). The administration of cocaine produces a persistent reduction in cystine/glutamate exchange in the nucleus accumbens via the xc- transport system, leading to elevated levels of synaptic glutamate (Madayag et al., 2007). N-acetylcysteine administration normalizes the xc- system stabilizing cystine/glutamate transport and decreasing synaptic glutamate (Grant et al., 2007; Madayag et al., 2007).

A limitation to substance abuse treatment has been the inability to target therapy due to the lack of available biomarkers (Elkashef & Vocci, 2003). The combination of determining the neurobiological effects of addiction with the known mechanisms of medications and supplements may prove to be useful for discovering biomarkers to help target specific pharmacological agents for subgroups of patients, predict response to medication, and predict relapse (Elkashef & Vocci, 2003). In this way,

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biomarkers may allow patients to reach sobriety in a more timely manner.

As evident from the above research, amino acid supplements can cause alterations in specific brain regions that are related to substance abuse, such as the nucleus accumbens (Blais & Janak, 2008). Potential drugs of abuse such as morphine, heroin, cocaine, alcohol, and stimulants have been shown to cause alterations in neurotransmitter signaling in the nucleus accumbens and thereby results in reinforcing pleasure responses and increases the likelihood of subsequent drug use (Floresco et al., 2008). These drugs lead to biochemical abnormalities that can be corrected with pharmacotherapy and/or amino acid supplementation. Furthermore, amino acid supplementation could potentially be monitored with biomarkers, such as urinary neurotransmitter assessment, as a way to determine the effectiveness of such an intervention.

The purpose of this study was to determine whether amino acid treatment, monitored by urinary neurotransmitter analysis, would lead to a decrease in relapse-rates for subjects at a residential rehabilitation facility. We hypothesized that urinary neurotransmitter analyses may act as predictive biomarkers that would identify relapse propensity and assist in monitoring treatment responses.

METHODS

Subjects were enrolled in a residential rehabilitation facility at the Courage to Change Ranch Addiction Recovery Program in Simla, Colorado. Upon arrival into the facility, subjects signed a consent form and a detailed patient history was obtained. Additionally, various surveys were filled out by each subject to determine their degree of drug dependency and to help reveal the potential chance of relapse. A urine specimen was collected by each subject following enrollment into the facility to determine the baseline levels of the neurotransmitters epinephrine, norepinephrine, dopamine, serotonin, glycine, taurine, gamma-aminobutyric acid (GABA), glutamate, phenylethylamine (PEA), and histamine. Urine specimens were analyzed by Pharmasan Labs, Inc. (Osceola, WI) by enzyme linked immunosorbent assays (ELISA). After collecting the baseline urine specimens, subjects were put on a nutritional supplement protocol, which included a proprietary blend of 5-HTP, taurine, L-theanine, N-acetyltyrosine, L-histidine, L-methionine, *Rhodiola rosea* extract, N-acetylcysteine, alpha-lipoic acid, and coenzyme Q10. A total of 173 subjects were initially enrolled in the study; however, only 64 subjects submitted urine specimens after 3-weeks of treatment. Of the 64 subjects that submitted specimens for second analysis, 43

subjects provided information as to whether they stayed sober or relapsed back into substance abuse.

Three types of drug dependencies were characterized across subjects: alcohol dependence, methamphetamine dependence, and other. Drugs other than alcohol and methamphetamine were combined into the “other” category due to an insufficient number of subjects with dependency to substances other than alcohol and methamphetamine. The “other” category consisted of heroin, cocaine, and polysubstance abusers.

Paired t-tests were used to determine statistical significance between baseline neurotransmitter values compared to follow-up values after 3-weeks of treatment for the 64 subjects to evaluate amino acid treatment. Further, chi-squared analysis was used to determine if sobriety was related to the type of drug dependence. Finally, a two-way ANOVA was conducted to determine whether differences existed in baseline and follow-up neurotransmitter levels in the 43 who provided information about sobriety following treatment.

RESULTS

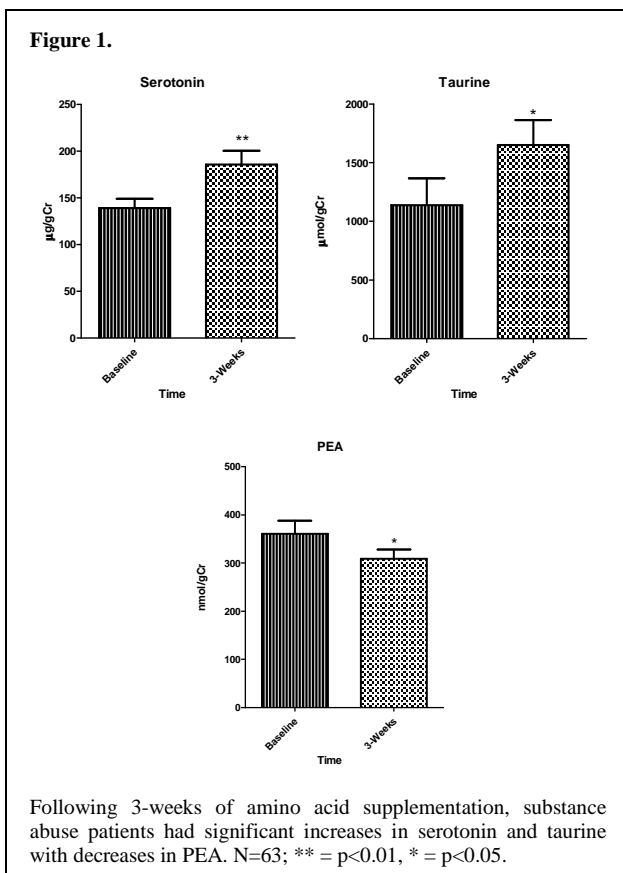
Among the 64 subjects that completed a neurotransmitter assessment following 3-weeks of treatment, statistically significant increases were found for serotonin ($p < 0.01$) and taurine from baseline levels ($p < 0.05$; Figure 1). Conversely, statistically significant decreases were observed for PEA ($p < 0.05$) following 3-weeks of treatment (Figure 1).

Chi-squared analysis did not show any relationship between the type of drug dependency and sobriety following 3-weeks of treatment. Two-way ANOVAs revealed significant differences in the baseline norepinephrine, serotonin, and PEA levels of subjects that remained sober vs those that relapsed. The average norepinephrine values of those that remained sober were significantly higher than in those that relapsed ($p < 0.05$) (Figure 2). Bonferroni post-tests revealed a significantly higher mean baseline norepinephrine value in subjects who remained sober compared to those that relapsed ($p < 0.05$) (Figure 2). A two-way ANOVA revealed that the average serotonin values of those that remained sober were significantly higher than those that relapsed ($p < 0.01$) (Figure 2). Finally, the average PEA values of those that remained sober were significantly higher than those that had relapsed ($p < 0.01$; Figure 2).

DISCUSSION

This study examined the effects of amino acid supplementation in subjects enrolled in a residential substance abuse rehabilitation facility. The results revealed that following 3-

weeks of amino acid supplementation there were significant increases in serotonin and taurine with decreased levels of PEA (Figure 1). In addition, baseline levels of norepinephrine, serotonin, and PEA were higher for subjects that remained sober versus those that relapsed following 3-weeks of treatment (Figure 2).



The results of this study indicated increased serotonin for substance abuse patients following 3-weeks of amino acid supplementation, in which 5-HTP was included. In the literature, oral administration of 5-HTP to rats was shown to increase the levels of serotonin in brain nuclei and urine (Lynn-Bullock et al., 2004). In cocaine dependent rats, 5-HTP enhanced serotonin concentrations in the nucleus accumbens and reduced the desire for cocaine following cocaine withdrawal (Harris et al., 2001). Observations from our study suggest that the oral administration of 5-HTP in substance abuse patients can successfully increase serotonin levels and may play a role in reducing drug-seeking behaviors.

Urinary taurine levels increased in subjects after 3-weeks of amino acid supplementation, in which taurine supplementation was included. Taurine supplementation has been shown to be neuroprotective and may improve cardiovascular

health (Nittynen et al., 1999). Oral administration of taurine has been shown to increase plasma and urinary taurine (Kopple et al., 1990). Alcohol consumption has been shown to interfere with sulfur-containing amino acid (SCAA) metabolism and lead to decreased pyridoxal-5'-phosphate and S-adenosylmethionine/S-adenosylhomocysteine ratio along with elevated homocysteine (Yang et al., 2009). This has serious health risks as elevated homocysteine is an independent risk factor for cardiovascular disease, cerebrovascular disease, dementia-type disorders, and osteoporosis-associated fractures (Maron & Loscalzo, 2008). Oral administration of taurine, a β -amino acid, can reverse the effects of alcohol on SCAA metabolism, thus decreasing homocysteine levels and the risk for cardiovascular disease while increasing urinary taurine levels (Yang et al., 2009).

PEA, an aromatic amine neurotransmitter, was found to be elevated at baseline, but levels decreased following 3-weeks of amino acid supplementation. Kusaga and colleagues (2002) found that PEA levels increased following the administration of methylphenidate and amphetamines. The decrease in PEA may have resulted from subjects discontinuing the use of stimulant drugs such as methamphetamine, which is structurally similar to amphetamines (Shoblock et al., 2003), for the duration of the study.

When neurotransmitter levels for those that stayed sober and those that relapsed following 3-weeks of treatment were compared, significant differences were found. Overall, those that remained sober following 3-weeks of treatment had significantly higher baseline norepinephrine values than those that relapsed. It is possible that the higher baseline norepinephrine could be a predictive measure used to indicate a better responder to treatment. Likewise, lower norepinephrine values may indicate the need for a more targeted treatment such as increased doses of amino acid supplementation.

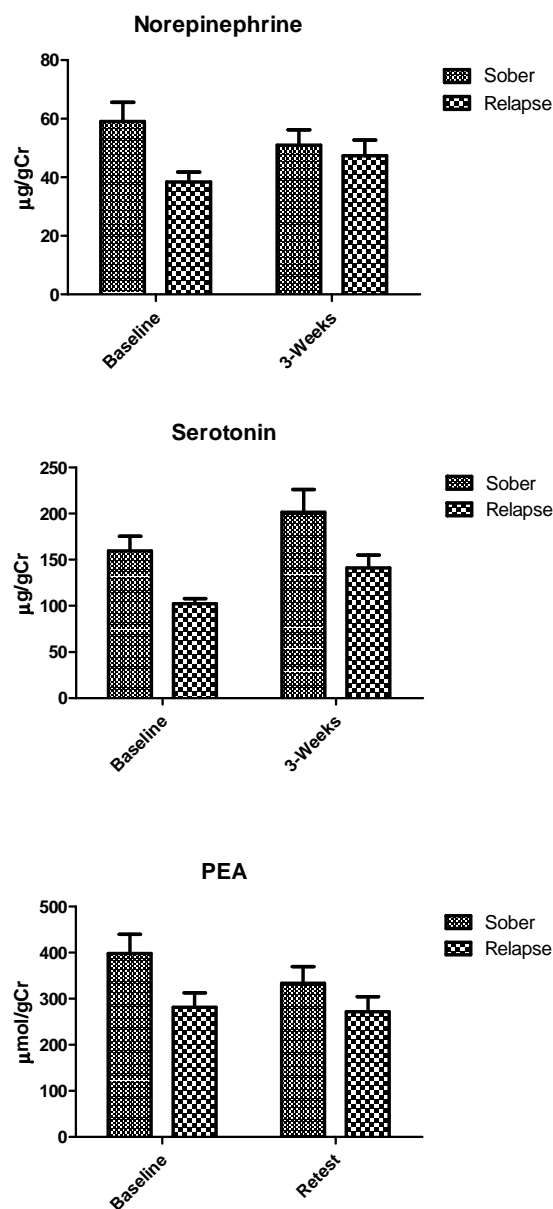
Baseline serotonin levels also differed for individuals that remained sober compared to those that relapsed following 3-weeks of treatment. Overall, baseline serotonin levels were significantly higher in sober individuals. For both groups the serotonin levels increased significantly at the end of 3-weeks of amino acid supplementation. Since 5-HTP acts as a precursor to serotonin (Lynn-Bullock et al., 2004), the use of 5-HTP may have led to the increased serotonin levels following 3-weeks of treatment. However, individuals who relapsed did not have the same magnitude of increase in serotonin suggesting that lower baseline serotonin values may serve as a predictive marker for relapse, which may warrant a more aggressive 5-HTP treatment. The higher serotonin levels observed in those who remained sober

following 3-weeks of amino acid treatment may have served to help decrease the chance of relapse.

Those that remained sober following 3-weeks of treatment had significantly higher baseline PEA values compared to those that relapsed. It is possible that higher baseline PEA values could be used as predictive measures to indicate a better response to treatment. Likewise, lower PEA values may be indicative of a need for a more aggressive treatment with amino acid supplementation. The lower PEA values observed in individuals who relapsed may also suggest the need to “self-medicate” with stimulant medications such as methylphenidate and amphetamines. Methylphenidate and amphetamines have been known to cause increased urinary PEA values leading to a rewarding response and enhanced concentration (Kusaga et al., 2002). It is possible that the lower baseline PEA values reflected a predisposition to “self-medicate” with stimulant medications and increased the chance of relapse.

The biochemical differences observed in the baseline neurotransmitter levels may have contributed to subjects’ continued sobriety or lack thereof. Individuals with lower baseline norepinephrine and serotonin levels may have also had a higher propensity to “self-medicate” with drugs. Markou and colleagues (1998) proposed a hypothesis suggesting that individuals with depression share biochemical similarities to those with drug dependence. They proposed that it was possible that those with depression may experiment with several types of drugs and are able to determine the drug or drug combinations that best normalize their neurochemical imbalances based on their symptomatology (Markou et al., 1998). For instance, stimulant medications may have enhanced monoaminergic neurotransmission by reversing deficits in serotonin, dopamine, and norepinephrine in depressed individuals (Jayanthi & Ramamoorthy, 2005; Paterson & Markou, 2007). Other substances such as alcohol, morphine, and nicotine may have enhanced monoaminergic mechanisms, which lead to an antidepressant-like effect (Heinz et al., 2003; Nowakowska et al., 2006; Rowlett et al., 2004). Support for this hypothesis was based on evidence that antidepressant medication appeared more effective in the reduction of drug use in depressed drug abusers versus non-depressed drug abusers, suggesting that antidepressants may replace the need for drugs of abuse (Moeller et al., 2007; Shoptaw et al., 2008). Therefore, biochemical abnormalities may have contributed to drug seeking behavior in an attempt to normalize an individual’s biochemistry. Therefore, the severity of the biochemical abnormality may be correlated with the severity of elicited drug use (Belknap et al., 2008).

Figure 2.



Norepinephrine, serotonin, and PEA were significantly higher for the sober group than the relapsed group. There was no significant difference from baseline to 3-weeks and no significant interaction for any of the parameters. N= 43.

CONCLUSION

The results of this study indicated significantly higher baseline neurotransmitters levels were related to sobriety. Those that had higher neurotransmitter levels at baseline were more likely to remain sober following 3-weeks of amino acid treatment. One limitation of the study was the lack of a control population where subjects did not utilize amino acid supplementation. Without the control population, the efficacy of amino acid supplementation was

difficult to interpret as a means to assist in the treatment of substance abuse. However, the study showed how neurotransmitter analysis may predict treatment responses to pharmacological agents, as observed in a residential rehabilitation facility for drug and alcohol abuse. Future studies should examine neurotransmitter fluctuations to treatments other than amino acid supplementation for substance abuse. In addition, future studies should determine whether relapse rates are dependent on the dose of amino acid supplementation in subjects with significant neurotransmitter deficiencies.

The possibility that biomarkers can be used to determine treatment responses could lead to a substantial decrease in economic costs associated with substance abuse. Urinary neurotransmitter analysis may be a predictive tool to help indicate the chance of relapse for individuals with substance dependence. Healthcare practitioners may use urinary neurotransmitter assessment to identify individuals with a high-risk for relapse thus warranting a more aggressive or extended therapy to increase the chance of obtaining sobriety and ultimately decrease the economic burden that substance abuse poses.

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