Coupling Genetic Addiction Risk Score (GARS) and Pro Dopamine Regulation (KB220) to Combat Substance Use Disorder (SUD)

Kenneth Blum\textsuperscript{1-10*}, Margaret A Madigan\textsuperscript{4}, Lyle Fried\textsuperscript{7}, Eric R Braverman\textsuperscript{6}, John Giordano\textsuperscript{5} and Rajendra D Badgaiyan\textsuperscript{9}

\textsuperscript{1}Department of Psychiatry & McKnight Brain Institute, University of Florida College of Medicine, USA
\textsuperscript{2}Department of Psychiatry and Behavioral Sciences, Keck Medicine University of Southern California, USA
\textsuperscript{3}Division of Applied Clinical Research & Education, Dominion Diagnostics, USA
\textsuperscript{4}Department of Neurogenetics, Igene, USA
\textsuperscript{5}National Institute for Holistic Addiction Studies, USA
\textsuperscript{6}Department of Clinical Neurology, Path Foundation NY, USA
\textsuperscript{7}Division of Neuroscience Based Addiction Therapy, The Shores Treatment & Recovery Center, USA
\textsuperscript{8}Eötvös Loránd University, Institute of Psychology, Europe
\textsuperscript{9}Department of Psychiatry, Wright State University Boonshoft School of Medicine and Dayton VA Medical Center, USA
\textsuperscript{10}Division of Reward Deficiency Syndrome, Nupathways, Inc., Innsbrook, MO, USA

\*Corresponding author: Kenneth Blum, Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL, USA; Tel: 352-294-4911; Fax: 352-392-9887; Email: dr2gene@gmail.com

Abbreviations: RDS: Reward Deficiency Syndrome; SMART\textsuperscript{™}: Systematic Medical Approach to Reward Transformation; GARS: Genetic Addiction Risk Score; DNA: Deoxyribonucleic Acid; DRD2: Dopamine Receptor D2 Gene; MOA: Monoamine Oxidase; SNPs: Single-Nucleotide Polymorphisms; SSRs: Simple Sequence Repeats

Introduction

We are proposing a generalized approach based on the Reward Deficiency Syndrome (RDS) conceptualization called the Systematic Medical Approach to Reward Transformation (SMART\textsuperscript{™}). This system consists of: early pre-disposition diagnosis (even in children) using the Genetic Addiction Risk Score (GARS) [1]; a validated RDS questionnaire [2]; urine drug testing during actual treatment that uses comprehensive analysis of reported drugs to determine compliance with prescription medications and non-abstinence illicit drugs [3]; and adjunctive treatment with a glutaminergic-dopaminergic optimization nutraceutical (KB220) to prevent relapse by induction of dopamine homeostasis [4].

Understanding reward deficiency syndrome (RDS)

I. RDS conceptualization

The biological processes of reward that underlie addiction to substances and all addictive, compulsive and impulsive behaviors are the basis of the RDS conceptualization [5,6]. RDS then is a deficiency, a hypodopaminergic condition that results from some combination of genetic variations, environmental stressors, and adverse molecular effects or blunting due to prolonged substance use or behavioral habituation [7-9]. The RDS concept was developed based on animal and human research that explored the molecular biology of neurotransmission, and behavioral genetics [8,10,11]. Understanding this concept, explained in the following paragraphs, is central to treating the abnormal psychology of personality and spectrum disorders, as well as, substance and non-substance (behavioral) addictions. To feel ordinary pleasure, complex interactions of neurotransmitters regulate the dopaminergic activity of the brain in the reward center -the mesolimbic system, particularly the nucleus accumbens. Individuals, who suffer from a lack of ordinary pleasure in their lives, are predisposed to use any means; substance or behavior, to activate dopamine release, relieve stress and feel healthy pleasure [12,13].
Genes are deoxyribonucleic acid (DNA), which directs the functional properties of proteins like neurotransmitters. Genetic alleles are unusual versions of a gene that can change genetic function they are called polymorphisms or variants. Early in the 1990’s a statistically significant association of severe alcoholism with a variant, the A1 allele of the Dopamine Receptor D2 Gene (DRD2) was discovered [14]. This variant was later associated with numerous other addictive, compulsive and impulsive behaviors. At the same time, a binding availability study found that functionally, the presence of the A1 allele resulted in lower dopamine receptor availability in the parts of the brain known to effect reward [15]. Other earlier studies had explored the role of neurotransmitters in pleasure. In the limbic neural circuitry serotonin, enkephalin, GABA, and dopamine work together in a complex cascade of activation and inhibition that result in the release of dopamine. Dopamine was identified as one of the most powerful neurotransmitters that control feelings of well-being and reward. Negative emotions and craving are the results of disruption of the intercellular brain reward cascade that leads to reduced dopamine availability [16].

II. Hypodopaminergic function

The hypodopaminergic trait is itself polygenetic (involves many genes) and may result from variations in a number of reward genes. Reward genes govern the function of the dopaminergic, serotonergic, endorphinergic, opioidergic, GABAergic, adrenergic, cholinergic pathways, as well as, many second messengers, like enzymes and mRNA. Many associations with other genes and these behaviors have also been identified [17]. Many genes that are involved in the function of the reward neurotransmitters in the brain have variations that result in hypodopaminergic function [10]. For example, individuals may have high Monoamine Oxidase (MOA) gene activity, an increased rate of mitochondrial dopamine catabolism, due to the effect of an allele. Other examples are reduced numbers of serotonin receptors, due to polymorphisms of the 5-HT2A receptorgene (-1438A/G). Serotonin transporter gene 5-HTTLPR polymorphisms also reduce synaptic serotonin levels, due to the biallelic (short and long alleles) and triallelic polymorphisms (including rs25531 A/G a single nucleotide variation) [18].

III. The epigenetics of stress and prolonged exposure

In addition to genetic polymorphisms, which reduce the availability of dopamine in the synapse, prolonged stress and long-term substance abuse also result in reduced cascade function and decreased dopamine release and may have a cumulative effect on vulnerability to addiction and other RDS Behaviors [19,20]. Harmful molecular effects or blunting occur due to prolonged substance use [21,22]. The repeated release of high amounts of dopamine into the synaptic cleft induces prolonged, heightened postsynaptic receptor activity, resulting in receptor down-regulation and, for this reason, further decreases dopamine function. Also, hypodopaminergic function, caused by genetic variations impacted by epigenetics, can induce impairments in the pre-frontal cortex-cingulated gyrus, which in turn leads to poor judgment and potential habit reinstatement or relapse [20,22].

Receptor down-regulation reported, in both obese rats and drug-addicted humans, is the reason habituated addicts require ever increasing substance or behavior to maintain the rewarding effect [20,23]. However after prolonged abstinence dopamine receptor super-sensitivity, an enhanced biochemical response develops, and reinstatement at the previous level of habituation in the case of substance abuse may lead to fatalities [24]. Environmentally induced epigenetic effects on the chromatin structure of the DNA due to stress or triggered by cues can increase craving. Stress-triggered craving involves the neurotransmitters corticotrophin-releasing factor and norepinephrine. These neurotransmitters necessitate the abundant release of dopamine (100X times resting state) and subsequently, temporary hypodopaminergic functioning, repeated, or prolonged stress can induce a chronic hypodopaminergic state. Cue-triggered craving involves the basolateral nucleus of the amygdala, the hippocampus, and through glutaminergic activation, causes the increased release of dopamine that if chronic ultimately leads to a hypodopaminergic state. Due to this hypodopaminergic trait (genetic) and state (environmental), it is known that drug intake or aberrant behaviors will escalate [25,26].

Genetic addiction risk score (GARS)

The Genetic Addiction Risk Score (GARS), is the first test to accurately predict vulnerability to pain, addiction, and other obsessive and compulsive behaviors, identified as RDS [27]. There is a need to classify patients at genetic risk to alcohol and drug-seeking behavior and relapse before or upon entry to pain and residential and or non-residential chemical dependency programs. Based on an extensive literature review, an addiction risk index consisting of 11 polymorphisms in 10 genes, involved in the neurological processing of reward, were identified and tested. The resulting genetic addiction risk score (GARS) included; six single-nucleotide polymorphisms (SNPs) in the DRD1, DRD2, DRD3, DRD4, COMT, and OPRM1 genes; four simple sequence repeats (SSRs) in the DAT1, DRD4, MAOA, and 5HTT transporter genes; and a dinucleotide polymorphism in the GABRA3 gene [9]. Blum’s laboratory sought to address genetic risk for alcohol and drug by evaluating whether the combined effect of reward gene polymorphisms that contribute to a hypodopaminergic trait, associate with RDS related substance abuse risk. Among those who consented to provide a saliva sample for DNA genotyping, 273 (derived from seven centers) also had ASI phenotypic information.

The patient population n=393, 17.6%, 80.7%, and 1.5% scored in the low, moderate and high severity range, respectively. The mean number of GARS alleles was 7.97 (S.D. = 2.34) and ranged between 3 and 17 alleles. The relationship between GARS genotype panel and the Alcohol Risk Severity Score using the Fishers Exact Test revealed a significant predicative relationship.
(X² = 8.84, df = 1, p = 0.004, 2-tailed) that remained significant after controlling for age (p < 0.01). A similar, though less robust, relationship was obtained from chi-square (p = 0.05) and linear regression (b = -0.122, t = -1.91, p = 0.10, 2-tailed) analyses of the ASI Drug Severity Risk Score. Blum et al. [28,29] details the construction of a genetic addiction risk score (GARS™) and its predictive relationship with ASI -MV derived alcohol and drug severity risk scores. Innovative strategies to combat epidemic opioid/opiate abuse, and death, based on the role of dopaminergic tone in pain pathways, are proposed. Sensitivity to pain may reside in the mesolimbic projection system, where genetic polymorphisms associate with a predisposition to pain vulnerability or tolerance. Pharmacogenomic testing of candidate genes like CB1, mu receptors, and PENK might result in pharmacogenomic, personalized solutions, and improved clinical outcomes. Identifying genetic risk for all RDS behaviors, especially in compromised populations, may be a frontline tool to assist municipalities in providing better resource allocation and possibly precision medicine [30].

**RDS questionnaire**

In conjunction with Zsolt Demetrovics in the Eötvös Loránd University, Institute of Psychology, Budapest, Hungary, an unpublished, 29 item RDS questionnaire reduced from 51 items generated based on the RDS theory, has been validated in over 1726 individuals attending college. The general reward deficiency factor was associated with gender, sensation seeking and impulsivity. Females show a higher degree of reward deficiency trait. Greater sensation seeking and impulsivity predict higher degrees of reward deficiency and risk seeking behaviors and are positively associated with sensation seeking and impulsivity [2].

**Pro-Dopamine regulator (KB220)**

A glutamnergic-dopaminergic optimization nutraceutical called KB220 has been developed that supports the brain reward system and induces "dopamine homeostasis". This agonistic nutraceutical has been shown to safely provide substantial clinical benefit to the victims of RDS and assist in recovery from addiction to opiates/opioids and other substance and non-substance addictions and behaviors [7,17,31-33]. DNA-directed compensatory over expression of the DA D2 receptors (a form of gene therapy) has been shown to result in a significant reduction in alcohol and cocaine craving behavior in drug-prefering rodents [34,35] and acute in vitro bromocriptine a strong agonist-induced D2 receptor proliferation in rats [36]. KB220 variants formulations have been studied extensively in both animals and humans. Pre-clinical and human trials using a variety of methodologies are reported on in a detailed review article [37] and Table 1 lists the studies of KB220 variants in a multiplicity of RDS populations. Interestingly, in abstinent heroin addicts, a pilot study of a single dose of KB220Z compared to placebo found improvement of the prefrontal-cerebellar-occipital neural network and activation of the NAc [38].

**Table 1: List of Clinical Studies: 1973 - 2016.**

| Year | Reference | Key points |
|------|-----------|------------|
| 1973 | Blum K, Calhoun W, Merritt J, et al. L-DOPA: effect on ethanol narcosis and brain biogenic amines in mice. Nature. 242: 407-409. | Increased brain L-DOPA increases brain dopamine in mice and causes inebriated mice to sleep. Dopamine, 1-tryptophan and alcohol work similarly in the brain. |
| 1974 | Blum K, Wallace JE, Calhoun W, et al. Ethanol narcosis in mice: serotonergic involvement. Experientia 30:1053-1054. | When mice were given alcohol and 1-tryptophan or saline the mice given 1-tryptophan went to sleep. The mice given saline did not. 1-tryptophan and alcohol work similarly in the brain. |
| 1987 | Blum K, Wallace JE, Trachtenberg MC, et al. Enkephalase inhibition: Regulation of ethanol intake in mice. Alcohol: 4: 449-456. | Mice genetically predisposed to like alcohol have a measured deficiency in enkephalin. D-phenylalanine and hydrocinnamic acid are substances known to stop the breakdown of enkephalin in the brain -the amount of enkephalin available in the brain increases. When the amount of enkephalin available in the brain increases both voluntary and forced intake of alcohol decreases. D-phenylalanine is one of the ingredients in NAAT. |

| Year | Reference | Key points |
|------|-----------|------------|
| 1988 | Blum K, Trachtenberg MC, Elliott CE, et al. Improvement of inpatient treatment of the alcoholic as a function of neurotransmitter restoration: a pilot study. The International journal of the addictions 23: 991-8. | First small clinical trial of SAAVE (precursor amino acid loading and enkephalinase inhibition -earliest version of NAAT). Designed to elevate levels of enkephalin(s), serotonin, catecholamines, and GABA, thought to be deficient in alcoholics. Compared to controls those who took SAAVE had lower building up to drink score, required no PRN benzodiazepines, ceased having tremors 24 hours earlier, and had less depression. |
| Year | Author(s) | Title and Summary |
|------|-----------|-------------------|
| 1996 | Blum K, Trachtenberg MC, Cook DW. | Neuroneutrient effects on weight loss in carbohydrate bingers: an open clinical trial. *Curr Ther Res.* 22: 217-233.  
Examining the effects of PCAL-103 (a NAAT) on compulsive eating and weight loss in 27 outpatients attending a supervised diet-controlled treatment program. The PCAL-103 average weight loss was 26.96 lbs vs 10.2 lbs in the control group. Relapse 18.2% in the PCAL-103 group vs 81.8% in the control group. |
| 1997 | DeFrance JF, Hymel C, Trachtenberg MC, et al. | Enhancement of attention processing by Kantroll in healthy humans: a pilot study. *Clinical Electroencephalography* 28: 68-75.  
Cognitive processing speeds in normal young adult volunteers were measured before and after 28-30 days of supplementation with a combination of amino acids (NAAT), vitamins and minerals. Cognitive processing speeds were enhanced by a statistically significant amplitude of the P300 component of the Event Related Potentials (ERP). |
| 2001 | Ross J. | Amino-acid precursor and enkephalinase inhibition therapy: evidence for effectiveness in treatment of Reward Deficiency Syndrome (RDS) with particular emphasis on eating disorders. *Mol Psychiatry.* Feb; 6(1 Suppl 1):S1-S8.  
Preliminary evaluation of six randomly selected former eating disordered female clients (three were also chemically dependent), contacted at 9 months and 3 years of treatment with amino-acid precursor and enkephalinase inhibition therapy. All 6 reported initial benefit, one relapsed at 6 months the other 5 all sustained, and in some cases exceeded expectations. 98% of 100 patients similarly treated and evaluated reported significant improvement in both mood and reduced substance craving. |
| 2004 | Chen TJ; Blum K, Payte, Jt, et al. | Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. *Medical Hypotheses* 63 (3): 538-48.  
A combination of Trexan (a narcotic antagonist) and amino-acids was use to detoxify either methadone or heroin addicts. Results were dramatic in terms of significantly enhancing compliance to continue taking Trexan. Trexan alone for rapid detoxification the average number of days of compliance calculated on 1000 patients is 37 days. 12 subjects tested, receiving both the Trexan and amino-acid therapy taking the combination for an average of 262 days. Suggests coupling amino-acid therapy and enkephalinase inhibition, while blocking the delta-receptors with a pure narcotic antagonist as a novel method to induce rapid detox in chronic methadone patients and prevent relapse, and testing this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphine. |
| 1990 | Brown RJ, Blum K, Trachtenberg, MC. | Relapse prevention using neuroneutrients SAAVE and Tropamine in DUI offenders; either alcohol or cocaine. Reduced relapse rates and enhanced recovery in 10-week outpatient setting. After 10 months’ recovery rate was SAAVE 73% and Tropamine 53%. |
| 1997 | Cold JA, NeuRecover-SATM in the Treatment of Cocaine Withdrawal and Craving: A Pilot Study. *Clinical Drug Investigation.* 12(1):1-7.  
A combination of Trexan (a narcotic antagonist) and amino-acids was use to detoxify either methadone or heroin addicts. Results were dramatic in terms of significantly enhancing compliance to continue taking Trexan. Trexan alone for rapid detoxification the average number of days of compliance calculated on 1000 patients is 37 days. 12 subjects tested, receiving both the Trexan and amino-acid therapy taking the combination for an average of 262 days. Suggests coupling amino-acid therapy and enkephalinase inhibition, while blocking the delta-receptors with a pure narcotic antagonist as a novel method to induce rapid detox in chronic methadone patients and prevent relapse, and testing this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphine. |
| 2004 | Blum K, Trachtenberg MC, Elliott CE, et al. | Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE. *Alcohol.* 5(6): 481-93.  
Double blind placebo controlled clinical trial of SAAVE of 62 people with Substance Use Disorder (SUD). Results reduced stress as measured by skin conductance, improved Physical and BESS (behavioral, emotional, social and spiritual) Scores, and had a six-fold decrease in leaving Against Medical Advice (AMA) rates. |
| 2004 | Blum K, Allsion D, Trachtenberg MC, et al. | Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30-day inpatient treatment program by the neuronutrient Tropamine. *Current Therapeutic Research* 43: 1204-1214.  
Comparison of the effects of Tropamine [T] – (amino acid and vitamin supplement), SAAVE [S]-(a neuronutrient supplement) and no supplement [C] on a group of cocaine abusers in a 30-day hospital treatment program. AMA rate [C] 37.5%, [S] 26.6%, and [T] 4.2 %. Tropamine decreased the AMA rate by significant reduction of drug hunger. |
| 1997 | Blum K, Trachtenberg MC, Cook DW. | Neuroneutrient effects on weight loss in carbohydrate bingers: an open clinical trial. *Curr Ther Res.* 22: 173-187.  
Relapse prevention using neuroneutrients SAAVE and Tropamine in DUI offenders; either alcohol or cocaine. Reduced relapse rates and enhanced recovery in 10-week outpatient setting. After 10 months’ recovery rate was SAAVE 73% and Tropamine 53%. |
| Year | Authors | Title | Summary |
|------|---------|-------|---------|
| 2006 | Blum K, Chen TJ, Meshkin B, et al. | Reward deficiency syndrome in obesity: a preliminary cross-sectional trial with a Genotrim variant. | Evaluated the effects of taking Haveos (Synaptamine™) on 61 compliant patients in a comprehensive outpatient clinical program. Results after 12 weeks include significant decrease in craving. Studies after 1 year include building up to relapse scores and ability to refrain from drug-seeking behavior both significantly improved. Dropout rate for alcohol users 7% and psychostimulant users 73%. |
| 2007 | Chen TJ, Blum K, Wake RL, et al. | Niacinotic Attenuation Program attenuates substance use disorder, a clinical subtype of reward deficiency syndrome. | 1-year prospective study that evaluated the effects of taking Haveos (Synaptamine™) on 61 compliant patients in a comprehensive outpatient clinical program. Results after 12 weeks include significant decrease in craving. Results after 1 year include building up to relapse scores and ability to refrain from drug-seeking behavior both significantly improved. Dropout rate for alcohol users 7% and psychostimulant users 73%. |
| 2008 | Blum K, Chen TJH, Downs BW, et al. | Synaptamine (SG839)™ An Amino-Acid Enkephalinase Inhibition Nutraceutical Improves Recovery of Alcoholics, A Subtype of Reward Deficiency Syndrome (RDS), Trends in Applied Sciences Research 2 (3): 132-138. | In an open clinical study Amino-Acid Enkephalinase Inhibition Nutraceutical improved symptomatology of 600 recovering Alcoholics. Emotional and behavioral recovery scores significantly improved after administration of oral and intravenous Synaptamine. Mean reductions for craving, depression, anxiety, anger, fatigue, lack of energy and crisis were all significantly greater than 50% (p<0.001). |
| 2009 | Blum K, Chen AL, Chen TJ, et al. | LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. Advances in Therapy 25 (9): 894-913. | Preliminary investigational study of evaluate the impact of polymorphisms of five candidate genes on treatment for obesity with NAAT. The formula for each patient was customized based on their genetic results. |
| 2010 | Blum K, Chen AL, Chen TJ, et al. | LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. | A novel experimental DNA-customized nutraceutical, LG839. Polymorphic correlates were obtained for a number of genes (LEP, PPAR-gamma2, MTHFR, 5-HT2A, and DRD2 genes) with positive clinical parameters tested in this study. Significant results were observed for weight loss, sugar craving reduction, appetite suppression, snack reduction, reduction of late night eating, increased energy etc. Only the DRD2 gene polymorphism (A1 allele) had a significant Pearson correlation with days on treatment. |

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| Year | Title                                                                 | Authors                                                                                   | Abstract                                                                                                                                                                                                 |
|------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2011 | "Dopamine Resistance" in brain reward circuitry as a function of D2R2 gene receptor polymorphisms in RDS: Syntaptamine complex variant (KB220) induced "Dopamine Sensitivity" and enhancement of happiness. XIX World Congress of Psychiatric Genetics, September 10-14th. Washington DC. | Blum K, Stice E, Liu Y, et al. | Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D2 agonist therapy. Part 2. Postgrad. Med. Nov; 122(6):214-26. Protracted Abstinence in Psychostimulant abusers. qEEG analysis in DRD2 A1 allele carriers. Compared to placebo-Synaptose Complex KB220iTm induced positive regulation of the dysregulated electrical activity of the brain in these addicts. |
| 2012 | In 129 patients a combination of IV and oral NAAR therapy (generic KB220) were assessed for Chronic Abstinence Symptom Severity (CASS) Scale over a 30-day period. Two scales were constructed based on this factor analysis: Emotion, Somatic, and Cognitive. All three scales showed significant improvement (P=0.00001) from pre-to post -treatments: t=19.1 for Emotion, t=16.1 for Somatic, and t=14.9 for impaired cognitive. A two-year follow-up in a subset of 23 patients showed: 21(91%) were sober at 6 months with 19(82%) having no relapse; 19(82%) were sober at one year with 18(78%) having no relapse; 21(91%) were sober at two years post-treatment with 16(70%) having no relapse. Note: these results of cause do not reflect any other recovery skills utilized by the patients including 12 steps program and Fellowship. | Miller M, Chen ALC, Stokes SD, et al. Early Intervention of Intravenous KB220IV Neuroadaptagen Amino-Acid Therapy (NAAT)™ Improves Behavioral Outcomes in a Residential Addiction Treatment Program: A Pilot Study. Journal of Psychoactive Drugs (in press December issue 2012). | This study examined the effects of combined administration of tyrosine, lecithin, L-glutamine and L-5-hydroxytryptophan (5-HTP) on heroin withdrawal syndromes and mental symptoms in detoxified heroin addicts. The results showed that the insomnia and withdrawal scores were significantly improved over time in participants in the intervention group as compared with those in the control group. A greater reduction in tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and total mood disturbance, and a greater increase in their vigor-activity symptoms were found at day 6 in the intervention group than in the control placebo group. |
| 2011 | Case study evaluating sustained weight loss with Synaptamine complex in conjunction with Diethypropion (Tenuate®), hormonal repletion therapy; use of the Rainbow Diet® and light exercise. After one year, the 58 year old patient’s BMT decreased from 32 to 25.4 kg/m² representing a 6.9 kg/m² reduction. His body fat composition decreased from 36.91% to 17.8% as measured by the Hologic DEXA scanner. | Blum K, Chen TJ, Morse S, et al. Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D2 agonist therapy. Part 2. Postgrad. Med. Nov; 122(6):188-213. | Intravenous Syntaptamine complex in protracted abstinence from alcohol and opiates analyzed by qEEG. Report that the qEEGs of an alcoholic and a heroin abuser with existing abnormalities (i.e., widespread theta and widespread alpha activity, respectively) during protracted abstinence are significantly normalized by the administration of 1 intravenous dose of Syntaptamine Complex Variant KB220iTmed. |
| 2010 | Targeting Noradrenergic and dopaminergic Mechanistic Sites, Hormonal Deficiency Repletion Therapy and Exercise: A case report. The American Journal of Bariatric Medicine. 25 (2):18-28, 2010. | Braverman ER, Braverman D, Acruí V, et al. | How to cite this article: Braverman ER, Braverman D, Acruí V, et al. Targeting Noradrenergic and dopaminergic Mechanistic Sites, Hormonal Deficiency Repletion Therapy and Exercise: A case report. The American Journal of Bariatric Medicine. 25 (2):18-28, 2010. | In 129 patients a combination of IV and oral NAAR therapy (generic KB220) were assessed for Chronic Abstinence Symptom Severity (CASS) Scale over a 30-day period. Three scales were constructed based on this factor analysis: Emotion, Somatic, and Cognitive. All three scales showed significant improvement (P=0.00001) from pre-to post -treatments: t=19.1 for Emotion, t=16.1 for Somatic, and t=14.9 for impaired cognitive. A two-year follow-up in a subset of 23 patients showed: 21(91%) were sober at 6 months with 19(82%) having no relapse; 19(82%) were sober at one year with 18(78%) having no relapse; 21(91%) were sober at two years post-treatment with 16(70%) having no relapse. Note: these results of cause do not reflect any other recovery skills utilized by the patients including 12 steps program and Fellowship. |
Lucid dreams may be associated with psychiatric conditions, including Post-Traumatic Stress Disorder (PTSD) and Reward Deficiency Syndrome-associated diagnoses. We present two cases of dramatic alleviation of terrifying lucid dreams in patients with PTSD. The medication visit notes reveal changes in the frequency, intensity and nature of these dreams after the complex putative dopamine agonist KB220Z was added to the first patient’s regimen. The second PTSD patient, who had suffered from lucid nightmares, was administered KB220Z to attenuate methadone withdrawal symptoms and incidentally reported dreams full of happiness and laughter.

Lucid dreams could be unpleasant or terrifying, at least in the context of patients, who also exhibit characteristics of Reward Deficiency Syndrome (RDS) and Posttraumatic Stress Disorder (PTSD). We present eight clinical cases, with known substance abuse, PTSD. The medication visit notes reveal changes in the frequency, intensity and nature of these dreams after the complex putative dopamine agonist KB220Z was added to the first patient’s regimen. The second PTSD patient, who had suffered from lucid nightmares, was administered KB220Z to attenuate methadone withdrawal symptoms and incidentally reported dreams full of happiness and laughter.

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Attention Deficit-Hyperactivity Disorder (ADHD) often continues into adulthood. Recent neuroimaging studies found lowered baseline dopamine tone in the brains of affected individuals that may place them at risk for Substance Use Disorder (SUD). This is an observational case study of the potential for novel management of Adult ADHD with a non-addictive glutaminergic-dopaminergic optimization complex KB200z. Low-resolution electromagnetic tomography (LORETA) was used to evaluate the effects of KB220z on a 72-year-old male with ADHD, at baseline and one hour following administration. The resultant z-scores, averaged across Eyes Closed, Eyes Open and Working Memory conditions, increased for each frequency band, in the anterior, dorsal and posterior cingulate regions, as well as the right dorsolateral prefrontal cortex during Working Memory, with KB220z. These scores are consistent with other human and animal neuroimaging studies that demonstrated increased connectivity volumes in reward circuitry and may offer a new approach to ADHD treatment. However, larger randomized trials to confirm these results are required.

**Reference**

Blum K, Oscar-Berman M, Dinubile N, Giordano J, Braverman ER, et al. (2013) Coupling Genetic Addiction Risk Score (GARS) with Electrotherapy: Fighting Iatrogenic Opioid Dependence. J Addict Res Ther 4(163).

**Conclusion**

Recently the hypothesis [39-43] that KB220Z would enhance resting connectivity patterns between reward and cognitive brain regions was tested in placebo-controlled rsfMRI experiments in the rat. Additionally, qEEG studies in humans found that KB220Z modulates theta power in the anterior cingulate cortex [44,45]. Double-blind controlled studies and others [37,46-48] have demonstrated positive effects on both craving attenuation and relapse prevention [48-50] and enhanced compliance to KB220z. These scores are consistent with other human and animal neuroimaging studies that demonstrated increased connectivity volumes in reward circuitry and may offer a new approach to ADHD treatment. However, larger randomized trials to confirm these results are required.

**References**

1. Blum K, Han D, Femino J, Smith DE, Saunders S, et al. (2014) Systematic evaluation of “compliance” to prescribed treatment medications and “abstinence” from psychoactive drug abuse in chemical dependence programs: data from the comprehensive analysis of reported drugs. PLoS One 9(9): e101475.

2. Zsolt Demetrovics, Róbert Urbán, K Blum (2016) Reward Deficiency Syndrome and Addictive Disorders. Hungary 4th International Conference on Pathological Gambling and Other Behavioural Addictions, Europe.

3. Blum K, Han D, Femino J, Smith DE, Saunders S, et al. (2014) Systematic evaluation of “compliance” to prescribed treatment medications and “abstinence” from psychoactive drug abuse in chemical dependence programs: data from the comprehensive analysis of reported drugs. PLoS One 9(9): e101475.

4. Blum K, Febo M, Fahike C, Archer T, Berggren U, et al. (2015) Hypothesizing Balancing Endorphinergic and Glutaminergic Systems to Treat and Prevent Relapse to Reward Deficiency Behaviors:
Coupling D-Phenylalanine and N-Acetyl-L-Cysteine (NAC) as a Novel Therapeutic Modality. Clin Med Rev Case Rep 2(8).

5. Blum K, Sheridan PJ, Wood RG, Braverman ER, Chen TJ, et al. (1996) The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J Soc Med 89(7): 396-400.

6. Blum K, Braverman ER, Holder M, Lubar JF, Monastra VJ, et al. (2000) Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 32(3-4): 1-112.

7. Blum K, Thanos PK, Badgayan RD, Febo M, Oscar-Berman, M, et al. (2015) Neurogenetics and gene therapy for reward deficiency syndrome: are we going to the Promised Land? Expert Opin Biol Ther 15(7): 973-85.

8. Comings DE, Blum K (2000) Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res 126: 325-341.

9. Blum K, Oscar-Berman M, Giordano J, Downs B, Simpatico T, et al. (2012) Neurogenetic Impairments of Brain Reward Circuitry Links to Reward Deficiency Syndrome (RDS): Potential Nutrigenomic Induced Dopaminergic Activation. J Genet Syndr Gene Ther 3(4).

10. Blum K, Febo M, BadgayanRD, Demetrovics Z, Simpatico T, et al. (2016) Common Neurogenetic Diagnosis and Meso-Limbic Manipulation of Hypodopaminergic Function in Reward Deficiency Syndrome (RDS): Changing the Recovery Landscape. Curr Neuropharmacol 15(1): 184-194.

11. Blum K, Futterman S, Wallace JR, Schweertner HA (1977) Naloxone-induced inhibition of ethanol dependence in mice. Nature 265:5589: 49-51.

12. Blum K, Gardner E, Oscar-Berman M, Gold M (2012) “Liking” and “Wanting” Linked to Reward Deficiency Disorder (RDS): Hypothesizing Differential Responsivity in Brain Reward Circuitry. Curr Pharm Des 18:1: 113-118.

13. K Blum, J Payne (1990) Alcohol & The Addictive Brain. The Free Press Simon & Schuster, New York, USA.

14. Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, et al. (1990) Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 263(15): 2055-2060.

15. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ (1991) Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry 48(7): 648-54.

16. K. Blum and G. P. Kozlowski (1990) Ethanol and neuromodulators interaction: a cascade model of reward. In: Alcohol and Behavior. (Eds.) H Ollat., S.Parve & H Parve VSP Press Utrecht, The Netherlands, USA.

17. Blum K, Febo M, Thanos PK, Baron D, Fratantonio J, et al. (2015) Clinically Combating Reward Deficiency Syndrome (RDS) with Dopamine Agonist Therapy as a Paradigm Shift: Dopamine for Dinner? Mol Neurobiol 52(3): 1862-1869.

18. Blum K, Oscar-Berman M, Bard D, Giordano J, Gold M (2013) Dopamine Genetics and Function in Food and Substance Abuse. J Genet Syndr Gene Ther 4(121).

19. Sotomayor-Zárate R, Abarca J, Araya KA, Renard GM, Andrés ME, et al. (2015) Exposure to repeated immobilization stress inhibits cocaine-induced increase in dopamine extracellular levels in the rat ventral tegmental area. Pharmacol Res 101: 116-123.

20. Hill E, Han D, Dumouchel P, Dehak N, Quatieri T, et al. (2013) Longterm Suboxone emotional reactivity as measured by automatic detection in speech. PLoS One 8(7).

21. Stice E, Yokum S, Blum K, Bohon C (2010) Weight gain is associated with reduced striatal response to palatable food. J Neurosci 30(39): 13105-13109.

22. Jenner P, Marsden CD (1987) Chronic pharmacological manipulation of dopamine receptors in brain. Neuropharmacology 26(7b): 931-940.

23. Bogomolova EV, Rauschenbach IY, Adonyeva NV, Aleskeev AA, Faddieva NV, et al. (2010) Dopamine down-regulates activity of alkaline phosphatase in Drosophila: the role of D2-like receptors. J Insect Physiol 56(9): 1155-1159.

24. Blum K, Chen TJ, Downs BW, Bowirrat A, Waite RL, et al. (2009) Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: proposing “deprivation-amplification relapse therapy” (DART). Postgrad Med 121(6): 176-196.

25. Martinez D, Saccone PA, Liu F, Slištejn M, Orlowska D, et al. (2012) Deficits in dopamine D2 receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. BioPsychoMed 71(3): 192-198.

26. Bonito-Oliva A, Södersten E, Spigolon G, Hu X, Hellysz A (2016) Differential regulation of the phosphorylation of Trimethyl-histone H3 at serine 28 in distinct populations of striatal projection neurons. Neuropharmacology 107: 89-99.

27. Blum K, Oscar-Berman M, Demetrovics Z, Barb D, Gold MS (2014) Genetic Addiction Risk Score (GARS): molecular neurogenetic evidence for predisposition to Reward Deficiency Syndrome (RDS). Mol Neurobiol 50(3): 765-766.

28. KB Blum, BC Haberstic, A Smolen, D Han, Marlene Oscar-Berman, et al. (2017) Genetic addiction risk score (GARS) predicts addiction severity index - MV alcohol and drug - Risk scores in a multi-center study. Submitted to PLURRENT.

29. Kenneth Blum, David Han, Mary Hauser, Bernard William Downs, John Giordano, et al. (2013) Neurogenetic Impairments of Brain Reward Circuitry Links to Reward Deficiency Syndrome (RDS) as evidenced by Genetic Addiction Risk Score (GARS): A case study. The IIOAB Journal 4(1): 4-9.

30. Kenneth Blum, BW Downs, Kristina Dushaj, Mona Li, Eric R Braverman, et al. (2016) The Benefits of Customized DNA Directed Nutrition To Balance The Brain Reward Circuitry And Reduce Addictive Behaviors. Precis Med (Bangalore) 1(1): 18-33.

31. Blum K, Simpatico T, Badgayan RD, Demetrovics Z, Fratantonio J, et al. (2015) Coupling Neurogenetics (GARS) and a Nutrigenomic Based Dopaminergic Agonist to Treat Reward Deficiency Syndrome (RDS): Targeting Polymorphic Reward Genes for Carbohydrate Addiction Algorithms. J Reward Defic Syndr 1(2): 75-80.

32. McBlaughlin T, Febo M, Badgayan RD, Barb D, Dushaj K, et al. (2016) KB220Z™ a Pro-Dopamine Regulator Associated with the Protracted, Alleviation of Terrifying Lucid Dreams. Can We Infer Neuroplasticity-induced Changes in the Reward Circuit? J Reward Defic Syndr Addict Sci 2(1): 3-13.

33. Steinberg B, Blum K, McBlaughlin T, Lubar J, Febo M, et al. (2016) Low-resolution electromagnetic tomography (LORETA) of changed brain function provoked by pro-dopamine regulator (KB220z) in one adult ADHD cases. Open J Med Case Rep 2(11): 11-21.

34. Thanos PK, Katana JM, Ashby CR Jr, Michaelides M, Gardner EL, et al. (2005) The selective dopamine D3 receptor antagonist SB-277011-A attenuates ethanol consumption in ethanol preferring (P) and non-preferring (NP) rats. Pharmacol Biochem Behav 81(1): 190-197.

35. Thanos PK, Michaelides M, Umeughi H, Volkow ND (2008) D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. Synapse 62(7): 481-486.

36. Boundy VA, Pacheco MA, Guan W, Molinoff PB (1995) Agonists and antagonists differentially regulate the high affinity state of the D2L receptor in human embryonic kidney 293 cells. Mol Pharmacol 48(5): 956-964.
37. Blum K, Oscar-Berman M, Stuller E, Miller D, Giordano J, et al. (2012) Neurogenetics and Nutrigenomics of Neuro-Nutrient Therapy for Reward Deficiency Syndrome (RDS): Clinical Ramifications as a Function of Molecular Neurobiological Mechanisms. J Addict Res Ther 3(5): 139.

38. Blum K, Liu Y, Wang W, Wang Y, Zhang Y, et al. (2015) rsfMRI effects of KB220Z on neural pathways in reward circuitry of abstinent genotyped heroin addicts. Postgrad Med 127(2): 232-241.

39. Duong TQ, Yacoub E, Adriany G, Hu X, U gorburil K, et al. (2002) High-resolution, spin-echo BOLD, and Gf-rfMRI at 4 and 7 T. Magn Reson Med 48(4): 589-593.

40. Febo M, Ferrie CF (2014) Oxytocin and vasopressin modulation of the neural correlates of motivation and emotion: results from functional MRI studies in awake rats. Brain Res 1580: 8-21.

41. Madularu D, Yee JR, Kenkel WM, Moore KA, Kulkarni P, et al. (2015) Integration of neural networks activated by amphetamine in females with different estrogen levels: a functional imaging study in awake rats. Psychoneuroendocrinology 56: 200-212.

42. Geonse JB, Logothetis NK (2006) Laminar specificity in monkey V1 using high-resolution SE-fMRI. Magn Reson Imaging 24(4): 381-392.

43. Liang Z, King J, Zhang N (2011) Uncovering intrinsic connectional architecture of functional networks in awake rat brain. J Neurosci 31(10): 3776-3783.

44. Miller DK, Bowirrat A, Manka M, Miller M, Stokes S, et al. (2010) Acute intravenous synaptamine complex variant KB220 "normalizes" neurological dysregulation in patients during protracted abstinence from alcohol and opiates as observed using quantitative electromyographic and genetic analysis for reward polymorphisms: part 1, pilot study with 2 case reports. Postgrad Med 122(6): 188-213.

45. Blum K, Chen TJ, Morse S, Giordano J, Chen AL, et al. (2010) Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D(2) agonist therapy: part 2. Postgrad Med 122(6): 214-226.

46. Blum K, Chen AL, Giordano J, Borsten J, Chen TJ, et al. (2012) The addictive brain: all roads lead to dopamine. J Psychoactive Drugs 44(2): 134-143.

47. Chen TJ, Blum K, Payte JT, Schoolfield J, Hopper D, et al. (2004) Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. Med Hypotheses 63(3): 538-548.

48. Brown RJ, Blum K, Trachtenberg MC (1990) Neurodynamics of relapse prevention: a neuronutrient approach to outpatient DUI offenders. J Psychoactive Drugs 22(2): 173-187.

49. Chen TJ, Blum K, Waite RL, Meskin H, Schoolfield J, et al. (2007) Narcotic Attenuation Program attenuates substance use disorder, a clinical subtype of reward deficiency syndrome. Adv Ther 24(2): 402-414.

50. K Blum, D Allison, MC Trachtenberg, RW Williams (1988) Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30 day inpatient treatment program by the neuronutrient Tropamine. Curr Ther Res 43(6): 1204-1214.

51. Blum K, Chen AL, Chen TJ, Braverman ER, Reinking J, et al. (2008) Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary. Theor Biol Med Model 5: 24.

52. Dahlgren A, Wargelius HL, Berglund KJ, Fahlke C, Blennow K, et al. (2011) Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study. Alcohol Alcohol 46(5): 509-513.

53. Szutorisz H, DiNieri JA, Sweet E, Egervari G, Michaelides M, et al. (2014) Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation. Neuropsychopharmacology 39(6): 1315-1323.

54. K Blum, RD Badgaiyan, Z Demotrovics, J Fanttonio, G Agan, et al. (2015) Can Genetic Testing Provide Information to Develop Customized Nutrigenomic Solutions for Reward Deficiency Syndrome? Clin Med Rev Case Rep 2(1).

55. Blum K, Meskin H,Downs BW (2006) DNA based customized nutraceutical “gene therapy” utilizing a genoscore: a hypothesized paradigm shift of a novel approach to the diagnosis, stratification, prognosis and treatment of inflammatory processes in the human. Med Hypotheses 66(5): 1008-1018.

56. Thanos PK, Hamilton J, O'Rourke JR, Napoli A, Febo M, et al. (2016) Dopamine D2 gene expression interacts with environmental enrichment to impact lifespan and behavior. Oncotarget 7(15): 19111-19123.

57. K Blum, J Femino, ST Teitelbaum, J Giordano, M Oscar-Berman, GMS (2013) Molecular Neurobiology of Addiction Recovery. The 12 Steps Program and Fellowship. Springer, New York, USA.