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Review Article

Multi-Locus Pro-Dopaminergic Restoration of Reward Brain Circuitry in Reward Deficiency Rescinds Mono-Pharmaceutical Targeting

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Abstract

Dopaminergic dysfunction in reward circuitry is well-documented as a contributor to addictive behaviors. Evidence indicates that changes in synchronous neural activity between brain regions mediating reward and cognitive functions may significantly contribute to substance-related disorders. In this commentary we highlight findings showing that the pro-dopaminergic nutraceutical (KB220) enhances functional connectivity between reward and cognitive brain areas in both animal and human studies. Animal studies demonstrate that KB220 activates important brain reward-related regions, including the nucleus accumbens, anterior cingulate gyrus, anterior thalamic nuclei, hippocampus, and prelimbic and infralimbic loci. Kb220 induced significant functional connectivity, enhanced neuroplasticity, and improved dopaminergic functionality within the brain reward circuitry with effects localized to these regions rather than broader distributed across the brain. In abstinent heroin-dependent individuals, acute KB220 administration significantly induced BOLD activation in caudate-accumbens dopaminergic pathways relative to placebo. Furthermore, data from 36 clinical trials and preclinical studies encompassing over 1,000 subjects, demonstrate that KB220 supports "dopamine homeostasis" across various reward deficiency behaviors. Clinical outcomes and quantitative electroencephalogy (qEEG) results underscore KB220's potential anti-craving/anti-relapse effects in addiction and other psychiatric disorders through direct or indirect dopaminergic modulation. Based on a review of the existing knowledge and further intensive investigation, we propose that instead of relying on mono-pharmaceutical approaches, the scientific community should endorse multi-loci dopaminergic restoration of reward brain circuitry as a fundamental paradigm for addressing mental illness.

Keywords: *Quantitative Electroencephalogy (qEEG); KB220; Reward Deficiency (RD); Genome-Wide Association Studies (GWAS); Alcohol Use Disorder (AUD)*

Introduction

In understanding the complex mechanisms underlying reward and pleasure processing, the finite activation of brain reward circuitry, culminating in the net release of dopamine at the nucleus accumbens (NAc), is influenced by shared genetic factor [1,2]. Moreover, the foundational principles of this process involve the Brain Reward Cascade, first characterized by our group in1989 [3]. The results of an investigation from our laboratory, along with Hungarian scientists demonstrated a significant overlap between substance and non-substance addictions and associated behaviors [4]. This important work underscores the necessity of evaluating potential commonalities in the psychological, genetic and epigenetic of reward-related pathways as well as their associated neural circuits. Certainly, uncovering these shared molecular neurobiological correlates will undoubtably provide a solid basis of support for concepts such as the Reward Deficiency (RD) or the coined syndrome (RDS). Based on extensive independent investigations and analysis of 1606 Pubmed articles linked to RD and 267 to RDS (accessed January 12, 2025), we posit that RD represents the "true" phenotype underlying not only "pre-addiction" [5,6], but also psychiatric disorders in general [7].

Comprehension these facts, paves the way for more logical and effective therapeutic approaches to solving the most perplexing and daunting conundrum of mental illness. By recognizing the intricate and multifaceted circuitry of neuronal dysfunction underlying reward deficiency and the component model of addiction, we propose herein, a common phenomenological and etiological milieu to explain the diverse manifestation of addictive behaviors [8].

In an attempt to develop a reductionist approach to understanding the complex biological underpinnings of mental disorders, we propose that dopamine, a key neurotransmitter regulated within the mesolimbic system, plays a central role in brain function impacted by both genetics and epigenetic factors [9,10]. Strong evidence links several dopaminergic regulatory genes, including DRD1, DRD2, DRD3,

DRD4, DRD5, DAT1, MAO and COMT to dysfunctions in brain reward pathways [11-15]. It is noteworthy that information derived from Genome-Wide Association Studies (GWAS), have identified hundreds of genetic variants with relatively a small effect ($R^2 < 0.002$) that contributes to Alcohol Use Disorder (AUD) [16-21]. Research into the neurogenetic basis of RDS, particularly the identification of reward gene polymorphisms, displays an important assessment tool for understanding an individual's unique genetic risk profile for developing substance and non-substance behavioral addictions. This insight offers a pathway termed Brain reward Cascade (BRC) for individualized risk assessment and targeted interventions, enhancing efforts to address addiction at its earliest stages (See BRC schematic figure 1).

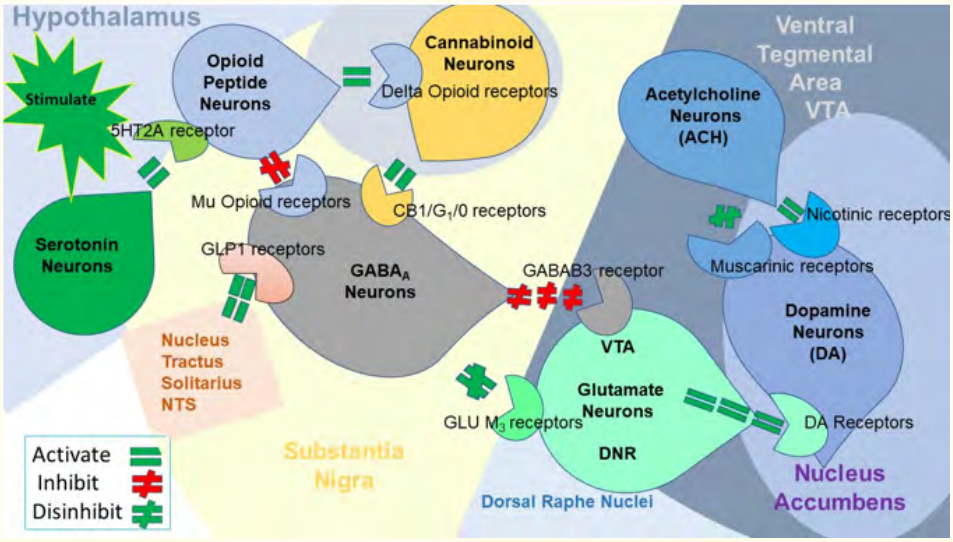

Figure 1: *The Mesolimbic Brain Reward Cascade (BRC). This cartoon illustrates the interaction of key neurotransmitter pathways involved in the BRC. Environmental stimuli in the hypothalamus initiates a cascade of neurotransmission that, through activation, inhibition, and disinhibition at mesolimbic receptor sites, ideally culminates in homeostatic dopamine release in the nucleus accumbens. Insufficient dopamine release, often linked to endorphin/dopamine deficiency results with feelings of unhappiness. In comparison, general (healthy) feelings of well-being depend on the dopamine homeostatic tonic set point (With permission -BLUM© 2024) [42].*

Numerous genes are implicated in addiction as pointed out by Li., *et al*. [22]. Dopaminergic pathways are regulated through a complex network of interconnected mesolimbic and prefrontal serotonergic-, cannabinoidergic, endorphinergic, GABAergic, and glutaminergic systems. These systems are influenced by various genetic polymorphisms as represented in the Genetic Addiction Risk Severity (GARS) test developed by Blum., *et al*. [23] (Table 1).

Gene	Polymorphism	Location	Risk Allele	Function Linked to Hypodopaminergia	Reference
DRD1	rs4531 or rs4532	Chr -5	A	rs4532 is known to reduce the function of the DRD1 gene, which is needed as a "go" drive to activate D1 receptors causing normal dopamine function.	Batel., *et al*. (2008) [24].

DRD2	rs1800497	Chr-11	A	rs1800497 equates functionally to 30 - 40% lower density of dopamine D2 receptors resulting hypodopaminergic function	Noble., *et al*. (1991) [25].
DRD3	rs6280	Chr3	C	Rs6280 in D3 causes an imbalance of the DRD3 function and is associated with Heroin Dependence.	Kuo., *et al*. (2014) [26].
DRD4	48 base repeat VNTR	Chr 11 exon 3	Above 7 R	Similar to the D2, the VNTR 7 R and above results in hypodopaminergia due to lower receptor function.	Van Tol (1998) [27]
COMT	rs4680	Chr 22	G	Carrying the 9 R allele leads to a high activity of catabolism of dopamine in synapse inducing a hypodopaminergia in the synapse.	Wang., *et al*. (2010) [28] and Denys., *et al*. (2006)
OPRM1	rs1799971	Chr 6	G	The G allele is the risk variant of the MOR 118A>G (p.Asn40Asp; SNP rs1799971) promotes a low dopamine function because there will be a lack of inhibition via the GABA inhibitory control of dopamine release at the reward site Nucleus Accumbens (NAc) inducing hypodopaminergia.	Ray., *et al*. (2011) [30]
DAT1	40 base repeat VNTR	Chr 5 exon 15	9R	Carrying the 9 R allele leads to a high activity inducing a hypodopaminergia in the synapse. The DAT1 clears excess dopamine released from the pre-neuron into the synapse and prevents uptake into the receptors on the next neuron.	Byerley., *et al*. (1993) [31].
MOA-A	30 base repeat VNTR	Chr X Promotor	3.5 R, 4R	The 3.5R and 4R variants are more active than 3R or 5R. Excessive amounts of dopamine are broken down in the presynaptic neuron, which may result is less dopamine availability for release into the synaptic cleft. Carriers of the 3.5 and 4R may display hypodopaminergia (low dopamine function).	Contini., *et al.* (2006) [32].

5HTTLPR	43 base repeat INDEL/VNTR plus rs 25531	Chr 17	LG, S	The risk variant has 43 base –pair 5″ insertion/deletion, S' at SNP rs25531. The long allele results in higher serotonin transporter mRNA transcription in human cell lines. The result is that Serotonin is highly reabsorbed from the synapse into the pre-nerve cell causing low serotonin content in the synapses to reduced function.	Merenäkk., *et al*. (2011) [33] and van der Zwaluw., *et al*. (2010) [34].
GABRB3	CA repeat DNR	Chr 15 (downstream)	181	GABRA3 gene and the risk variant is CA-Repeat, whereby allele 181 results in higher activity. This risk allele, if overexpressed, will cause low dopamine function hypodopaminergia leading to SUD because of inhibition of dopamine release at the reward site.	Namkoong., *et al*. (2008) [35].

Table 1: *GARS® is based on the following genes linked to hypodopaminergia.*

Brainstorm consortium quantified the genetic sharing of 25 brain disorders from GWAS of 265,218 patients and 784,643 control subjects and determined their association to 17 phenotypes from 1,191,588 people [36]. One interesting finding from this work highlights the fact that psychiatric disorders share common variant risk, while neurological disorders are more distinct not only from one another but from psychiatric disorders. One important pharmaceutical challenge is focus on single locus targeting compared to a multi-loci therapeutic approach. The potential answer may reside in the old adage OGOD [37] (one-gene one disease), which is exemplified by Huntington's disease that took the life of the famous folk singer Woody Guthrie and his two daughters. It is important to understand unlike the one-gene one disease epitome, psychiatric disorders, notably polygenic comprise a multi-locus very complex phenotype as described by Lander and Schork [38]. It is important to note that while medical genetics was revolutionized in the 1980s by attempting to apply simple Mendelian diseases, psychiatric disorders do not comply with simple inheritance patterns. While it seemed unfathomable in the late 1980's that since there are at least 20,000 genes in the human genome, the accurate allelic prediction seemed unattainable. However, the first clue was initiated by the seminal work of Blum and Noble [39]. Along these lines, Stice., *et al.* [40] evaluated the notion that humans with genotypes putatively associated with low dopamine signaling capacity (e.g. TaqIA A1 allele of DRD2-141C Ins/Ins genotype; DRD4 7-repeat or longer allele, DAT1 9-repeat allele, and the Val/met COMT genotype) revealed that increasing the number of risk alleles per genotype is correlated with reduced reward system activity. Thus, the take home message, is that the multi-locus genetic composite provides a more accurate and sensitive index of vulnerability to impaired reward system function than any single genotype alone [also see 41].

Is it possible to achieve "dopamine homeostasis" through a multi-locus therapeutic approach?

McLellan., *et al*. [5], suggested that despite the enormous efforts made by the federal government, including funding, development, and delivery of certain treatments (Medication Assisted Treatment (MAT)) to individuals with SUD, treatment penetration remains below 20%. Unfortunately, there is currently no real magic bullet or "cure" for SUD. These authors correctly profess that in the diabetes field

facing a similar dilemma, increased treatment penetration through early-stage diabetes detection, referred to as "prediabetic." The inclusion of "pre-addiction" as a clarification in the DSM has been advocated by Volkow (director of NIDA) and Koob (director of NIAAA). This concept emphasizes the importance of developing tools to categorize individuals at mild, moderate, and high risks for future addictive behavior. In response to this suggestion and based on Blum's group work and many international scientists, it has been concluded that the pre-addiction classification is best described by a construct known as dopamine dysregulation at the mesolimbic reward circuit. This dysregulation, referred to as reward deficiency or net hypo-dopaminergia underscores the core neurobiological mechanisms contributing to vulnerability to addiction [6,42].

As of January 13, 2025, a total of 1,606 articles are listed in PubMed, using the term "Reward Deficiency" with approximately 47% authored independently of our lab. A total of 267 articles are listed using the search term "Reward Deficiency Syndrome". Certainly, the term "pre-addiction" echoes the historical advances in the diabetic field, but scientifically the real evidence resides with concepts linked to brain neurotransmitter dysregulation, including both deficits, and even surfeit as observed in adolescence. One missing piece of the puzzle ignores individuals with early-stage SUDs, instead most providers tend to focus almost exclusively on those with serious, chronic addictions [43]. Moreover, indeed to capture the psychological correlates or epigenetic of RDS, we have proposed the GARS [7] test as well as the RDSQ2920 pencil and paper test [44]. As of January 13, 2025, PubMed lists 99 articles involving GARS.

Importantly, clinical trials and animal imaging studies have demonstrated pro-dopamine regulatory effects of KB220, a nutraceutical formulation. KB220 (powdered form) is comprised of the following ingredients: Thiamine, 15 mg (1033% of Daily Value); Vitamin B6, 10 mg (500%); Chromium poly nicotinate 200 mcg (166%) and a fixed dose of Synaptose. Synaptose is a combination of amino acids and herbs that contains DL-Phenylalanine, L-Tyrosine, Passionflower Extract; a Complex containing Arabinogalactans, N-Acetylglucosamine, Astragalus, Aloe Vera, Frankincense Resin, White Pine Bark Extract, and Spirulina; Rhodiola; L-Glutamine; 5-Hydroxytryptophan (5-HTP); Thiamine Hydrochloride; Pyroxidal-5-phosphate and Pyridoxine HCl. The powder was manufactured by Cephram, Inc. (New Jersey).

To assist in displaying both animal basic science and human clinical trials regarding KB220 variants and ingredients positive benefits and impactful bench to bed outcomes we developed table 2 for scrutiny.

Pro-Dopamine Regulator (KB220 and variants)	Disorders
A clinical trial with Synaptamine Complex Variant KB220™ via IV (with 600+ alcoholic patients) which resulted in significant reductions in RDS behaviors [46].	Significant reduction of many RDS behaviors
Chronic symptoms were significantly lessened, as measured by the Chronic Abstinence Symptom Severity (CASS) Scale [47]. Paired sample t-tests of pre/post-treatment scales revealed a significant decrease (p = .00001) from treatment times: for somatic (t = 16.1), for emotion (t = 19.1), and for impaired cognition (t =14.9) [47]. At a two-year follow-up, 23 of the participants who underwent KB220 IV treatment (a minimum of five IV treatments over a seven-day period) and then the oral form of the compound for 30+ days: at six months, 91% (n = 21) remained sober and 82% (n = 19) were free of relapse; at one year, 82% (n =19) were sober, 78% (n = 18) had no relapse; at two years, 91% (n = 21) were sober and 70% (n = 16) had no relapse [47].	Polydrug abuse maintain sobriety over a 2 year period

KB220, in comparison to the placebo, displays activation of the caudate brain area and possibly a leveling off of heroin-generated abnormal connectivity in the putamen (a region associated with emotionality [48].	Fixing functional brain connectivity in heroin dependence
KB220Z significantly augments, compared to placebo, functional connectivity in the reward system and higher areas within rats [49]. Functional connectivity, brain connectivity recruitment (perhaps due to neuroplasticity), and dopaminergic function throughout the brain reward network were found [49].	Activation of dopamine brain pathways and neuroplasticity
CJ, a 38-year-old with a history of SUD and comorbid ADHD (inattentive type), with chronic shopping and hoarding behaviors. After taking KB220 for four weeks, the patient reported a marked enhancement in mental status and various behaviors, including a decrease in shopping and hoarding. A lifelong history of nightmares was eradicated. Her locus of control shifted toward internal [50].	Significant reduction of abnormal hoarding behavior
KB220Z (via SQ and IP) strikingly and instantaneously reduced binge drinking of a solution of 10% ethanol in rats (females and males) [51]. There was no influence of SQ KB220Z on 3% sucrose ingestion. Elevated activity in the open field and duration in the open arm part of the EZM was moderately reduced. [51].	Significant reduction in binge drinking
KB220 was used as a detoxification treatment for opioid-dependent patients instead of opioids. Out of 17 subjects, merely three received Buprenorphine/Naloxone (Bup/nx) in concert with KB220Z. Only three participants had a relapse while on KB220 in the initial two weeks of the study. The rest 82% were sustained on KB220Z. The participants were maintained without any supplementary Bup/nx for 120 days and, in one specific participant, for 214 days, thus decreasing opioid-seeking [52].	Significant decrease in withdrawal symptoms in heroin dependence
JN was a 77-year-old and had a memory decline. Treatment with KB220 was tested using the Animal Naming Test (ANT). This resulted in greater scores ($p = 0.04762$) on the ANT. The patient's pretest scores increased from the 30^{th} percentile to the 76^{th} percentile with a single administration to the 98^{th} percentile at six months with the second administration [53]	Significant reduction of memory decline
A 51-year-old obese woman with comorbid PTSD and depression with a suicide attempt was studied using KB220. Also, she experienced frightening nightmares related to her childhood sexual/physical abuse from her family (one perpetrator was her father with alcohol use disorder). After KB220, her frequency and type of dreams changed dramatically to happiness. A second patient, a 39-year-old female with PTSD, also suffered from frightening nightmares. KB220Z to diminish withdrawal symptoms from methadone and subsequently described positive dreams [54].	Significant reduction PTSD induce nightmares and depression

Willuhn., *et al*. reported that substance use, and other addictive behaviors increased as dopaminergic function was reduced. Blum's group assessed the use of KB220Z™ on the reward circuitry in a study involving ten people with a heroin use disorder in protracted abstinence (on average, 16.9 months), aimed at reducing opioid intake. The randomized placebo-controlled crossover study divulged an increase in BOLD fMRI activation within the caudate-accumbens-dopaminergic pathways (KB220 vs. placebo) following a one-hour acute administration. The compound decreased resting-state activity in the putamen of abstinent participants and increased functional connectivity in a neural circuit that comprised the dorsal anterior cingulate, nucleus accumbens, medial frontal gyrus, occipital cortex, posterior cingulate, and cerebellum [55].	Significant attenuation of opioid intake by affecting functional connectivity in abstinent heroin addicts
This was the first report to reveal the contribution of the PFC in the qEEG response to a D2 agonist (Synaptose Complex KB220Z™), which was most apparent in those with the A1 allele of the D2 dopamine receptor. In polydrug abusers, KB220Z™ prompted regulation of brain electrical. The results suggest a phase change in electrical activity from low amplitude/power to a more regulated activity (with an increase of 6.169 mV) throughout the PFC [56].	Regulation of EEG in abstinent psychostimulant abusers
We present a case series of four patients with a striking and persistent assuagement of nightmares in those diagnosed with PTSD/ADHD and/or opioid use disorder. The cessation of such nightmares was seen in 10-12 months post-treatment without recurrence. Following the seeding of the brain regions of the dorsal hippocampus, they found enhanced connectivity across numerous regions of interest (with the exception of the PFC), displaying neuroplasticity [57].	Significant reduction in nightmares in those diagnosed with PTSD/ADHD and/or opioid use disorder
In a male diagnosed with full-blown RDS, including sexual addiction and repetitive paraphilia, within one week of KB220z, the repetitive paraphilia was abolished. There were also several other positive effects, such as enhanced focus. This remained after discontinuing the compound, which suggested a neuroplastic change [58].	Significant reduction in sexual addiction and repetitive paraphilia, within one week of KB220z
A 72-year-old male with a diagnosis of ADHD was examined using low-resolution electromagnetic tomography (LORETA) at baseline and one hour after administration of the KB220z compound. Tasks including eyes-closed, open, and working memory were employed. Z-scores averaged across these revealed increases in various frequency bands within the anterior, dorsal, and posterior cingulate areas, as well as the right DL-PFC, during the working memory task with the compound [59]	Significant augmentation of working memory in ADHD
Blum's group reported that the qEEGs of patients: one with alcohol use disorder and one with heroin use disorder with abnormalities (i.e., pervasive theta and pervasive alpha activity, respectively) during prolonged abstinence (reduced heroin intake) are considerably normalized by the administration of a single IV dose of Synaptamine Complex Variant KB220™ [60]	Normalization of qEEGs in both alcoholism and heroin dependence
The main ingredient in the patented KB220 is d-phenylalanine (DPA), an inhibitor of carboxypeptidase prolonging enkephalin activity. Blum's group observed a significant attenuation of both forced and volitional ETOH intake, respectively, by both acute and chronic therapy with hydrocinnamic acid (a metabolite of DPA) and D-phenylalanine [61]	Significant reduced alcohol intake by increasing brain enkephalins*

L-DOPA amplifies ethanol-induced narcosis in mice [62]. The enhancement of monoamines by L-DOPA administration may be the reason. This work indicates the importance of dopamine and alcoholism. ETOH augmentation	Evidence showing the importance of dopamine in sleep*
Blum's group completed a study using SAAVE KB220 in a residential program for alcohol use disorder in a double-blind protocol for 30 days (n = 22). The compound increases monoamines, enkephalins, and GABA, all of which might be functionally deficient in alcohol use disorder. The compound, versus placebo, (1) had a decreased building up to drink score (1 vs. 2) (2) which did not require benzodiazepines PRN (0% vs. 94%), (3) discontinued tremors sooner (72h. vs. 96h.), and (4) did not lead to severe depression (0% vs. 24%) as measured on the MMPI [63]	Significant reduction of alcohol induced withdrawal tremors and required benzodiazepines
Blum's group completed a second study with the SAAVE KB220 compound in a residential program for those with alcohol use disorder and polydrug users in a double-blind protocol for 30 days (n = 62). Participants on the compound (vs. placebo) showed a decreased skin conductance level, which divulged a decreased- stress response; they had enhanced Bess and Physical scores; and post detoxification, they had a sextuple decrease in leaving against medical advice (AMA) [64].	Significant reduction of stress and AMA rate
Blum's group completed a third study with the SAAVE KB220 compound variants in a residential program for those with cocaine use disorder (Tropamine: compound variant stimulant abuse), alcohol use disorder (SAAVE: compound variant for alcohol abuse), and no compound for 30-days (n = 54). AMA rates for groups varied: Tropamine (4.2%), SAAVE (26.6%), and no compound (37.5%). Additionally, Tropamine reduced the craving for stimulants [65].	Significant reduction of cocaine relapse and AMA rates
Blum's group completed a fourth study with the SAAVE KB220 compound in an outpatient 10-week program for DUIs (SAAVE: AUD; Tropamine: CUD; n = 60). The compounds promoted recovery rates and reduced relapse rates (percentages given respectively): AUD (73%; 26%) and CUD (53%; 47%) compared to known rates of relapse (87-93%) [66]	Significant rec0ver y in DUI offenders
In another study by Blum's group, carbohydrate binge-eaters (n = 27) were given PCAL-103 (KB220 variant) in a 90-day outpatient program at a bariatric clinic. Sixteen patients received the compound (vs. n = 11 controls). The mean weight loss was 26.92 lbs. (vs. controls at 10 lbs.) Relapse rates were significantly less in the compound group (18.2%) versus the control group (81.8%) [67].	Significant loss of weight in carbohydrate binge-eaters
This is the initial report in humans of the effects of daily ingestion of a particular amino acid mixture, Kantrol [KB220], on cognitive event-related potentials (ERPs) related performance. Cognitive ERPs were created by two computerized visual attention tasks: the Spatial Orientation Task (SOT), and Contingent Continuous Performance Task (CCPT), in typical young adult participants (acting as their own controls) before and after approximately 30 days of compound ingestion. A statistically significant amplitude augmentation of the P300 component of the ERPs [focus] was seen after KB220 for both tasks, as well as improvement with respect to cognitive processing speeds, indicating enhanced focus [68]	Significant increase in focus and cognitive tasks
In a state psychiatric hospital, 12 CUD patients were enrolled in a randomized, double-blind, placebo-controlled study using a KB220 variant (similar to Tropamine: n =8) vs. control (placebo: n = 4). The results divulged cocaine craving decreased with the compound vs. control [69].	Significant decrease in cocaine craving

In a study, amino acid precursors paired with an enkephalinase inhibitor were used with six female patients with a history of eating disorders (three were comorbidly chemically dependent). All participants claimed initial benefit, with only one participant relapsing at six months. Additional data was collected with more patients with a history of eating disorders (n = 100), with 98% claiming improved mood and reduced cravings [70].	Significant decrease in eating disorder preventing relapse and reduced food cravings
In a one-year outpatient program, Blum's group conducted a study using Synaptamine ™ (a KB220 variant) in SUD/RDS. Participants (n = 76; 31 females, 45 males) with a mean age of 33 years had diagnoses of SUD. During one year of treatment, various measures showed significant mean decreases: anger ($p < 0.001$), depression ($p < 0.001$), stress ($p = 0.002$), anxiety ($p < 0.001$), and drug craving ($p < 0.001$), and scores of building up to relapse ($p <0.001$). With regard to recovery, energy ($p < 0.001$) and drug-seeking refraining ($p < 0.001$) both increased also in one year [71].	Significant reduction of anger, stress, drug craving and enhanced energy in substance use disorder
Blum's group wanted to test the combination of a narcotic antagonist with an enkephalinase inhibitor (DLPA) and other amino acid precursors to promote dopamine release in methadone-maintained patients (n = 12, compared to controls n = 1,000) to assist with compliance. The experimental group received a combination of Trexan and KB220 and was free of relapse for a mean of 262 days, which was significantly greater ($p < 0.0001$) than the controls [72].	Combination of KB220 and Trexan to induce compliance in methadone maintenance
Blum's group conducted their first Precision Behavioral Management (PBM®) study using a DNA with a customized compound formulation (Geno-Trim, a KB220 variant) in 24 participants with obesity (due to RDS) completed a questionnaire [73]	Significant reduction of RDS behaviors using customized DNA -KB220 in obesity
Blum's group examined chromium picolinate (CrP: an ingredient in the KB220 compound; n = 60) versus placebo (n = 62) for use in those with obesity (total n = 122) in those tested for variants of the DRD2 genes (A1 and A2). Carriers of the double A2 allele experienced significant weight loss. Carriers of a single or double copy of A1 showed no changes. The authors theorized that D2 receptor density interacted with CrP treatment and weight loss [74]	Showing interplay between the DRD2 gene and Chromium picolinate in obesity and weight loss*
Based on scientific/medical literature, numerous candidate genes have been found that correlate with obesity, including D2 dopamine receptor, serotonin receptor (5-HT2a), methylenetetrahydrofolate reductase (MTHFR), Peroxisome Proliferator-Activated Receptor gamma (PPAR-y) and Leptin (OB) genes. One research study examined these five polymorphisms to develop a DNA-customized KB220 variant (LG839). Within this study, 21 participants were examined for differences in BMI at baseline and post-treatment (mean 41 days, up to 2,870 days). The weight loss for the participants was significant [75]	Significant reduction of BMI using customized DNA information and KB220 variant
Another study used LG389 in concert with genotypes (n = 1,058). A subset of this group (n = 27) of Dutch ancestry demonstrated significant weight loss and associated significantly lessening sugar cravings, snacks, late-night eating, and an increase in appetite suppression, sleep, happiness, and energy. Those with the A1 allele of the DRD2 correlated with an increase in days of continuing treatment [76]	Significant weight loss reduction with lessoned sugar craving, improved sleep, happiness and energy
Dopamine has been called the "anti-stress molecule." In a study with Blum's group, they examined the use of a KB220 variant (Synaptamine) for reducing anxiety in those with AUD and SUDs (polydrug users). This was a double-blind, placebo-controlled study. Those on the compound (n = 28) vs. placebo (n = 22) were measured as having significantly reduced stress based on SCL [77]	Significant stress reduction in-patient substance use disorder

One study looked at heroin withdrawal and detoxification with the coadministration of various amino acids/precursors (5-HTP, L-Tyrosine, L-Glutamine, and Lecithin; n = 41) versus placebo (n = 42). For those in the treatment group (versus placebo), there was a significant decrease in tension-anxiety, depression-dejection, anger-hostility, disturbance in mood, fatigue-inertia, and an increase in vigor-activity [78].	Amino acid (similar to KB220) reduced heroin withdrawal detoxification including depression, anxiety, and fatigue.
This case study examines a 12-year-old Caucasian male with no prior psychiatric issues who presented with a sudden onset of severe anxiety, depression, emotional liability, and suicidal ideation. Genotyping and GARS testing revealed risk polymorphisms in the dopamine-related genes including DRD2/ANKK (Taq1A), OPRM1 (A/G), DRD3 (C/T), and MAOA (4R) linked to hypodopaminergia. The patient was subsequently placed on research ID-KB220ZPBMPOLY (POLYGEN®), and albeit the possibility of bias, based upon self and parental assessment, a marked rapid improvement in psychiatric symptoms was observed. In the second phase of treatment (102 days on KB220), standard antibody testing, revealed positivity for Lyme. Antibacterial therapy started immediately, and KB220z was discontinued to provide a wash-out period. A monotonic trend analysis of outcomes showed consistent symptom improvement with antibacterial therapy. Our recommendation, albeit only one case, is to utilize and further research a combined therapeutic approach, involving precision-guided DNA testing and pro-dopamine regulation along with antibacterial therapy, as well as glutathione to address offensive enhanced cytokines, in patients with suspected PANDAS/CANS [79].	Significant improvement of all PANDAS/CANS
A 26-year-old male with a history of multiple neuropsychiatric diagnoses, including ADHD, PTSD, and sensory integration disorder, underwent qEEG analysis to explore the effects of KB220 on brain function. The patient's EEG was recorded 60 minutes before and after oral administration of KB220, observing changes in various frequency bands indicative of cognitive and alertness states. Significant alterations were observed in the patient's EEG post-KB220 administration. There was a notable reduction in Delta activity, suggesting increased alertness. Theta and Alpha activities increased, indicating enhanced working memory and neuronal synchrony. Beta activity changes suggested improved focus and cognitive processing. These shifts point towards restoring dopamine homeostasis, potentially enhancing brain activity and cognitive functions [80]	Significant restoration of EEG in ADH/PTSD
Subject self-administered GDOC using one-half ounce twice a day for one month. During the first three days, unique brain activation occurred; resembling white noise after 30 minutes and sensation was strong for 45 minutes and then dissipated. He described effect as if his eyesight improved slightly and pointed out that his sense of smell and sleep greatly improved. Subject experienced a calming effect similar to meditation that could be linked to dopamine release. He also reported control of going over the edge after a hard day's work, which was coupled with a slight increase in energy, increased motivation to work, focus and multi-tasking, with clearer purpose of task at hand. The subject felt less inhibited in a social setting and suggested Syndrome that GDOC increased his Behavior Activating System (reward), while having a decrease in the Behavior Inhibition System (caution) [81]	Significant increase in focus, multi-tasking, motivation as less inhibition in social gatherings suggesting an inhibition in the Behavior Inhibition System (caution).
A complete list of PubMed related articles [82]	All RDS behaviors summary

Table 2: *Summary of published research related to KB220 variants and ingredients.*

**Individual ingredients in KB220.*

Are KB220 variants putative modulators of dopamine homeostasis?

The development of KB220 was produced following the first report showing the effect of enkephalinase inhibitor D-phenylalanine on reducing alcohol intake. [61]. Importantly, the development of KB220 complex is based on a multi-locus approach designed to interact with the brain reward cascade with the final intent of facilitating dopamine release throughout the reward circuitry. In fact, our laboratory showed that dopamine release occurred in meso-limbic brain reward regions; enhanced functional connectivity and even enhanced dopaminergic neuronal recruitment [48]. In support of evidence for the possibility of KB220 variants to modulate or induce dopamine homeostasis can be revealed through careful scrutiny of table 2 and the references to 36 clinical human trials and animal studies of KB220 [45-82]. One element is the finding, for example, of enhanced areas of activation which could have therapeutic value, especially in view of the attenuated brain gray matter volume during cocaine administration to humans [as reported by Connolly., *et al*. [83].Thus, it is possible that one potential mechanism involves the COMT inhibition by Rhodiola Rosea, a component of KB220, which could increase dopamine levels in the synapse and subsequently augment dopaminergic activity [84]. Moreover, it is noteworthy, that Cocle., *et al*. [85] reported that drug-specific associations amongst brain-circuitry reactivity to dopamine modulation and individual differences are linked to trait impulsivity, revealing dissociable drug-personality interaction effects across distinct dopamine-dependent cortico-subcortical networks [85]. Along these lines Konova., *et al*. [86] observed that administration of the dopamine-releasing agent methylphenidate to non-abstinent cocaine users resulted in region-specific changers in the strength of connectivity, whereby striatal regions are less connected while cortico-cortical and cortico-limbic regions reveal greater connectivity [86]. In addition, the robust finding of an enhanced connectivity volume following administration of KB220 [48] compared to placebo induced neuroplasticity and as such has important clinical relevance in addicts with blunted mesolimbic functional connectivity. Finally, Tomasi., *et al*. [86] concluded that relative to neutral cues, exposure to food and cocaine cues activates the cerebellum, orbitofrontal, inferior frontal, and premotor cortices and the insula but disengage the cuneus and Default Mode Network (DMN) (See figure 2).

Figure 2: *Schematic of multi-locus restoration with KB220.*

In addition, figure 3 provides high level representation KB220 nutraceutical mechanism of action and neurotransmitter system (s) involved in the finite release of dopamine ant the VTA-NAc.

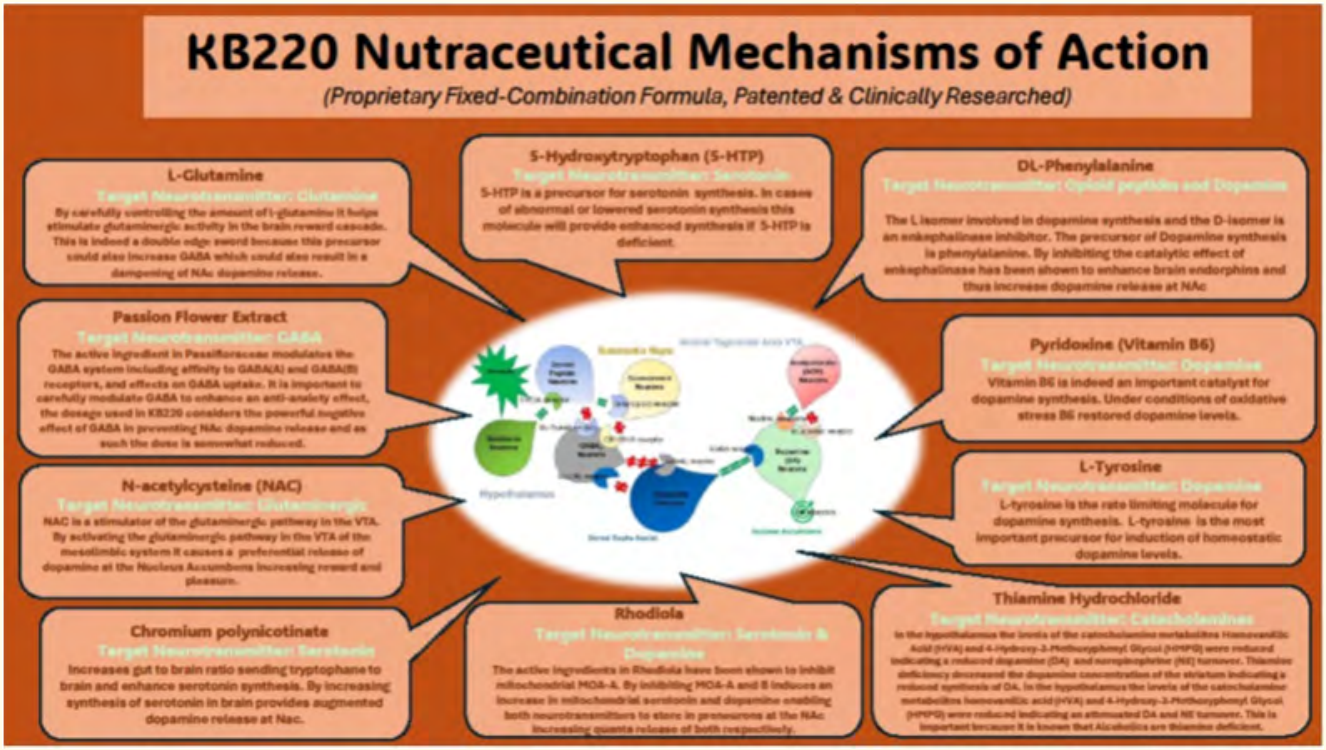

Figure 3: *A schematic of multi-locus pro-dopaminergic restoration of reward brain circuitry in reward deficiency rescinds mono-pharmaceutical targeting branded as NEUROSTASIS™.*

FDA consideration in the face of RDS

In face of an American opioid/psychostimulant/alcohol/cannabis crisis, marked by rising overdose fatalities, we are proposing a paradigm shift in treatment approaches. Currently, the FDA has approved pharmaceuticals for the treatment of opioid, alcohol, and nicotine addiction, however, no approved medications for psychostimulants or even cannabis use disorder. While it is laudable that the FDA continues to address this global issue, we propose that the FDA embrace a novel therapeutic target for the treatment and prophylaxis of opioid and psychostimulant abuse - induction of DNA-guided dopamine homeostasis. We refer to this novel therapeutic target as the Anti-Reward Deficiency Restoration Solution (ARDS) [87].

One important thought is that the neuroscience and neurological community may eventually have the clinical ability to appropriately categorize addiction severity, according to genotype and possession of risk alleles. A promising goal is the identification of high risk vulnerability, along with safe, non-addicting ARDS natural nutrigenomics that involves a multi-locus modality rather than powerful monistic therapeutic targeting, especially not promoting dopaminergic attenuation instead of induction of "dopamine homeostasis".

The FDA has defined narrow therapeutic index (NTI) drugs as "those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life- threatening or result in persistent or significant disability or incapacity". In fact, as of January 5, 2024, there are neurological based 33 drug products, with 14 distinct active ingredients, specified as NTI drugs in their respective product- specific guidance's (PSGs) for generic drug development with NTI [See https://www.fda.gov/drugs/cder-conversations/setting-and-implementing-standards-narrow-therapeutic-index-drugs].

It is important to note that the FDA does not approve chemicals as treatments for any disease. Instead, it approves specific product(s) for the treatment of specific diseases or conditions with specific doses and routes of administrations. In addition, it also determines if a mechanism of action has been elucidated. For the FDA to consider multiple mechanisms of action, as suggested above, the scientific community must design their basic as well as clinical studies and trials accordingly. With this important statement developed by one of the co-authors JK (worked at the FDA for 10 years), while there is emerging evidence that the FDA has recently approved multiple pharmaceutical agents to be combined in one product, we would like to point out a few refuting remarks about KB220. These include 1) KB220 while consisting of a number of botanicals (chemical ingredients) is indeed one product 2) KB220 as a product indeed has been studied in both pre-clinical and clinical trials (36 to be exact) for specific disorders or even specific diseases and falls under one specific disorder /syndrome/disease referred to as RDS 3) in terms of a singular mechanism of action (MOA), KB220's singular MOA is to activate reward processing inducing enhanced dopaminergic functionality by stimulating dopaminergic neurons in the brain reward circuitry, increase required functional connectivity, increase recruitment of dopamine neurons, increase synaptic and even mitochondrial concentrations of serotonin, endorphins, glutamate, and dopamine, induction of neuroplasticity, and as such increase dopamine release at the meso-limbic NAc. The simplistic MOA is based on human heroin abstinent dependent subjects, KB220 induces "dopamine homeostasis "as a proposed FDA approved singular claim for all RDS behaviors. It is noteworthy that a botanical product may be classified as a food or drug under FDA&C ACT. Along these lines scientists at TranspliceGen Holdings Inc. (Austin, TX.) are in development of a novel description of a chemical nomenclature for KB220. The working chemical's name is "STABAGNACFPHST" consisting of salicylic acid- tyrosol- n-acetylcysteine, arabinogalactans- boswellia- L-Glutamine -anthraquinones- N-acetylglucosamine- chromium- flavonoids-dl-phenylalanine-phycocyanin-pyridoxine- hydroxytryptophan- salidroside- terpenoids- L-tyrosine. The working brand name is NEUROSTASIS™.

It is noteworthy that we developed table 3 to enhance readership comprehension regarding differences between pharmaceutical and nutraceuticals.

Pharmaceuticals (Prescription Drugs)	Nutraceuticals (Foods/Supplements)
Governed by FDA in USA	Governed by FDA in USA, plus FTC for advertising claims
Cost to develop billions	Cost to develop in thousands
Targeting one or two sites in the body mono-therapeutics predominant	Multi-locus therapeutic targeting
Usually, high adverse side effects	Usually, low adverse side effects
Claims based on FDA approval studies	Claims based on structure function, classical nutrient deficiency, general well-being, nutrient content, disease reduction, with required science evidence
Doctor prescription required	No doctor prescription required
Most covered by insurance	Most not covered by insurance
Even with insurance coverage high cost in life threatening disease	Lower costs to consumer even without insurance in many cases
General people's consensus could be harmful	General people's consensus higher trust
Potential of addiction for many psychoactive drugs	Low potential for addiction with even psychoactive compounds

Global revenue totaling 1.6 trillion dollars in 2023	Global revenue totaling 591 billion dollars in 2023, but rate of growth is 7.6 percent CARG
Mostly synthetic chemicals	Derived from natural and synthetic sources
Provide disease fighting chemicals	Provide essential nutrients and beneficial substances for overall well-being.
Play a role in immediate relief of disease symptoms	Play a crucial role in the prevention and treatment of disease
Targeted disease treatment	Holistic health promotion
Conventional treatment a stand alone	Not a replacement for pharmaceuticals but could be adjunctive
Pharmaceuticals represent a fascinating intersection of food and medicine.	Nutraceuticals, a portmanteau of "nutrition"
FDA regulated with strict clinical trials (Phase I-IV); Standardized global regulations; Rigorous safety and efficacy testing required	FDA and FTC oversight (DSHEA guidelines); Varying international regulations; Less stringent approval process
Prescription drugs approved for treating specific medical conditions	Food or food components providing medical or health benefits
10-15 years development timeline; Billions in development costs; Mandatory clinical trials; Patent protection	Shorter development timeline; Thousands in development costs; Optional clinical studies; Limited patent protection
Single target mechanism; Precise dosing requirements; Well-documented drug interactions; Immediate therapeutic effects	Multi-target approach; Flexible dosing; Less documented interactions; Gradual therapeutic effects
Well-documented side effects; Thorough safety testing; Strict contraindication guidelines; Regular safety monitoring	Limited side effect documentation; Variable safety testing; General safety guidelines; Limited safety monitoring
Strict GMP compliance; High batch consistency requirements; Mandatory stability testing; Stringent quality control	Variable GMP compliance; Lower batch consistency requirements; Optional stability testing; Variable quality control
Double-blind controlled trials required; Extensive efficacy documentation; Post-market surveillance mandatory	Historical use evidence accepted; Variable efficacy documentation; Limited post-market surveillance
Prescription required; Controlled distribution; Insurance coverage common; High entry barriers	Over-the-counter access; Multiple distribution channels; Limited insurance coverage; Lower entry barriers
High consumer costs; Insurance coverage available; High development costs	Lower consumer costs; Out-of-pocket expenses; Lower development costs
Standard medical practice; Electronic health record integration; Professional monitoring required	Complementary medicine; Limited health record integration; Self-monitoring common
Optimized delivery systems; Documented absorption rates; Controlled release options	Basic delivery systems; Variable absorption rates; Limited release control
Stringent testing methods; Regular impurity profiling; Shelf-life guarantees	Basic testing methods; Limited impurity profiling; Estimated shelf-life
Regulated waste disposal; Carbon footprint monitoring; Environmental assessments	Basic waste management; Limited environmental monitoring; Optional assessments; Most of the manufacturing is green with biowaste
Personalized medicine integration; Advanced delivery systems; AI-driven development	Increasing standardization; Improved quality control; More clinical studies
1.6 trillion dollars globally	591 billion dollars globally with 7.6% CAGR

Table 3: *Comparison between pharmaceuticals and nutraceuticals.*

Conclusion

Several studies have shown that objective DNA polymorphic identification can be used to identify drug and alcohol risks in more effective ways than just subjective diagnostic surveys such as family history. The DNA guided pro-dopamine regulation therapies, such as KB220, is currently the subject of a number of clinical trials to resolve the RDS dilemma. In this commentary we point out via 36 human clinical trials and animal research that that administration of KB220 results in induction of "dopamine homeostasis" across a remarkable array of reward deficiency-related behaviors. Animal studies demonstrate that KB220 activates important brain reward-related regions, including the nucleus accumbens, anterior cingulate gyrus, anterior thalamic nuclei, hippocampus, and prelimbic and infralimbic loci. Kb220 induced significant functional connectivity, enhanced neuroplasticity, and improved dopaminergic functionality within the brain reward circuitry with effects localized to these regions rather than broader distributed across the brain. In abstinent heroin-dependent individuals, acute KB220 administration significantly induced BOLD activation in caudate-accumbens dopaminergic pathways relative to placebo. These results derived from over 1000 subjects accessing clinical outcomes and other quantitative electroencephalogy (qEEG) investigative results underscores a putative anti-craving/anti-relapse role of KB220 in not only addiction but many psychiatric disorders by direct or indirect dopaminergic interaction. Based on a review of the existing knowledge and further intensive investigation, we are proposing that instead of mono-pharmaceutical targeting, endorsement by the scientific community of multi-locus dopaminergic restoration of reward brain circuitry should become the new norm for all mental illness.

Author Contribution

The initial draft was developed by Kenneth Blum, Albert Pinhasov, and Debasis Bagchi. The figures were developed by Abdalla Bowirrat, Margaret A. Madigan, and Daniel Gastelu. Alexander Lewandrowski edited the entire manuscript. All co-authors made significant edits and proved the final manuscript.

Conflict of Interest

Kenneth Blum is the inventor and patent holder of GARS and pro-dopamine regulators and is a paid consultant for PeakLogic. Kevin T. Murphy is the founder and CEO of PeakLogic and the Sunder Foundation. Dr. Anand SwaroopI is president of Cepham located at Somerset, NJ.

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