REVIEW ARTICLE

Neuronutrient Amino-Acid Therapy Protects Against Reward Deficiency Syndrome: Dopaminergic Key to Homeostasis and Neuroplasticity

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Abstract: Willuhn *et al.*, observed that habitual cocaine use was correlated with reductions in D2/D3 receptors linked to decreased cue activation in occipital cortex and cerebellum. Dopamine agonist therapy maintains dopamine function and is relapse prevention tactic focused on psychoactive drug and behavioral addictions. Medication Assisted Treatment (MAT) with emphasis on glutaminergic medications fails in the long-term treatment of Reward Deficiency Syndrome Behaviors (RDS). While the careful use of "dopamine antagonist-therapy" short-term is supported, the research-based concept of "dopamine agonist therapy" in long-term is proposed. Neurogenetics and epigenetics are important in understanding treatment response and clinical outcomes. The neuro–mechanisms involving "dopamine homeostasis" are key to understanding recovery from drug and non–drug addictive behaviors. For example, patients who carry the DRD2 A1 allele (30-40 less D2 receptors) should consider Neuronutrient–Amino-Acid therapy (KB220 variants) a prevention modality. DRD2 A1 allele carriers show amplified striatal function of L-amino acid decarboxylase, prior to dopamine biosynthesis. Another example is the effect of Acute Tyrosine Phenylalanine Depletion (ATPD) on decision-making and reward found carriers with amino-acid deficiency (ATPD). They experienced attenuated reward and reduced decision-making ability as quantified by Iowa Gambling Task (IGT). Future research should be directed at asking the question; Would "dopamine agonist therapy" using KB220 variants reduce methylation and increase acetyl groups to enhance DRD2 expression especially in DRD2 A1 allele carriers and lead to increased dopamine function and a reduction of drug and non-drug seeking behaviors?

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1. INTRODUCTION

Reward Deficiency Syndrome (RDS) was a term first used in 1996 to describe a group of behaviors that result from the lack of adequate pleasure or satisfaction in life. Genetic researchers have identified the lack of wellbeing as being associated with a dopamine deficiency. The RDS behaviors are all addictive obsessive and impulsive behaviors. including both substance and non - substance (process) addictions [1]. Dopamine must be regulated to reduce aberrant craving and drug seeking. The genetic variations and epigenetic changes to DNA function in the reward circuitry result in diminished dopaminergic activity. This decreased dopamine function sets up the brain to be more sensitive to stress especially in the older individuals. In terms of therapeutic targets, we are cognizant that each genetic polymorphism will affect the function of the brain reward circuitry and will need to be identified across the CNS. There are numerous genes implicated in this organization, but it is known that the normal function of this important reward system works as a cascade known as the "Brain Reward Cascade" [2]. One goal in the treatment of drug and or behavioral

addictions is to induce stabilization of dopaminergic function or "dopamine homeostasis."

While somewhat controversial regarding dopamine surfeit or deficit [3] dopamine homeostasis is a laudable treatment goal. The proposed goal in long–term treatment is to enhance dopamine release by employing mechanisms tied to GABA regulation, and inhibition of enkephalinase. This enhanced dopamine release will induce anti-stress states and diminish stress induced addictive behaviors. In a literature review, we intend to show that by utilizing compounds that either control GABA transmission or inhibit GABA transmission, higher amounts of dopamine will be released at the nucleus accumbens (NAc). Numerous compounds have been shown to stimulate glutaminergic sites through N-methyl-D-aspartate (MDMA) receptors. However, this is the first anti-craving compound developed to enhance this mechanism for long-term treatment and relapse prevention. We also now know that epigenetic effects can alter DNA expression both through histone methylation or de-acetylation. We ask the question: Is it possible that brain reward circuitry is set up preferentially to synthesize more dopamine when challenged with a "Neuronutrient Amino-Acid" formula?

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1.1. Genes and Life Style

During 2013 the National Survey on Drug Use and Health found that 24.6 million Americans (ages >12 years) used illicit drugs within the last month, and 21.6 millón were classified as having a substance use disorder (SUD). The same survey approximated that of 6.9 million illicit drug users, 4.2 million of them had marijuana, 1.9 million had pain reliever, 855,000 had cocaine, and 517,000 had heroin use disorders. In 2014, almost six percent of college students was smoking marijuana on a daily or near-daily basis, defined as smoking marijuana 20 or more times in the previous 30 days [4]. These numbers confirm that the significant threat SUDs poses to overall public health and requires our urgent attention

The Food and Drug Administration (FDA) has approved several medications for alcohol, nicotine, and opiate dependence treatment. Nonetheless, these medications do not deliver the best form of therapy. Presently, the FDA has not approved any medications for the treatment of substance use disorders of cocaine, methamphetamine, or cannabis. There is an imperative for the development of safe and effective treatment for these drugs of choice.

Before we delve into an attempt to provide neuroscience evidence for revolutionary changes in Medication Assisted Treatment (MAT), it seems necessary to report some new thinking. Ideas related to our genome that impact not only addiction liability but also other pressing issues.

The hypothesis is that in the treatment of any individual for addictive behaviors (drug and non-drug) ones' genetic makeup may have relevant predictive value in lifestyle choices like the ability to accept a higher power (spirituality) and even their political views. Consideration of these qualities may sound like a diversion from the matter at hand, but they are indeed part of the holistic understanding of any individual.

Novel evolutionary concepts linked to a developing scientific application known as omics, in this case, the genome, we are suggesting that spiritual, social, and political behaviors may be associated with inheritable reward gene polymorphisms, as revealed in addiction. Blum *et al.*, [5] and Boardman *et al.*, [6] have proposed that gene polymorphisms analyses may potentially aid in expecting liberalism or conservatism in partisan connections and friendships. For example, both alcoholism and obesity occur in large social networks, and are induced by friends to partake, have similar genotypes, specifically the DRD2 A1 allele. Similarly, voting and connection to specific political groups are differentially correlated to numerous reward genes including 5HTT, MOA, DRD2, and DRD4, potentially forecasting liberalism or conservatism. Certainly, even in politics, "birds of a feather flock together" (homophily). While the above correlates to not only social views, but group participation, the genes related to happiness or anti-stress include, but are not limited to, these reward gene polymorphisms.

1.2. Neuroscience-Based Treatment Modalities

In the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders, Substance addiction is defined by a combination of symptoms such as tolerance, and withdrawal, further substance intake for relieving withdrawal, amplified ingestion past initial intention to use, and failure to decrease consumption. For example, spending a substantial amount of time acquiring drugs or recuperating from drug effects. Negligence of other areas of life like family, and the continuance of consumption, despite dealing with adverse results.

The NAc continúes to be implicated in addiction. Within the NAc circuitry neurotransmitters have been associated with compulsive drug use and relapse. The glutamate system, in particular, has been associated with relapse after abstinence. Poor dopamine system function has been associated with compulsive drug consumption. The glutamate homeostasis hypothesis involves the influence of the relationship between synaptic and extrasynaptic levels of glutamate, on the prefrontal cortex (PFC) to NAc pathways [7].

Following recurring drug consumption, deregulation of this homeostasis escalates glutamate discharge from the PFC to the NAc during relapse. Glial cells also contribute to this hypothesis. Glial cells form the connections between the NAc and the PFC by modifying glutamate levels in synaptic and extrasynaptic spaces. Cocaine self-use and withdrawal, on the contrary, grows glutamate receptor 1 (GluA1) of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) the surface manifestation of subunit receptors at the NAc. Additionally, cocaine self-use and withdrawal induce the creation, also at the NAc, of subunit glutamate receptor 2 (GluA2), deficient in Ca2+-permeable AMPA receptors (CP-AMPARs). Antagonism of the CP-AMPARs decreases cravings. It is imperative to investigate further the AMPA receptor subunit arrangement and differences at the NAc for an increased understanding of glutamatergic plastic alterations [8]. NAc activity can be stimulated by other factors apart from glutamate and dopamine, such as brain-derived neurotrophic factor (BDNF), can and stimulate variations in dendritic spine density. BDNF also stimulates drug behaviors including self-administration and relapse [9].

1.3. Epigenetics and Addiction

The addition of a methyl group (CH3) to another molecule (like an enzyme, RNA, chromosome/DNA, toxin, or protein) is Methylation. The inclusion or reduction of a methyl group causes great alterations as they can either activate or deactivate DNA. Aging is marked by the gradual loss of cytosine methylation in the genome. Methylated cytosines (5mC) inhibit gene transcription and DNA cleavage by restriction enzymes. Apoptosis which requires DNA fragmentation is prevented by cleavage inhibition. Principal mechanisms are antioxidants catalyze the re-methylation of cytosine by altering the activity of DNA methyltransferases while free radicals catalyze the demethylation of 5mC. Methylation and or deacetylation are necessary methods to ensure constant repair work to DNA. For example, methylation is also essential for converting homocysteine into the good, mood-elevating methionine, glutathione, and SAMe molecules. Proper methylation is required for the following processes: reducing homocysteine; protecting telomeres to slow down the aging process; preventing hormone imbalances; creating SAMe, the precursor to serotonin and dopamine. Methylation is also the processes by which serotonin is converted to melatonin for sleep; helping the thyroid to make thyroxine, and turning the stress response on and off. Detoxification of dangerous chemicals and heavy metals, supporting the liver's detox process, turning genes on and off, and neurotransmission facilitation are all accomplished via Methylation. Cycling the heart's ATP; making glutathione to detox cells; correcting chronic fatigue, correcting fibromyalgia, building the immune system; assimilating vitamin B12, managing blood pressure, as well as optimizing male sexual performance are all methylation processes. They also support nerve transmission; protecting myelin, support neuroendocrine balance, heal, muscle trauma; support bone, make insulin and protect the mitochondrial production of ATP. It is known that less than optimal methylation may inhibit the ability of the body to create the building blocks (purines and pyrimidines) that are needed for new DNA and RNA synthesis as well as keeping telomeres long instead of short. Intermediates of methylation pathways are known to decrease with age and decline in methylation pathway function. DNA methylation decreases with age. On the other hand, Methylation can also affect reward genes with concomitant drug seeking behaviors especially psychostimulants [10].

Drug and or behavioral addictions are progressive, debilitating mental illness characterized by uncontrollable and compulsive substance and non-substance seeking behavior despite the mental and physical consequences associated with being addicted [11]. Cer-

tainly, chronic exposure to drugs of abuse can alter gene expression in crucial brain reward regions. The ventral tegmental area (VTA), NAc, and PFC are all involved [12]. Stimulants can influence epigenetic processes by increasing overall histone H3 and H4 acetylation in the NAc following both acute and chronic cocaine administration [13].

The BDNF gene polymorphism (Val68 to Met) has recently been implicated in alcoholism [14], as well as other addictions. Graham *et al.*, [15] reported that acute self- administration of cocaine increases BDNF protein in the NAc. Moreover, infusions of BDNF into the VTA [16] induce an increase in cocaine self-administration in rats, indicating that BDNF can facilitate reward-related behaviors as seen in behavioral/drug addictions. Furthermore, Grimm *et al.* [17] found that post cocaine exposure; there is a persistent release of BDNF in the VTA and NAc. Others have also shown a similar response in the striatum [18] during withdrawal.

Kumar *et al.* [19] found that histone alterations contribute to cocaine's influence on BDNF in an addictive animal model. Chronic cocaine exposure stimulated acetylation of histone H3 at the BDNF gene promoter region in the striatum; This effect continued after the last cocaine injection for 24 hours indicating the function of epigenetic mechanisms on cocaine's BDNF regulation.

Acute injection of cocaine enhances manifestation of the instantaneous initial genes *c-fos* and *fosB* in the NAc by promoting histone H4 acetylation on their corresponding proximal promoter sites [19-21] the mechanism through which this induction of *fosB* occurs was shown to be via the histone acetyltransferase CREB-binding protein (CBP). During the severe use of cocaine, it was demonstrated that CBP is enlisted to the *fosB* promoter space and acetylates histone H4 causing an overall rise in *fosB* expression [22] in the NAc.

Histone deacetylases (HDAC) enzymes are vital in modifying gene activity by inducing repressive influence on transcription modifications of the chromatin structure. It is known that there are 11 mammalian HDAC enzymes classified into four distinct HDAC families; class I, IIa, IIb, and IV, grouped according to sequence homology, subcellular localization, and expression patterns [23]. Moreover, it was shown that the loss of the class II HDAC, HDAC5, results in an enhanced response to cocaine reward post conditioned place preference (CPP), and this effect was specific to HDAC5 with no changes observed in HDAC9 knockout mice [13, 24]. The effect of cocaine within the NAc involved partial rescue HDAC5 including acetylation of target genes including the NK1 receptor, Gnb4, Suv39H1, and RapGEF6, within the NAc.

Also, Romieu *et al.* [25] and Sun *et al.* [26], show that HDAC inhibitors can regulate cocaine-induced addiction behaviors in rodents. In fact, the pan-HDAC inhibitor, sodium butyrate, can help regulate cocaine's effects and this inhibitor has been shown to provide therapeutic effects in neurodegenerative disease [27]. Kumar *et al.* [19] previously demonstrated a synergistic effect of the co-administration of sodium butyrate and cocaine. Co-administration, lead to increased cFos expression and increased histone H3 acetylation at the cFos promoter. While further work is necessary we are beginning to understand the importance of epigenetic effects especially those that relate to I HDAC inhibitors like *N*-(2-aminophenyl)-4-[*N*-(pyridin-3-yl-methoxycarbonyl) aminomethyl] benzamide (MS-275) [28].

The bottom line is that prolonged use of drugs of abuse and possibly behaviors like pathological gambling, hypersexuality may lead to long-term changes in brain function suggesting that alterations in gene activity and amino acid deficiency may contribute to the phenotypes seen in addicted individuals [29-36].

There are now a plethora of studies in both humans and animals suggesting the importance of transcription and downstream targets in the effects of drugs of abuse and possibly process addictions. Certainly, the role of epigenetics in the maintenance of seeking behavior, in the same generation and potentially even in second and even third generations, has been agreed upon by most informed neuroscientists. However, this information has not as yet translated to medication-assisted treatment especially during recovery. More work is required to describe fully how long-term aspects of addiction following drug exposure are mediated by epigenetic changes to specific downstream targets.

2. ARE WE MEETING TREATMENT EXPECTATIONS? FAILED RESPONSE

2.1. Glutaminergic Medication

Many of MAT FDA approved drugs favor glutaminergic targets. Moreover, they require review to elucidate shared neurochemical mechanisms and their promise as anti-craving agents. There are a number of studies of known medications that have effects on the glutaminergic system such as N-acetyl-L-cysteine (NAC) and Modafinil that potentially have anti-craving properties. There are also some short-term controlled clinical studies that have highlighted anti- glutamatergic (Acamprosate, topiramate) and GABAergic (Vigabatrin) agents, and agonist replacement therapy (sustained-release methylphenidate, d-amphetamine) for substance abuse. It is important to consider mental disorder co-occurrence of many addictions and the potential of common mechanisms of craving and impulsivity [37]. The most promising treatment is a combination of pharmacotherapies with behavioral therapies.

2.2. N-acetyl-L-cysteine (NAC)

Bauza *et al.* [38] have investigated the effects of a cysteine-glutamate transporter enhancer on the neurochemistry and behavior in nonhuman primates addicted to cocaine and amphetamine. The hypothesis was that NAC, a cysteine prodrug, would augment extrasynaptic glutamate release, diminishing stimulant (amphetamine or cocaine) prompted surges in extracellular dopamine and related behavioral stimulation. However, unlike the results, of rodents studies and human clinical trials [39,40]; self-administration and the behavioral stimulant effects of cocaine or amphetamine on non-human primates were not attenuated by NAC although dopamine surges were diminished in cocaine but not amphetamine.

Although all clinical studies are preliminary and utilized relatively small sample sizes, the somewhat stable anti-addictive properties of NAC, mostly in cocaine, postulate convincing proof that this medication, [39, 40], combined with other agents that reestablish glutamate homeostasis could provide pharmacotherapeutic support in the management of RDS.

2.3. Modafinil

The psychostimulant drug modafinil acts by exciting α-adrenoceptors, subduing GABA discharge, hindering the dopamine transporter, or motivating hypothalamic orexin-containing neurons [41, 42]. Although a majority of studies propose that dopamine has stimulant properties [43-45], Modafinil has been observed increasing extracellular levels of glutamate in several brain areas involving the dorsal striatum, hippocampus and diencephalon [46-48] without changing glutamate synthesis [49].

Based on pro-dopaminergic activation by Modafinil and its low addiction liability, its use as an anti-abuse liability drug has been investigated but has shown mixed results. There are some examples of how Modafinil impedes the function of dopamine and as such, leads to anti-reward effects. Bodenmann *et al.* [50] reported that Modafinil could maintain the high functional activity of COMT Va/Val genotype, thereby leading to reduced dopaminergic signaling [50]. Reduced dopaminergic signaling, is caused by the well-known proficiency of COMT enzyme (Val/Val) that disintegrates dopamine rapidly, causing there to be little dopamine in the synapse, while interestingly, the less efficient COMT enzyme

(Met/Met) keeps dopamine in the synapse for much longer [51]. Modafinil was also shown to up-regulate the expression of the dopamine transporter gene once again inducing a hypodopaminergic trait/state in the human synapse [52].

2.4. Acamprosate

The FDA approved drug Acamprosate (calciumacetyl-homotaurinate) is derived from homotaurine, a nonspecific γ-aminobutyric acid (GABA) agonist. The drug is poorly absorbed (i.e., <20%) and requires doses in the range 2–3 grams per day to demonstrate efficacy. A suggested primary mechanism of action of acamprosate is that acamprosate exerts its actions through glutamatergic mechanisms [53, 54]. Specifically, acamprosate decreased the stimulation of neuronal firing induced by iontophoretic use of L-glutamate onto cortical neurons in vivo, and subdued excitatory postsynaptic potentials (EPSPs) induced by glutamate and N-methyl-D-aspartate (NMDA). Further confirmation for the NMDA antagonist like mechanisms of acamprosate results from studies indicating that this amalgam antagonizes NMDA-induced excitatory postsynaptic currents (EPSCs) in hippocampal neurons [55] and upregulates NMDA receptor subunit manifestation comparable to that seen following treatment with non-competitive NMDA antagonist MK-801 [55, 56]. However, Popp and Lovinger [57] found no effect of acamprosate on NMDA-mediated synaptic transmission in the CA1 region of the hippocampus. Nevertheless, others have discovered that acamprosate, in fact, enhances NMDA receptor roles in the hippocampal CA1 region [58] and the NAc [59]. Studies have proven that contact of acamprosate with the glutamate-, spermidine-, and/or MK-801-delicated binding site of the NMDA receptor [60-62], and as such, acamprosate is suggested to be a "NMDA modulator."

While the exact molecular aim(s) of acamprosate are not yet recognized [63, 64], modern theories imply that acamprosate reestablishes balances between excitatory and inhibitory amino acid neurotransmission caused by prolonged alcohol use [63, 65-67].

In the mid-1980's, Lhuontre *et al*. were the first to show that acamprosate reduced the incidence of relapse in alcoholics [68]. Following this early study, some meta-analyses demonstrated effect sizes ranging from small to moderate concerning reducing alcohol consumption, alcohol craving, and promoting abstinence [63, 69-75]. In fact, it was observed that acamprosate was equally effective to the placebo in decreasing the relapse rates in a medical setting [76]. Further studies have also confirmed a lack of effectiveness of acamprosate in decreasing alcohol use or desire, or encouraging abstinence [77-80]. However, others have implied that the start of acamprosate treatment succeeding detoxification creates declines in alcohol desire as opposed to treatment while using alcohol actively [81]. LoCastro *et al*. [82] showed improvements in non-drinking related outcomes, measures of quality of life were superior in acamprosate versus placebo-treated patients. Certain identification of a subset of alcoholics may respond better to its benefits [83, 84]. Regarding other behavioral addictions, Raj (2010) found some benefit in the treatment of pathological gambling [85]. Concerning the value of acamprosate in addiction treatment of other abused drugs or behavioral addictions like pathological gambling, larger studies do not exist, and the smaller published studies have varied results. An example is a new case supporting the possible use of acamprosate in treating pathological gambling [85]. In contrast, Kampman (2011) found no significant effects in the use of acamprosate for the treatment of cocaine disorders [86]. These negative findings are discouraging because numerous rodent studies have revealed that acamprosate reduces the habituated reward effects of cocaine as well as drug- and cue-primed restoration of cocaine-seeking behavior [87-89].

2.5. Gabapentin

Gabapentin is an anticonvulsant medication that disrupts neuronal transmission by inhibition of presynaptic voltage-gated Na+

and Ca2+ channels [90-92]. Consequently, gabapentin acts to inhibit the release of various neurotransmitters, including glutamate [93-99].

While studies have found that gabapentin is effective in mitigating the symptoms of alcohol withdrawal due to moderate to severe CNS hyperexcitability and convulsions [100-107], its role as anti-drug abuse agent remains questionable. Several studies report that gabapentin (with dose ranges of 600–1200 mg/day) does not reduce the use of cocaine [108, 109], while others indicate that gabapentin decreases cocaine use and craving [110-114]. Despite some positive results with 600-1500mg/day [115-118] in reducing alcohol intake and prolonged abstinence, others, unfortunately, have described no effects of similar doses of gabapentin on alcohol craving [119, 120]. Conflicting results indicate the need for further examination of gabapentin efficacy.

Gabapentin has been shown to reduce alcohol consumption, and craving [115-117] and prolong abstinence from alcohol use [118]. Other investigators, however, have shown that gabapentin does not reduce methamphetamine use [121], exhibits limited effects on facilitating abstinence from smoking [122], and does not enhance subjective withdrawal symptoms in opiate-dependent subjects [123]. Thus far, gabapentin has not been scientifically tested for efficacy of addiction treatment and may even exacerbate alcoholism.

2.6. Topiramate

Topiramate, similar to anticonvulsants such as gabapentin and lamotrigine, functions through multiple mechanisms: inhibition of presynaptic voltage-gated Na+ and Ca2+ channels (thereby inhibiting the release of neurotransmitters including glutamate) and activation of type A GABA (GABAA) receptors [90, 91, 124]. Topiramate also works as an antagonist at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) [125, 126]. These antagonist effects on the AMPA receptor are active in mediating drug self-administration and relapse potential [127-130], and notable because of the involvement of this glutamate receptor subtype in the neuroadaptive changes resulting from drugs of abuse. Reported effective doses of topiramate range from 75–350 mg/day.

Furthermore, topiramate may also aid in the amelioration of benzodiazepine withdrawal symptoms [131] in addition to attenuation of alcohol withdrawal symptoms similar to the amelioration observed with gabapentin and lamotrigine [132]. Some recent studies have demonstrated the efficacy of topiramate in reducing alcohol craving, heavy consumption, and alcohol's subjective effects [133-139]. Topiramate ability to decrease compulsive drinking may be a result of its modulation of impulsivity and improvement of behavioral inhibition [140]. One study in particular reported indications that topiramate performed better than naltrexone, the "gold standard" in anti-alcoholism medication, in prolonging abstinence and decreasing continuous drinking and relapse [141].

Topiramate has been shown to reduce craving and cocaine use in cocaine-dependent individuals [142, 143]. However, the small sample sizes of these two clinical studies are limiting factors [144]. One case report, in particular, demonstrated that topiramate may reduce the use of methylenedioxymethamphetamine (MDMA, "Ecstasy") [145]. For cigarette smokers, a few small studies have shown the benefits of topiramate in supporting abstinence from smoking [134, 146, 147]. Topiramate's ability to prolong abstinence from smoking may be gender-specific, with comparatively better responses in males [148]. One study, though, found that topiramate increased the subjective effects of withdrawal from smoking, and the rewarding effects of a smoked cigarette without cue-induced craving [149]. This effect parallels the results seen with lamotrigine. Overall this challenges the potential use of topiramate as an aid in smoking cessation. It has been shown to enhance the positive sensations and effects of methamphetamine [150]. Topiramate may have potential in the treatment of addiction to alcohol

and possibly cocaine and nicotine although more comprehensive research is needed to determine its efficacy as a therapeutic for treating addiction. The effects of Topiramate have been linked to specific gene polymorphisms.

Regarding behavioral addiction, some recent small-scale studies and case reports indicate that topiramate is a potential treatment agent. Observed positive effects of topiramate include reduction of relapse to problematic gambling [151] and reduction of compulsive eating and sexual behavior [152-154]. It is clear that the clinical application topiramate should be further investigated to treat non-drug addictions. However, long-term utilization should be considered with caution because it may stimulate GABA signaling and attenuate dopamine release.

2.7. Dopamine Agonist Therapy: Changing the Recovery Landscape

In the right direction other compounds that are enkephalinase inhibitors affect dopamine release. Dopamine increases in dialysates from the striatum of freely moving rats were induced using the enkephalinase inhibitor sodium nitroprusside. This compound has not yet been studied by itself as an anti- craving substance [155].

Existing neurologic circuits, particularly the brain reward system and the dopamine D2 receptors, shed light on reward mechanisms affecting behavioral craving [156]. Overall the effect of neurotransmitter activity within the mesolimbic system results in the release of dopamine in NAc that interacts with dopamine D1-D5 receptors. This dopamine release results in the feeling of reward [1, 157-168]. Consequently, this "reward cascade" [2] involves serotonin release and subsequent stimulation of hypothalamic release of enkephalin. This enkephalin, in turn, acts to inhibit GABA in the substania nigra, regulating the amount of DA released the "reward site," the NAc [169-171] through the raphe nuclei. That idea that NAc dopamine maintains and controls our normal drives relating to pleasure is well established [172-174]. In fact, dopamine is thought of as the anti-stress and pleasure molecule [175-179]. Synaptic release of dopamine stimulates some receptors (D1-D5), leading to increased feelings of well-being and stress reduction [180-182]. Positron emission tomography (PET) has demonstrated that when levels of D2 receptors in non-dependent individuals compared to levels of D2 receptors in drug and alcohol dependent subjects D2 receptor levels are substantially lower [183].

In animals, overexpression of the D2 receptor via vector delivery of the D2 gene resulted in a notable reduction of alcohol consumption [184-187]. KB220 variations of the dopamine agonistic agent can normalize brain function by a number of neurochemical effects including restoration of brain dopamine at the reward site, reduction of excessive craving behaviors, and induction of enhanced resting state functional connectivity [188]. Table **1** is a list of preclinical and clinical studies that were important in the development of KB220 variations. The research has been carried out over 43 years and during that time the experimental substance has been called many names, some to describe its function as understanding changed and grew, for example, Neuronutrient Amino Acid Therapy (NAAT) and some due to product development, for instance, Genotrim and SAAVE.

3. NEUROCHEMICAL MECHANISMS FAVOR AMINO ACID –ENKEPHALINASE INHIBITION THERAPY

3.1. Background

Volkow *et al.* pointed out that recent development of effective treatments for alcoholism has increased public interest in pharmacologic therapies [223]. A meta-analysis of randomized controlled studies was produced to determine appropriate forms of pharmacotherapy for the treatment of alcohol dependence. It was concluded that several pharmacotherapeutic agents exhibited safe

and effective qualities in the long-term, intermediate-term, and short-term periods of follow-up. In this case, the agents were acamprosate, naltrexone, and fluoxetine and citalopram, respectively. Studies involving zimeldine, nialamide, L-dopa, viloxazine, and Tetrabamate failed to demonstrate significant efficacy for these agents in alcoholism treatment. Similarly, lithium, phenytoin, bromocriptine, apomorphine, and buspirone demonstrated ambiguous and mixed results. With these circumstances, continued research is needed to identify the methods of pharmacotherapy that would fit the needs of different patients.

To reiterate meta-analyses also show poor compliance with naltrexone and acamprosate [224]. Specifically, a systematic review of the literature (1990-2002) and meta-analysis of randomized and controlled clinical trials assessing acamprosate and naltrexone therapy for alcohol dependence was inconclusive. Estimates of effect were calculated according to the fixed-effects model. Primary outcomes such as relapse and abstinence rates, cumulative abstinence duration and treatment compliance were considered. Thirty-three studies met these inclusion criteria. Acamprosate was associated with a marked improvement in abstinence rate and days of cumulative abstinence. Meanwhile, short-term administration of naltrexone reduced the relapse rate significantly but was not associated with a significant modification in the abstinence rate. Due to insufficient data, naltrexone's efficacy over prolonged periods was not able to be determined. It is possible that implantable naltrexone may increase compliance in the longer – term (about 4-12 months). Acamprosate demonstrated a good safety pattern and an improvement in treatment compliance. Naltrexone was well tolerated and although it had had more side effects it was nevertheless not associated with lowered adherence to treatment. Despite these findings, overall compliance was relatively low with both medications [224].

Acamprosate and naltrexone are both effective as adjuvant therapies for alcohol dependence in adults. The former is especially useful in a therapeutic approach that targets abstinence, whereas naltrexone is better suited to programs aimed at managing consumption. Both are safe and acceptably tolerated, although compliance remains the main concern in clinical applications.

With this information, we are proposing that compounds like NAC, Acamprosate, sodium nitroprusside, and others are not very effective clinically. However combined with compounds known to enhance brain opioid peptides might have a much better outcome. They could lead to enhanced neuroplasticity following drug abuse [225] and prevention of relapse to substance and non-substance-related addictive behaviors

3.2. Compounds Directed to Enhance Brain Opioids

As far as is known, a combination of glutaminergic activators with compounds to inhibit enkephalinase to act as therapeutic agents to treat RDS has not been explored.

"Enkephalinase," a peptidase capable of degrading enkephalins, has been characterized in man, in both plasma and cerebra-spinal fluid (CSF). D-phenylalanine (d-Pha) was shown to decrease enkephalinase activity in plasma and CSF in humans [226]. In fact, another enkephalinase inhibitor Bestatin significantly reduced alcohol intake in genetically bred alcohol-preferring rats [226] known to have low brain endorphin levels.

In morphine-sensitive Wistar rats i.p. inoculation of 300-600 mg/kg d- d-Pha did not change the nociception (tail-flick test), but evoked a dose-dependent analgesic effect in morphine-resistant rats. Chronic morphine administration induced tolerance as d-Pha injection evoked an analgesic effect in morphine-sensitive rats. It is implied that morphine-resistant rats exhibit congenital enkephalinase activity while morphine-tolerant rats have an acquired elevated level of enkephalinase activity, which blocks morphine analgesic action.

Table 1.   Pre-clinical and clinical studies that lead to the development of dopamine agonistic, amino acid and enkephalinase inhibition therapies.

	Preclinical Studies	
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 [189].	Increased brain L-DOPA increases brain dopamine in mice and causes inebriated mice to sleep. Dopamine, l-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 [190].	When mice were given alcohol and 1-tryptophan or saline the mice given 1-tryptophan went to sleep, while, the mice given saline did not. 1-tryptophan and alcohol work similarly in the brain.
1987	Blum K, Wallace JE, Trachtenberg MC, *et al*. Enkephalinase inhibition: Regulation of ethanol intake in mice. Alcohol: 4; 449-456 [191].	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.
	Clinical Studies	
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 [192].	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.
	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 [193].	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.
	Blum K, Allison 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 [194].	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.
1990	Brown RJ, Blum K, Trachtenberg, MC, Neurodynamics of relapse prevention: a neuronutrient approach to outpatient DUI offenders. Psychoactive Drugs 22: 173-187 [195].	Relapse prevention using neuronutrients SAAVE and Tropamine in DUI offenders; either alcohol or cocaine. Reduced relapse rates and enhanced recovery in 10 week outpatient setting. After ten months recovery rate was SAAVE 73% and Tropamine 53%.
	Blum K, Trachtenberg MC, Cook DW. Neuronutrient effects on weight loss in carbohydrate bingers; an open clinical trial. Curr Ther Res.48: 217-233 [197].	Examine the effects of PCAL-103 (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.
1996	Cold JA, NeuRecover-SATM in the Treatment of Cocaine Withdrawal and Craving: A Pilot Study. Clinical Drug Investigation. 12(1):1-7 [198].	Small preliminary study of the efficacy of NeuRecover-SATM (formerly Tropamine+TM) in the treatment of cocaine withdrawal and craving. Cocaine craving decreased significantly in the NeuRecover-SATM 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 [199].	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 statistically significant amplitude of the P300 component of the Event Related Potentials (ERPs). FOCUS IMPROVED

	Preclinical Studies	
Year	**Reference**	**Key points**
	Blum K, Cull JG, Chen TJH, *et al.* Clinical evidence for effectiveness of Phencal™ in maintaining weight loss in an open-label, controlled, 2-year study. Current Therapeutic Research 55(10) 745-763 [200].	Of 247 Outpatients in a very-low-calorie fasting program 130 who were having difficulty attaining their desired weight or maintaining their desired weight constituted the experimental group who took PhenCal™ and the rest 117 took vitamins 117 were the control group. The PhenCal™ group compared to the control lost twice as much weight, regained 14.7% of the weight while the control group regained 41.7%, decrease in food cravings for females 70% and males 63%, and decreased in binge eating for females 66% and males 41%.
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):S1-8.	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 [201].	A combination of Trexan (a narcotic antagonist) and amino-acids was used 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.
2006	Blum K, Chen TJ, Meshkin B, *et al.* Reward deficiency syndrome in obesity: a preliminary cross-sectional trial with a Genotrim variant. Adv Ther. 2006; 23(6):1040-1051 [202].	Consumption of large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates production and usage of dopamine within the brain. Obesity is due to the need to make up for inadequate dopaminergic activity in the reward center of the brain. This has been called reward deficiency syndrome (RDS) used to categorize such genetic biologic influences on behavior. RDS must be addressed at the same time as behavioral modifications are implemented to adequately treat obese patients. In this small observational trial; 24 individuals completed a survey on which they documented 15 categories of benefit during their experience with a GenoTrim a NAAT formulation customized to DNA. Statistical analysis of the survey results demonstrated that stress reduction lead to improved sleep, enhanced energy, and improved focus and performance, reduced appetite, loss of unwanted weight, decreased body inches and enhanced well-being.
	Chen TJ, Blum K, Waite RL, *et al.* Gene \Narcotic Attenuation Program attenuates substance use disorder, a clinical subtype of reward deficiency syndrome. Advances in Therapy 24: 402-414 [203].	A one-year prospective study evaluated the effects of taking Haveos (Synaptamine™) on 61 compliant patients in a comprehensive outpatient clinical program. Results after 12 weeks include a significant decrease in craving. Results after one year include building up to relapse scores and ability to refrain from drug-seeking behavior both significantly improved. The dropout rate for alcohol users 7% and psychostimulant users 73%
2007	Blum K, Chen TJH, Downs BW, *et al.* Synaptamine (SG8839),™ 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% ($p<0.001$).
	Chen TJH, Blum K, Kaats G, *et al.* Chromium Picolinate (Crp) A putative Anti-Obesity Nutrient Induces Changes In Body Composition As Function Of The Taq1 Dopamine D2 Receptor Gene. Gene Ther Molboil 11; 161-170 [205].	Chromium Picolinate (CrP) was tested against placebo in groups of obese patients tested for the Taq1 Dopamine D2 Receptor Gene. In carriers of the DRD2 A2 genotype weight loss and other changes in body composition were significant. They were not significant for patients with the A1/A1 or A1/A2 allele. These results suggest that the dopaminergic system, specifically the density of the D2 receptors, confers a significant differential therapeutic effect of CrP in terms of weight loss and change in body fat.

(Table 1) Contd....

		Preclinical Studies	
Year	**Reference**	**Key points**	
	Blum K, Chen TJH, Williams L, *et al.* A short term pilot open label study to evaluate efficacy and safety of LG839, a customized DNA directed nutraceutical in obesity: Exploring Nutrigenomics. Gene Ther. Mol. Boil. 2007; 12: 371-382 [206].	Preliminary investigational study to 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.	
2008	Blum K, Chen AL, Chen TJ, *et al.* LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. Adv Ther 25 (9): 894-913 [207].	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.	
	Blum K, Chen TJH, Chen ALC, *et al.* Dopamine D2 Receptor Taq A1 allele predicts treatment compliance of LG839 in a subset analysis of pilot study in the Netherlands. Gene Ther Mol Biol 2008; 12: 129-140 [208].	Hypothesized that genotyping certain known candidate genes would provide DNA-individualized customized nutraceuticals that may have significant influence on body re-composition by countering various genetic traits. Genotyped for the dopamine D2 receptor (DRD2), methylenetetrahydrofolate reductase (MTHFR), serotonin receptor (5-HT2a), Peroxisome Proliferator Activated Receptor gamma (PPAR-γ), and Leptin (OB) genes. Systematically evaluated the impact of polymorphisms of these five candidate genes as important targets for the development of a DNA-customized nutraceutical LG839 [dl-phenylalanine, chromium, l-tyrosine other select amino-acids and adaptogens] to combat obesity with special emphasis on body recomposition as measured by Body Mass Index (BMI). In the 41 day period, we found a trend in weight loss whereby 71.4% of subjects lost weight.	
2009	Blum K, Chen ALC, Chen TJH, *et al.* Putative targeting of Dopamine D2 receptor function in Reward Deficiency Syndrome (RDS) by Synaptamine Complex™ Variant (KB220): Clinical trial showing anti-anxiety effects. Gene Ther Mol Biol 13: 214-230 [209].	Brain dopamine has been implicated as the so-called "anti-stress molecule." The present study investigated anti-anxiety effects of Synaptamine Complex [KB220], a dopaminergic activator, in a randomized double-blind placebo-controlled study in alcoholics and poly-drug abusers attending an in-patient chemical dependency program. Patients receiving Synaptamine Complex [KB220] had a significantly reduced stress response as measured by SCL, compared to patients receiving placebo.	
2010	Braverman ER, Braverman D, Acrui 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 [210].	A 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 25.4kg/m2 representing a 6.9kg/m2 reduction. His body fat composition decreased from 36.91% to 17.8% as measured by the Hologic DEXA scanner.	
	Miller DK, Bowirrat A, Manka M, *et al.* Acute intravenous synaptamine complex variant KB220™ "normalizes" neurological dysregulation in patients during protracted abstinence from alcohol and opiates as observed using quantitative electroencephalographic and genetic analysis for reward polymorphisms: part 1, pilot study with 2 case reports. Postgrad Med. 122(6):188-213 [211].	Intravenous Synaptamine 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 Synaptamine Complex Variant KB220™	
	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):214-226 [212].	Protracted Abstinence in Psychostimulant abusers. qEEG analysis in DRD2 A1 allele carriers. Compared to placebo -Synaptose Complex KB220Z™ induced positive regulation of the dysregulated electrical activity of the brain in these addicts.	

Preclinical Studies		
Year	**Reference**	**Key points**
2011	Blum K, Stice E, Liu Y, *et al.* "Dopamine Resistance" in brain reward circuitry as a function of DRD2 gene receptor polymorphisms in RDS: Synaptamine complex variant (KB220) induced "Dopamine Sensitivity" and enhancement of happiness. XIX World Congress of Psychiatric Genetics, September 10-14th. Washington DC [213].	Synaptamine Complex Variant [KB220] ™ as an activator of the mesolimbic system and administration significantly reduces or "normalizes" aberrant electrophysiological parameters of the reward circuitry site. Based on our QEEG studies presented herein we cautiously suggest that long-term activation of dopaminergic receptors (i.e., DRD2 receptors) will result in a proliferation of D2 receptors leading to enhanced "dopamine sensitivity" and an increased sense of happiness. Oral KB220 showed an increase of Alpha activity and an increase low Beta activity similar to 10-20 sessions with Neurofeedback.
2012	Chen D, Liu Y, He W, *et al.* Neurotransmitter-precursor-supplement Intervention for Detoxified Heroin Addicts. Huazhong University of Science and Technology and Springer-Verlag Berlin Heidelberg [Med Sci 32(3):422-427 [414].	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 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
2012	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 44: 398-409 [215].	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 Emption, t=16.1 for Somatic, and t= 14.9 for cognitive impairment. 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-year 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.
2012	Blum K, Oscar-Berman M, Stuller E, et al. 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 [216].	New Definition of Addiction by American Society of Addiction Medicine (ASAM) is base Reward Cascade (BRC) Impairment leads to aberrant craving behavior and other behaviors such as Substance Use Disorder (SUD) due to a "hypodopaminergic" trait/state. Any impairment due to either genetics or environmental influences on this cascade will result in a reduced amount of dopamine release in the brain reward site. After over four decades of development, neuro-nutrient therapy has provided important clinical benefits when appropriately utilized.
2013	Blum K, Oscar-Berman M, Femino J, *et al.* Withdrawal from Buprenorphine/Naloxone and Maintenance with a Natural Dopaminergic Agonist: A Cautionary Note. J Addict Res Ther 4(2). doi: 10.4172/2155-6105.1000146 [217].	A case study of a 35-year-old female in the film industry with a history of chronic pain from reflex sympathetic dystrophy and fibromyalgia. Total monthly prescription costs including supplemental benzodiazepines, hypnotics and stimulants exceeded $50,000. Withdrawal symptoms were carefully documented when she precipitously stopped taking buprenorphine/naloxone. At 432 days post Suboxone® withdrawal the patient is being maintained on KB220Z, has been urine tested and is opioid free. Genotyping data revealed a moderate genetic risk for addiction showing a hypodopaminergic trait.
2015	McLaughlin T, Blum K, Oscar-Berman M, *et al.* Putative dopamine agonist (KB220Z) attenuates lucid nightmares in PTSD patients: Role of enhanced brain reward functional connectivity and homeostasis redeeming joy. J Behav Addict 4(2):106-115. doi: 10.1556/2006.4.2015.008 [218].	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.

(Table 1) Contd....

	Preclinical Studies	
Year	**Reference**	**Key points**
	McLaughlin T, Blum K, Oscar-Berman M, *et al*. Using the Neuroadaptagen KB200z™ to Ameliorate Terrifying, Lucid Nightmares in RDS Patients: the Role of Enhanced, Brain-Reward, Functional Connectivity and Dopaminergic Homeostasis. J Reward Defic Syndr. 2015; 1(1):24-35 [219].	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). Eight clinical cases, with known substance abuse, childhood abuse and diagnosed PTSD/RDS were presented. The administration of a putative dopamine agonist, KB200Z™, was associated with the elimination of unpleasant and/or terrifying, lucid dreams in 87.5% of the cases presented, whereas one very heavy cocaine abuser showed a minimal response. These results required the continuous use of this nutraceutical. If these results in a small number of patients are indeed confirmed, we may have found a frontline solution to a very perplexing and complicated symptom known as lucid dreams.
	Blum K, Liu Y, Wang W, *et al*. rsfMRI effects of KB220Z™ on neural pathways in reward circuitry of abstinent genotyped heroin addicts. Postgrad Med. 2015; 127(2): 232-241. [188].	KB220Z induced an increase in BOLD activation in caudate-accumbens-dopaminergic pathways compared to placebo following 1-hour acute administration in abstinent heroin addicts. Increased functional connectivity was observed in a putative network that included the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum. The results suggest a putative anti-craving/anti-relapse role of KB220Z in addiction by direct or indirect dopaminergic interaction.
2016	McLaughlin T, Febo M, Badgaiyan RD, Barh 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 [220].	The four patients initially reported a gradual but, then, complete amelioration of their long-term, terrifying, lucid dreams, while taking KB220Z. The persistent amelioration of these dreams continued for up to 12 months, after - KB220Z. These particular cases raise the scientific possibility that KB200Z increases both dopamine stability as well as functional connectivity between networks of brain reward circuitry in both rodents and humans. In order to attempt to understand the possibility of neuroplasticity, we evaluated the effect of KB220Z in non-opioid-addicted rats utilizing functional Magnetic Resonance Imaging methodology. While we cannot make a definitive claim because rat brain functional connectivity may not be exactly the same as humans, it does provide some interesting clues. We did find following seeding of the dorsal hippocampus, enhanced connectivity volume across several Regions of Interest (ROI), with the exception of the pre- frontal cortex. Interestingly, the latter region is only infrequently activated in lucid human dreaming, when the dreamer reports that he/she had the thought that they were dreaming during the lucid dream.
2016	Bruce Steinberg, Kenneth Blum, Thomas McLaughlin, Joel Lubar, Marcelo Febo *et al*. Low-Resolution Electromagnetic Tomography (LORETA) of changed Brain Function Provoked by Pro-Dopamine Regulator (KB220z) in one Adult ADHD case. Open J of Clin. Med. Case Rep. 2;(11) [221].	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.
	Duquette LL, Mattiace F, Blum, K, *et al.* Neurobiology of KB220Z-Glutaminergic-Dopaminergic Optimization Complex [GDOC] as a Liquid Nano: Clinical Activation of Brain in a Highly Functional Clinician Improving Focus, Motivation and Overall Sensory Input Following Chronic Intake. Clin Med Rev Case Rep 3(5):104 [222].	We disclose self-assessment of a highly functional professional under work-related stress following KB220Z use, GDOC for one month. Subject self-administered GDOC using one-half-ounce twice a day. He reported that during 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, increased focus and multi-tasking, with clearer purpose of task at hand. Subject felt less inhibited in a social setting and suggested that GDOC increased his Behavior Activating System (reward), while having a decrease in the Behavior Inhibition System (caution).

In acupuncture-resistant rabbits, d-Pha injection induced an analgesic effect, which was enhanced and prolonged by auriculo-acupuncture stimulation. It has been suggested that the recovery of pain sensibility after acupuncture analgesia is determined by enkephalinase's activation by d-Pha inhibitory effects [228].

Blum *et al.* (1987) first reported altered alcohol intake in mice with a genetic predisposition to alcohol preference and that the mice exhibited innate brain enkephalin deficiencies [228]. Successful attenuation of both volitional and forced ethanol intake, respectively, was the result of acute and chronic treatment using hydrocinnamic acid and d-Pha, which are both known carboxypeptidase (enkephalinase) inhibitors. Since these agents raise brain enkephalin levels through enkephalinase inhibitory activity, we propose that excessive alcohol intake and abuse may be managed or regulated by alteration of endogenous brain opioid peptides.

D-Pha, bacitracin, and puromycin all produce prolonged naloxone-reversible analgesia in mice. This analgesic potency is similar to that of compounds such as Thiorphan an inhibitor of met-enkephalin degradation by mouse brain enzymes. D-Pha potentiates acupuncture analgesia in mice and humans and has been used to ameliorate a variety of human chronic pain conditions [230].

Much evidence demonstrates that various compounds, which inhibit the degradation of met-enkephalin, can produce naloxone-reversible analgesia in mice. Such compounds also potentiate the analgesia observed with treatment by acupuncture, foot shock, and transcutaneous nerve stimulation in animals and humans. Potency or efficacy of these analgesics parallels their ability to act as inhibitors of enkephalinase in the brains of mice. D-Pha is an example of an enkephalinase inhibitor and has been successful in the management of chronic intractable pain in humans and as an adjunct in theee treatment of many other painful conditions with acupuncture. D-Pha has a hypotensive effect and effects on behavior and does not induce tolerance and dependence when used long-term in animals and humans [226]. Furthermore, Ehrenpries suggested that various compounds that inhibit the degradation of enkephalins, as expected, produce naloxone reversible analgesia. They also induce analgesia produced by enkephalins and acupuncture. D-Pha is also an anti-inflammatory, proving to be beneficial to chronic, intractable pain in human patients. Russel and McCarty [231] proposed the enkephalinase inhibitors may be effective in some human "endorphin deficiency diseases" including depression, schizophrenia, convulsive disorders and arthritis. Such compounds may alleviate other conditions associated with decreased endorphin levels such as opiate withdrawal symptoms.

Chen *et al.* [232] successfully tested the hypothesis that by combining a narcotic antagonist and amino-acid therapy consisting of an enkephalinase inhibitor (D-Pha) and neurotransmitter precursors (L-amino acids) to stimulate the release of dopamine, compliance in methadone patients would be facilitated. These methadone patients were detoxified using naltrexone, a narcotic antagonist [232]. In this regard, Thanos and associates [185] found that delivery of the DRD2 gene into the NAc, via an adenoviral vector, significantly reduced both alcohol intake (64%) and ethanol preference (43%) in ethanol preferring rats. This increased level of DRD2 receptors then returned to baseline with concomitant restoration of ethanol preference. Overexpression of DRD2 produced a similar result in ethanol non-preferring rats in both alcohol preference reduced (16%) and alcohol intake reduced by (75%). These findings underline the concept that elevated levels of DRD2 may be protective against alcohol abuse as reported by Volkow *et al.* [233]. In several studies, the A1 allele, in particular, has also been shown to associate with heroin addicts. Furthermore, other dopaminergic receptor gene polymorphisms have been correlated with opioid dependence. Kotler *et al.* [233] revealed that the 7 repeat allele of the DRD4 receptor is significantly over-presented in the opioid-dependent cohort and confers a relative risk of 2.46 [233]. This finding has been confirmed by Li *et al.* [235] for the 5 and 7 repeat

alleles in a study involving a Han Chinese case-controlled sample of heroin addicts [235]. Analogously, Duaux *et al.* [236] found a significant association with homozygote alleles of the DRD3-Bal 1 in French Heroin addicts [236]. Strong supportive evidence was discovered in a study by NIAAA, suggesting that across multiple populations, DRD2 is a susceptibility gene for substance abusers [236]. Several other human clinical trials showed a reduction of opiate, cocaine, alcohol and sugar craving behavior by utilizing amino acid and enkephalinase inhibition therapy, see Table 1. While there is positive evidence for the utilization of d-Pha as a potential anti-craving agent by itself the addition of the entire KB220 complex; amino acid precursors like L-phenylalanine, L-glutamate and L-tyrosine will better assist in releasing dopamine.

4. DOES THE ADDICTIVE BRAIN FAVOR AMINO-ACID THERAPY?

The hypothesis has been that D2 receptor stimulation can be accomplished, via the use of a natural and therapeutic nutraceutical formulation KB220 that increases proliferation of D2 receptors by inducing DA release. Increased D2 receptor proliferation then induces a reduction of cravings in addictive patients. As seen in the research of Thanos *et al.* discussed above [185,187] DNA-directed compensatory overexpression of the DRD2 receptors (an example of gene therapy) can cause a significant reduction in craving behavior in alcohol preferring and cocaine self-stimulating rodents. Harnessing natural dopaminergic repletion as a strategy to promote long-term dopaminergic activation may ultimately lead to a safe and effective therapy for RDS behaviors including SUD, Attention Deficit Hyperactivity Disorder (ADHD), Obesity and other reward deficient aberrant behaviors. This strategy is further supported by the role of dopamine in the NAc where it acts as a "wanting" messenger in the mesolimbic DA system [238].

Research has shown that proliferation of D2 receptors along with G proteins results from prolonged stimulation of DA receptors by agonists. Boundy *et al.* demonstrated that that stimulation of DA receptors by Bromocriptine, the pure D2 receptor agonist, results in proliferation of D2 receptors over a 14-day period in transfected kidney cells and also in *Spodoptera frugiperda* insect cells [239]. They also demonstrated that administration of a dopamine antagonist caused the proliferation of D2 antagonist receptors. These findings suggest that environmental manipulation may result in receptor proliferation despite existing genetic antecedents. Understanding the nature of agonist activity may explain these observations; agonist activity primarily involves stimulation of transcribed mRNA. Negative feedback that enhances mRNA-directed D2 receptor proliferation is caused by activation of the DRD2/mRNA. This enhanced DRD2 proliferation is important to note as an increase in substance seeking is caused by a scarcity of DA D2 receptors [159, 240]. If decreased D2 receptors correlated with increased craving behavior, then an increase in D2 receptors should, therefore, result in a reduction of craving behavior. A solution that stimulates DA release at the NAc naturally, as opposed to pathways in which potent dopamine agonists lead to dopamine down-regulation, should prove effective. Essentially, using precursor amino acids and simultaneous enkephalinase/COMT inhibition may systematically induce the natural release of dopamine without side effects, such as dopamine receptor downregulation, otherwise seen with other pharmaceuticals. While dopamine activation often occurs with targeted pharmaceuticals such as Bromocriptine or other DA agonists [241], an approach that uses a strategy that mimics the brain's natural reward cascade may provide positive therapeutic results.

5. WHY THE ADDICTIVE BRAIN FAVORS AMINO–ACID THERAPY [NAT™]

It has been established that after prolonged abstinence from drugs of choice, individuals will experience a more euphoric high, which can lead to relapse. This clinically observed "super sensitiv-

ity" might point toward the existence of genetic dopaminergic polymorphisms. Paradoxically, it is interesting to note that bromocriptine, a dopaminergic agonist, causes an increase in brain reward activity in individuals who carry the DRD2 A1 allele compared to DRD2 A2 carriers. Since A1 carriers, in comparison to A2 carriers, exhibit much lower D2 receptor density, A1 carriers should theoretically experience a reduced sensitivity to dopamine agonist activity. However, low D2 receptor density corresponds to increased reward sensitivity to bromocriptine. Furthermore, with chronic or long-term D2 agonists-therapy, there is a proliferation of D2 receptors *in vitro*. However, *in vivo* studies show the opposite a downregulation of D2 receptors after Bromocriptine administration [242]. This unexpected activity may make clear the importance of utilizing amino acid therapy. Before dopamine is synthesized L-amino acid decarboxylase undergoes striatal activity, which is associated with the A1 allele. Specifically, Laakso *et al.* [243] reported that the A1 allele corresponds to the increased activity of striatal L-amino acid decarboxylase in healthy Finish subjects [243]. They found that heterozygous carriers of the A1 allele (A1/A2; 10 subjects) had significantly higher [18%] ([18F] -FDOPA uptake in the putamen than subjects without the A1 allele (A2/A2; 23 subjects).

These results are evidence that carriers of the A1 allele have increased activity of L-amino acid decarboxylase, which is an important enzyme for trace amine synthesis, and which is present in the final step of dopamine synthesis. This biochemical finding is beneficial for carriers of the A1 allele having reduced DRD2 receptors. It seems reasonable that because of this known deficit the brain has set up a protective mechanism to drive more dopamine synthesis. As such the lower D2 expression due to the A1 polymorphism (a risk for all addictive behaviors) may be overcome by increased activity of L-amino acid decarboxylase, especially when confronted with increased amino acid precursors like L-phenylalanine and l-tyrosine part of amino-acid therapy as suggested herein.

Carriers of the DRD2 A1 allele, then, may have an interesting intrinsic -protective mechanism waiting for amino-acid introduction such as L-phenylalanine and L-tyrosine (rate-limiting substrates in the synthesis of dopamine). Moreover, Ortez *et al.* [244] recently reported that in "tyrosine hydroxylase deficiency" the dopamine transporter (DAT) and vesicular monoamine transporter type 2 were up-regulated leading to a hypodopaminergic trait [244]. Kim *et al.* [245] also showed that locomotor activity responses of these Dopamine-deficient (DA-/-) mice to dopamine D2 receptor agonists were 13-fold greater than the response elicited from wild-type mice [245]. Moreover, when Vrshek-Schallhorn *et al.* investigated the effects of the Acute Tyrosine Phenylalanine Depletion (ATPD) on decision making and reward, it was found that carriers with this amino-acid deficiency experienced an attenuated reward and reduce decision-making ability, as measured by the Iowa Gambling Task [34].

Separate and different from the effects of genetic mutations (variations and polymorphisms), the environment via epigenetics may produce profound effects that impact drug and non-drug seeking behaviors by changing gene expression. Many new insights have come from recent understanding, of how the environment through epigenetics modifies gene expression which alters brain function. By the insertion of methyl groups into histones on the chromatin structure of the gene, the chromatin can (wrap tightly) and turn off; or by the insertion of acetyl groups into histones the gene chromatin structure can (unfurl) and be turned on. In fact, chronic cocaine in mice induces a noticeable shift of the balance from genetics to epigenetics whereby there is an enhanced sensitivity to drugs and addiction risk. A single injection of cocaine can cause changes in gene expression in the NAc. It has been established that in the absence of drug addiction (possibly even in non-substance addiction, for example, gambling) methyl type

marks predominate keeping certain genes quite. However, cocaine causes acetyl groups to predominate and chromatin to loosen and genes involved in the pleasurable response to drugs or behaviors to come alive. The importance of dopaminergic homeostasis including the usual expression of the DRD2 gene has been recently underscored by an analysis of epigenetic effects linked to this gene.

Hillemacher *et al.* evaluated epigenetic DNA-methylation patterns in the DRD2-gene in lifetime history of pathological gamblers and provided evidenced for significantly higher methylation levels in non-abstinent (12 to 30 months) and participants without treatment-seeking behavior compared to abstinent gamblers [246]. Consequently, the authors determined that indeed there is a pathophysiological relevance of altered DRD2-expression caused by changes in DNA methylation in pathologic gambling. Moreover, Groleau *et al.* found that women with bulimic-spectrum disorder compared to women without an eating disorder showed significant increases in DRD2 methylation levels particularly in those women who were sexually abused during childhood [247].

These genetic and epigenetic effects may carry over to future generations and could explain why better compliance to amino-acid therapy as protective mechanism especially in carriers of the D2 receptor-deficient DRD2 A1 allele [241, 248]. We now must ask if "dopamine agonist therapy" such as with KB220 variants can reduce methylation and increase acetyl groups to enhance DRD2 expression even in DRD2 A1 allele carriers leading to increased DA function and reduction of drug and non-drug seeking behaviors?

6. CONCLUSION

Willuhn *et al.* found that as dopaminergic function decreases, cocaine consumption and other addictive behaviors increase [249]. Long-term cocaine abuse is linked to D2 and D3 receptor decrease and lowered stimulation of the occipital cortex and cerebellum. In particular, dopamine agonist therapy, a therapy that conserves and repairs dopamine functioning, may potentially serve as a successful approach to relapse prevention in psychoactive drug and behavioral addictions.

After a mixed review of Medication Assisted Treatment (MAT), we have pinpointed the failures of glutaminergic medications, specifically in the chronic treatment of RDS behaviors. Both neurogenetics and epigenetics are incredibly important in addiction treatment response and clinical outcomes. According to scientific research, we suggest the use of "dopamine agonist therapy" for long-term and concur with the careful use of short-term "dopamine-antagonistic therapy." A plethora of the literature provides robust examples of genetic and epigenetic links to relapse and the possibility of relapse prevention. Our proposal is that due to higher rates of hospitalization and perhaps mortality of DRD2 A1 allele carriers (30-40 less D2 receptors) [250] enhanced relapse prevention tactics such as the neuronutrient –amino-acid therapeutic (KB220 variants), should be considered. The reasoning behind this proposal is linked to the understanding of neuro–mechanisms connecting "dopamine homeostasis" to addiction recovery from drug and non–drug addictive behaviors. Luckily, the addicted brain, specifically DRD2 A1 carriers, favors Neuronutrient –Amino-Acid therapy due to an increased sensitivity to dopaminergic activity promotion [208]. Carriers of the DRD2 A1 allele display augmented striatal-activity of L-amino acid decarboxylase which might favor increased dopamine synthesis when amino acid precursors are available. Ultimately, future research should be focused on the role of "dopamine agonist therapy" using KB220 variants. Knowing that heightened dopamine function can cause a decline in drug and non-drug seeking behaviors, can methylation be lowered, and acetyl groups increased in order to develop better DRD2 expression, particularly in DRD2 A1 allele carriers? This must await intensive investigation.

CONFLICT OF INTEREST

Kenneth Blum, PhD is the holder of a number of US and Foreign patents issued and pending related to Nutrigenomics and Nutraceuticals. Through IGENE LLC., Dr. Blum licensed the Genetic Addiction Risk Score (GARS) ™ to BodySync, Inc. with a sales license to Dominion Diagnostics. He is a paid consultant of Dominion Diagnostics, LLC, IGENE, LLC. Dr. Blum is a member of the scientific advisory board of Dominion Diagnostics, LLC and Rivermend Health. Dr. Blum is Chief Scientific Advisor of Dominion Diagnostics, LLC and LaVitaRDS. Dr. Blum serves as Neuroscience advisor to Summit Estates Recovery Center and The Shores Treatment & Recovery Center Drs. Blum (Chairman), Badgaiyan, Thanos and Febo are members of LaVitaRDS Scientific Advisory Board. Dr. Blum is also the Scientific Director of Path Foundation NY. The authors state that there are no other conflicts of interest.

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