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Current Neuropharmacology, **2018**, *Volume* **1**

Genetic Addiction Risk Testing Coupled with Pro-Dopamine Homeostasis, and Electro Therapy, May Overcome Aberrant Reward Seeking Behaviors: Analytic Evidence

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Abstract

The endemic of legal opioid iatrogenic induced prescription drug abuse is of major world-wide concern, whereby in the United States alone one person is dying from fatal overdose every 17 minutes. Understanding pain pathways and the role of dopaminergic tone in the neurophysiology of pain relief provides potential therapeutic solutions especially when tied to genetic testing. In 2013, an estimated 24.6 million Americans aged 12 or older—9.4 percent of the population—had used an illicit drug in the past month. This number is up from 8.3 percent in 2002. The increase mostly reflects a recent rise in use of marijuana, the most commonly used illicit drug. However, opioid misuse is indeed a devastating unwanted issue. It has been reported that the overall genetic contribution to the variance of Substance Use Disorder (SUD) is approximately 60% but each candidate gene evaluated by GWAS is relatively small. In an attempt to combat this global endemic we are proposing a number of alternative strategies. Prevention of death due to opioid overdose and attenuation of prescription abuse should focus on strategies that target 1) high-dosage medical users; 2) persons who seek care from multiple doctors; 3) persons involved in "drug diversion"; 4) genetic testing for addiction liability and severity indices; 5) non-pharmacological analgesic

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treatments such as electrotherapy and pro-dopamine regulation to induce homeostasis. In term of administering the gold standard Buprenorphine dosing should be based on appropriate pharmacogenetic testing (PGX) especially in African-Americans. Understanding the interaction of Reward Deficiency Syndrome and Anti- reward chronification in terms of pain mechanisms may help improve clinical outcomes a necessary giant step forward to combat an unwanted worldwide endemic.

Keywords: Anti reward chronification, Reward Deficiency Syndrome, Pain, Opioids, fatal overdose, Dopamine, genetic testing, electro therapy, Precision Addiction Management.

1. INTRODUCTION

Currently, the U.S.A. is in the middle of an epidemic of opioid overdoses. From 1999 until 2010, prescription opioid-related overdose deaths increased significantly, as have their prescriptions [1]. In 2015, such overdoses accounted for 33,091 deaths, with half resulting from prescriptions [2]. Furthermore, it has been estimated that two million people in the U.S. have a substance use disorder (SUD) with opioid prescriptions. Treatment for this has been expected to cost $75.8 billion a year [3]. While there are a number of proven strategies available to manage chronic pain effectively without opioids [4-6] there is still need to develop what has been termed *"Reward Deficiency Solution System" (RDSS)* or Precision Addiction Medicine (PAM)™ based on analytic evidence as presented herein, that could translate to the changing prescribing practices an essential step in addressing the opioid overdose epidemic and its adverse effects on US population and even across the globe.

1.1. Analytics of genetic addiction risk score (GARS)

To understand our goal involving the development of Genetic Addiction Risk Score (GARS™) panel of reward gene polymorphisms [7, 8] and a clinical outcome, the rationale is provided herein. The interaction of neuro-transmitters and genes that control the release of dopamine are the Brain Reward Cascade (BRC) [9]. Variations within the BRC, whether genetic or epigenetic, may predispose individuals to addictive behaviors and altered pain tolerance. This concept has been established by a group of concerned scientists and clinicians that has examined the GARS, the first test to accurately predict vulnerability to pain, addiction, and other compulsive behaviors, defined as Reward Deficiency Syndrome (RDS) [10]. Innovative strategies to combat the epidemic of opioid, iatrogenic prescription drug abuse and death, based on the role of dopaminergic tone in pain pathways, have been proposed [11-13]. Sensitivity to pain may reside in the mesolimbic projection system, where genetic polymorphisms associate with a predisposition to pain vulnerability or tolerance [14]. They provide unique therapeutic targets that could assist in the treatment of pain and identify risk for subsequent addiction involving RDS and anti-reward symptomatology [15].

Pharmacogenomic testing of candidate genes like dopamine transporter, mu receptors, and catabolic enzymes of dopamine-like COMT seem parsimonious [8]. Understanding these concepts will result in pharmacogenomics, personalized solutions, and improved clinical outcomes. Genetically identifying the risk for all RDS behaviors, especially in compromised populations (e.g., African–Americans, and poverty populations), might be a front line tool to assist municipalities in providing better resource allocation[16].

Blum's group in unpublished research (a four year sojourn) sought to address genetic risk for alcohol/drug seeking by evaluating the combined effect of reward gene polymorphisms [a genetic addiction risk score (GARS) of 11 polymorphisms and ten genes] contributing to a hypodopaminergic-trait, was associated with Reward Deficiency Syndrome (RDS) related substance abuse risk. Their patient population included 393 poly-drug abusers attending eight independent treatment centers from around the United States. Clinical severity of alcohol and drug use behaviors was assessed using the Addiction Severity Index (ASI). A saliva sample for DNA genotyping was derived from n = 273 (from seven centers) combined with ASI phenotype. The average age of our analysis sample was 35.3 years of age (S.D. – 13.1, Range: 18-70) of which 57.8% (n = 160) were male and 88.1% (n = 244) self-reported their race as White. Among the patient population n=393, 17.6%, 80.7%, and 1.5% scored in the low, moderate and high severity range, respectively. The mean number of GARS alleles was 7.97 (S.D. = 2.34) and ranged between 3 and 17 alleles. All genotypes were in Hardy-Weinberg Equilibrium (HWE). Preliminary examination of the relationship between GARS genotype panel and the Alcohol Risk Severity Score using the Fishers Exact Test revealed a significant predictive relationship ($X2 = 8.84$, $df = 1$, $p = 0.004$, 2-tailed). This exact association remained significant even after controlling for age ($p < 0.01$). A similar, though less robust, relationship was obtained from chi-square ($p = 0.05$) and linear regression ($b = -0.122$, $t = -1.91$, $p = 0.10$, 2-tailed) analyses of the ASI Drug Severity Risk Score. Correcting this result

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along a priori lines revealed a p-value = 0.05 (1-tailed) for the association between the GARS panel and ASI Drug Severity Risk score [7].

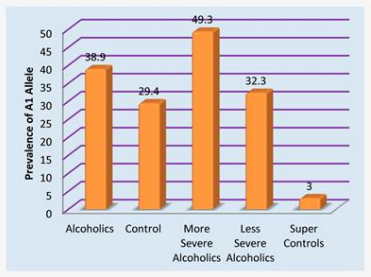
It is important to realize that the GARS test as a predictor of high risk for RDS behaviors that have been associated with the ASI, a clinical predictive test, cannot display false positives because it measures an entire panel of gene polymorphisms to predict drug and alcohol severity as a cluster. This type of testing does not appropriately allow for performing a ROC analysis. It is noteworthy that subject-based DNA was genotyped and the data were analyzed at the Institute for Behavioral Genetics (IBG) at the University of Colorado Boulder. The results divulged a significant association between a summed score of all GARS panel risk alleles (variant forms) and both the ASI-MV alcohol and drug severity indices in a total of 273 subjects from seven addiction clinics. Their test results show that if a patient carries any combination of 4 GARS risk alleles, it is predictive of drug severity, or any combination of 7 GARS risk alleles it is predictive of alcohol severity ($p<.05$, $P<.004$ respectively). It is of interest that they found 100% of these patients from chemical dependency treatment programs carry at least one risk allele [7].

In fact, the larger the amount of risk alleles, the greater the prediction of drug or alcohol use severity. Furthermore, family problems, psychological issues, and medicalization significantly correlated as well. One notable caveat was that if they changed any specific SNP, the significance was lost. This caveat speaks to the question of counting alleles vs. odds ratios and employing real non-RDS controls. Also, when they multiply a fixed number to provide power to any gene in the GARS, the significance is lost. This strongly suggests the importance the selection of the alleles in the GARS panel. Any deviation will produce false results that may occur with other tests that have no research to validate their test results.

1.2. RDS-free "super "controls

To date, there has not been the development of RDS controls, and that is why counting is quite acceptable as verified by other investigators with non-addicting gene panels [17]. We further hypothesize that follow-up gene research in this area, resulting in confirmation of positive correlations with dopaminergic polymorphisms, and utilizing highly screened controls (eliminating any addictive, compulsive and impulsive behaviors in both proband and family) may have significant ramifications. In this regard, earlier studies from Blum's group showed the importance of non-RDS controls [18]. In a neurology and family practice clinic in Princeton, it was found that after using a computerized program to eliminate every possible RDS behavior in the proband and family members of 183 patients, only 30 patients were free of any RDS behavior. When the DRD2 A1 allele was genotyped in the unscreened population the A1 allele (known to cause a 30-40% reduction in the number of DRD2 receptors) was observed in about 33%. However, in the highly screed non-RDS controls the A1 allele was found in only one patient which translates to 3.3% [19] (see figure 1). We now propose that to harness appropriate genetic association studies the investigators need to make sure that hidden RDS behaviors have been systematically eliminated from their so-called controls otherwise spurious results could ensue [20].

Figure 1-Prevalence of DRD2 A1 allele in unscreened and RDS Free controls



1.3. RDS as an endophenotype

We believe that by proposing RDS as the "true" phenotype rather than for example subtypes like Substance Use Disorder (SUD) or Behavioral Addictions (BA) will result in changing the recovery landscape. To help understand our platform technology Blum et al. [9], have published this concept earlier in this journal. Abnormal behaviors involving dopaminergic gene polymorphisms often reflect an insufficiency of normal feelings of satisfaction or RDS. Evidence has shown RDS from a dysfunction in the "brain reward cascade," a complex interaction among neurotransmitters (primarily dopaminergic and opioidergic) [21]. A family history of addictions or alcoholism may predispose individuals to be born with a deficiency in neurotransmitters, resulting from issues in either the synthesis or receptors for them. Additionally, chronic exposure to stress and substances of abuse might also lead to a compromise in the brain reward cascade. Blum et al. [9] evaluated the potential association of four variants of dopaminergic candidate genes in RDS (dopamine D1 receptor gene [DRD1]; dopamine D2 receptor gene [DRD2]; dopamine transporter gene [DAT1]; dopamine beta-hydroxylase gene [DBH]).

Blum et al. [9] genotyped an experimental group of 55 subjects derived from up to five generations of two independent multiple-affected families compared to rigorously screened control subjects (e.g., N = 30 super controls for DRD2 gene polymorphisms). Data related to RDS behaviors were collected on these participants plus 13 deceased family members.

Of the family members that were genotyped, the DAT1 10/10 and DRD2 Taq1 alleles were significantly ($p < 0.015$) more frequently present in the RDS families than controls. Interestingly, the TaqA1 allele was present in 100% of those within Family A (N = 32); whereas this was found in only 47.8% of those within Family B (11/23 participants). Additionally, there were no significant differences between either group for other genetic variants.

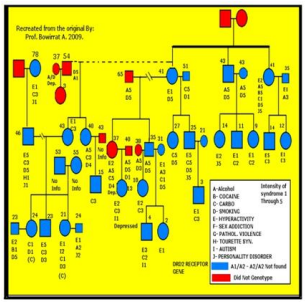


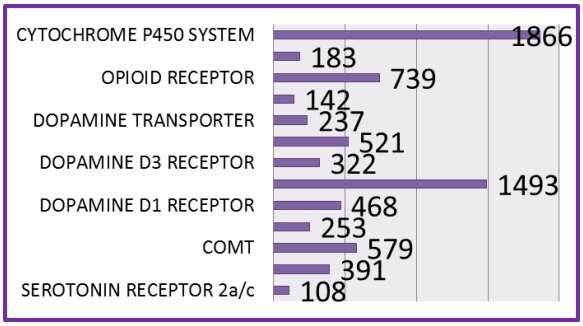
Figure 2. Genotype results of the D2 dopamine receptor gene polymorphisms of family A (n = 32) that were identified with multiple Reward Deficiency Syndrome (RDS) behaviors [9].

Although this was a limited sample, and linkage analysis was necessary, their results do support the potential role of polymorphisms in dopaminergic pathways that are related to RDS behaviors. These results emphasize the importance of a nonspecific RDS endophenotype and suggest an understanding of how evaluating single subset behaviors of RDS may lead to spurious results. Utilization of a nonspecific "reward" phenotype may be a paradigm shift in future association and linkage studies involving dopaminergic polymorphisms and other neurotransmitter gene candidates.

1.4. Bayes theorem and at birth predictability to RDS

Specifically, the D2 dopamine receptor and the dopaminergic system as a whole have both been implicated within the mesolimbic reward system of the brain. Dysfunction of the D2 dopamine receptors leads to pathological substance seeking behaviors. Decades of research from Blum's group and various others like Elman and Borsook (clinical antireward chronification analysis), have indicated that genetics play an important role in vulnerability to severe substance seeking behavior and pain mechanisms. Blum et al. [22] proposed that variants of the D2 dopamine receptor gene are essential common genetic determinants in predicting compulsive disease. Blum et al.[15] determined through the Bayes approach that when they added up many RDS behaviors and apply the Predictive Value (PV), they found a 74.4% value. This translates to the unfortunate fact that when a child is born with the DRD2 variant (A1 compared to A2 [usual], he or she will have a 74 % chance that in the future they have a high risk for RDS behaviors and could become addicted. In this regard, the full GARS panel has not as yet been analyzed using Bayes Theorem [22], but we are very confident that the PV would even be higher. To help understand the rationale for selection of the reward genes in the GARS panel we provide a graphic representation of the number of association studies listed in PubMed as of 11-12-17. Most association studies of cause analyze both case controls and disease phenotype [see figure 3].

Figure 3. GARS Panel Association Studies



As stated earlier the GARS report is a restricted cluster of gene polymorphisms that predict both drug and alcohol severity based on ASI. It is not specific to any drug per se but to an array of RDS substance and non-substance addictive behaviors. The exciting concept of RDS is that the common genetic rubric of hypodopaminergia predisposes individuals to all addictive behaviors. The reduced net release of dopamine in the reward center of the brain (N. Accumbens) is indeed the culprit. It is well known from many metabolic/pathophysiology studies from both NIDA and NIAAA that "Dopamine Homeostasis" is a laudable goal and well –known that it is the combined result of genetics (DNA) and epigenetics (environmental components) [23-25].

Blum's group and others have published extensively on the neurogenetics of brain reward systems concerning the genes related to dopaminergic function in particular [26, 27]. In 1995, Blum coined "Reward Deficiency Syndrome" (RDS), to portray behaviors found to have a gene-based association with hypodopaminergic function [22]. RDS as a useful concept has been embraced in many subsequent studies, to increase our understanding of addictions, and other obsessive, compulsive, and impulsive behaviors. Interestingly, in one published study, Blum et al., were able to describe lifetime RDS behaviors in a recovering addict (17 years sober) blindly by assessing resultant Genetic Addiction Risk Score (GARS) data only [28]. We hypothesized that genetic testing at an early age might be a useful preventive strategy to reduce or eliminate pathological substance and behavioral seeking activity [29]. In this situation, we examined a selected group of genes, and their polymorphisms, and associated RDS risk while utilizing

GWAS there is evidence for convergence to reward candidate genes [30]. The evidence presented in many studies serve as a plausible brain-print providing relevant genetic information that will reinforce targeted therapies, to improve recovery and prevent relapse on an individualized basis [31]. The primary driver of RDS is a hypodopaminergic trait (genes) as well as epigenetic states (methylation and deacetylation on chromatin structure) related to transgenerational effects of maternal depression and addiction [32, 33]. As David E. Smith [34] points out, addiction medicine readily accepts the neuroscience of addictions. In fact, RDS is recognized as a pathology due to a change in the brain reward cascade. This, in itself, provides the impetus for the continued study and of related genetics for early diagnosis and evidence-based therapies.

To reiterate, we first described the RDS concept in a general article in the American Scientist and today over 625 publications are listed in PubMed (11-13-167) that deal with "Reward Deficiency," and another 1174 articles deal with "Dopamine Dysregulation." RDS is currently found and defined in MS-Word, Gates and included in SAGE Encyclopedia of Abnormal Psychology and Clinical Psychology (2017). While there is a plethora of literature emphasizing the importance of dissecting the role of dopamine into "wanting" and "liking," these concepts dovetail onto the RDS model. The basic idea was adopted in the ASAM new definition of Addiction in 2011.

1.5. The benefits of GARS testing for substance use disorder

Previously as mentioned earlier, Blum's group in unpublished work investigated the potential of GARS to predict vulnerability or risk for both drug and alcohol severity as measured by the ASI. However, a frequently raised question relates to what is the benefit of GARS™ testing in known addicts already in treatment programs [11]. Based on our work, it appears evident that GARS testing in those with various addictive behaviors is vitally important.

1.6. Denial

Many patients in addiction treatment programs deny that they have a biological problem and cannot control their addictions. Various campaigns including "the war on drugs," the "just-say-no", has been the leading approach to substance use disorders (SUDs) required one outcome: abstinence, and one methodology: spiritual connection with a higher power, as the ideal solution for SUDs [35, 36]. Many did not become abstinent; many rejected the spiritual approach; such people were seen as in denial. A significant shift in the addiction and recovery field began in the 1990s following the discovery of the genetic connection and molecular neurobiological evidence for the 12 steps [36]. Subsequently, the Substance Abuse and Mental Health Services Administration in 2005 convene leaders in the field to develop principles for recovery. Significant changes included viewing SUDs as a chronic reoccurring disease requiring long-term support.

Complete abstinence is not a requirement for all persons with SUDs. There are "many pathways to recovery," not only the 12-Step approach". A sustained and continued recovery is often self-directed with personal choices, an extended support system of peers and allies, and community reinforcement and the use of research-based interventions. So many in recovery and currently in treatment are in denial, and the addiction medicine community is attempting to promote recovery-oriented approaches, to reduce misconceptions, labeling, and stigmatization and improve recovery for individuals, families, and communities [37]. Providing real evidence using a GARS test to predict risk for both substance and non-substance severity helps remove denial.

1.7. Guilt/shame

A widespread response from those with substance use disorder includes a profound sense of shame and guilt [38]. Addiction is a lonely person-level phenomenon. Indeed, feelings of shame about one's addiction, is not necessarily a mistake. It is part of the nature of addiction, part of the standard phenomenology of addiction, and is often a source of motivation in the healing process. Addiction literature has recently attempted to return to normative concepts including choice and drinking goal responsibility in understanding how to treat addiction [39].The ongoing effort to help remove both guilt and shame is compatible with an investigation of genetic causes of addiction. Indeed, there can be shame without blame. There is the documented view that reveals in many cases that addicts fail to be able to exert self-control capacities and are ashamed of both this fact and the fact that they are failing to live a good human life [40]. It is understandable that patients realize the false premise ***"Just Say No"*** to stop normally is not enough. For this, we are working toward nutraceutical interventions that help addicts stop using, by induction of "dopamine homeostasis" which is a necessary condition for any and all further healing. Eventually, work in genetics will yield simple interventions that adjust genes for those with a predisposition. We believe that novel interventions possibly in the future might work, to arrest addiction, and as such acknowledge that epigenetic impact on reward gene expression is a cornerstone cause of addiction. It is conceivable, albeit, not as an excuse, providing biological and genetic (GARS) evidence to predict risk for both substance and non-substance severity helps remove both guilt and shame in patients.

1.8. Genogram confirmation

In many, if not most, addiction treatment programs, patients need to provide a detailed family history, including various addictions, within a Genogram/family tree [41]. A

genogram is a pictorial configuration of an individual's family and medical history. This mapping extends far beyond a regular genealogical mapping which allows treatment providers and clinicians a way to search for potential patterns heredity and psychological factors that punctuate relationships. It is a multi-generational diagram one's family and extended. This will enable caretakers and treatment providers a simple way to view various relationship dynamics, to review identify various trends and developmental influences. Each individual on a genogram is represented by a symbol of unique placement. These symbols are linked with lines to illuminate dynamic patterns and individual qualities. Such charts are used by professionals in many fields which study and work with people including doctors, researchers, psychiatrists, counselors, and psychologists.

Medical and behavioral researchers often use the results of a conglomerate of multiple genograms to uncover recurring patterns in the data. Interviewing people from multiple generations and subsequently coding such clues for possible correlation or even potential causal relationships between generational learning or genetics. Additionally, this multigenerational mapping might reveal complex relationships between socioeconomic and environmental factors that may influence an individual's or even a family's functioning and development. Offering the GARS test to a person's family in treatment is the best way to confirm the risk of addiction in the family (an extended market) and help reinforce the genetic basis of the Genogram.

1.9. Medication-assisted treatment (MATS) dosing

The rate of people seeking treatment for opiate addiction is at an all-time high. One primary concern is that legal prescriptions in 2016 for opioid analgesics reached approximately 297 million [42]. In 2017, one company that manufactures Oxycontin® generated a revenue of $3.1 billion. Moreover, death from prescription drug overdoses has been referred to as the "silent epidemic." Indeed, approximately one US citizen is dying every 17 minutes from an accidental prescription drug overdose.

There is a plethora of scientific research divulging successful treatment of opioid dependence/addiction with buprenorphine or the buprenorphine-naloxone combination (Suboxone®/Zubsolve ®). However, long-term maintenance on these should be done with caution. There may often be severe withdrawal even with tapering of the dosage. Additionally, Hill et al. [43] show a long-term flat affect with chronic Suboxone® and other unwanted side effects including diversion and anhedonia (possible suicide attempts). It seems prudent to employ genetic testing as a way of improving treatment outcomes. Comprehending the interaction of reward circuitry involvement in a treatment such as buprenorphine and genotypes can provide a novel framework to augment a patient's clinical experience and benefits during opioid replacement therapy.

It is a top priority to recognize that clinical outcome in patients with drug-addictions, including alcoholism, may depend upon dopaminergic genes and their associated polymorphisms [44]. Lawford et al.[45] in a double-blind study, revealed that bromocriptine (a DRD2 agonist) or placebo, administered to alcoholics [some with either the A1 (A1/A1 and A1/A2 genotypes, others only with the A2 (A2/A2 genotype) allele of the DRD2 gene, that the most significant improvement in anxiety and craving occurred in the bromocriptine-treated A1 alcoholics. Importantly, the attrition was highest in the placebo-treated A1 alcoholics suggesting treatment outcome is a function of genotype.

The feasibility of treating RDS based upon pharmacogenetics has been further underscored by Blum et al. [46].This group found that the DRD2 gene variant (A1 allele vs. A2 allele) had a significant Pearson correlation with the numbers of days within treatment ($r = 0.42$). Compared to the DRD2 A1-carriers, the number of days within treatment with the dopamine promoting compound KB220 was 51.9 ± 9.9 SE (95% CI, 30.8 to 73.0) versus for the DRD2 A1+ carriers was 110.6 ± 31.1 (95% CI, 38.9 to 182.3). As expected, the attrition was highest in the $A1^{-}$ genotype group. It was suggested that the genotype might be a predictor of compliance and treatment persistence. Moreover, a relapse might depend upon the DRD2 A1 allele which could affect treatment response. Dahlgren et al. [47] provided the first report of an association between the TaqI A1 allele and a substantially increased relapse rate in alcohol-dependent patients.

Along similar lines, Noble & Ritchie [48] measured [3H] Naloxone binding in the frontal gray cortex, caudate nucleus, amygdala, hippocampus and cerebellar cortex obtained postmortem alcoholics and non-alcoholics. When these individuals were grouped by the presence/absence of D2 A1 allele, [3H] naloxone binding was significantly less in all brain regions examined of subjects with the A1 allele than in those without this allele. Notably, there was a significant difference expressed within the caudate nucleus. The authors suggested that the decreased [3H] naloxone binding observed in subjects with the A1 allele might be a compensatory response to their decreased dopaminergic modulation of opiate receptor activity. This is very important for Vivitrol® therapy for the treatment of Opioid Use Disorder (OUD).

Interestingly, Gerra et al. [49] provided clear evidence that the dopaminergic system is linked to buprenorphine treatment response in heroin-addicted humans. Unexpectedly, they found no significant difference between responders and non-responders to buprenorphine within the frequency of kappa opioid receptor (OPRK1) 36G>T SNP. However, for the dopamine transporter (DAT) the rate of the polymorphism (SLC6A3/DAT1), allele 10, was much significantly higher in "non-responder" than in "responder" individuals (64.9% vs. 55.93%). Additionally, the frequency of the category of other alleles was higher in responder than in non-responder individuals (11.02% vs. 2.13% respectively). Our interpretation of these results dovetails with the work of others showing significantly better compliance and treatment outcome based on dopaminergic polymorphisms whereby hypodopaminergic traits mediate a better response during treatment. Our group hypothesizes that carriers of the nine allele of the DAT1 would confer a better treatment response with buprenorphine due to its faster transport activity resulting in a hypodopaminergic trait.

Finally, Barratt et al. [50] while not showing significant differences in methadone or buprenorphine maintenance outcomes regarding ***Taq1 A1 allele*** carriers, did show in successful methadone patients, significantly less A(1) allele carriers had withdrawal than non-A (1) carriers ($p = 0.04$). Moreover, Blum et al.[51] found in a genetically determined patient with hypodopaminergic trait at 432 days post-Suboxone® withdrawal, abstinence was maintained on the dopamine agonist KB220Z, as verified by urine tested were opioid-free. Data of genotypes divulged a moderate risk of addiction with a hypodopaminergic trait. Consistent with these findings, Makhinson and Gomez-Makhinson [52] also observed a case of a withdrawal syndrome from buprenorphine. The symptoms included restlessness resistant to both clonidine and benzodiazepines. It was successfully treated with the D2 agonist pramipexole.

The continuing controversy over either dopamine antagonists versus agonists, or dopaminergic surfeit or deficit, was the recent topic of a paper published in Nature Neuroscience. Specifically, Willuhn et al. [53] revealed that as the rate of cocaine increased, phasic dopamine decreased in the ventromedial striatum (VMS). This provides evidence for the "deficit" and treatment with an agonist.

As has been proposed previously, activation rather than blocking mesolimbic dopaminergic reward circuitry in the long-term treatment of RDS is the preferred modality [54]. Although the acute treatment may consist of antagonism of postsynaptic NAc dopamine receptors (D1-D5), long-term treatment should consist of activation of the DA system, such as the release and activation of DA in the NAc. This proposed theory suggests that an addict's excessive craving behavior is attributed to the reduction in the number of D2 receptors, which can be an effect of carrying the DRD2 A1 allelic genotype. In contrast to this, a standard or sufficient density of D2 receptors results in reducing craving. A primary goal of treatment and even preventing such substance use & misuse might be to induce a proliferation of D2 receptors in individuals with the genotype making them genetically vulnerable. While, in vivo experiments that used a typical D2 receptor agonist induce down-regulation, in many in vitro experiments results have demonstrated that notwithstanding genetic antecedents, the constant stimulation with a known D2 agonist, such as bromocriptine, often results in significant proliferation of D2 receptors in the DA system [55]. However, chronic treatment results in down-regulation instead of up-regulation or balance, as is proposed for KB220Z [56]. That is a reason for failure in treatment with powerful D2 agonists.

1.10. Risk populations

In other unpublished work but presented by Chapman et al. [57] it was found that African-Americans carrying CYP3A4 Genotype *1B the extended metabolic Buprenorphine genotype *I/*1B (43%) and *1B/1B* (42%) compared to ~9000 Caucasians (26%) differed significantly. Besides buprenorphine personalized dosing, the genetic-addiction risk-testing panel approach can provide useful information for, preliminary screening for high-risk patients in pain clinics and relapse-prevention. Data from a funded 1R41MD012318-01 (recipients -Blum & Gondre-Lewis) grant will involve African-Americans carrying CYP3A4 Genotype *1B the extended metabolism Buprenorphine genotype coupled with GARS to address the problem of diversity and addiction risk. It is a fact, that specific genetic variation (as seen in GARS) like that observed in, for example, the opioid mu receptor (reduce the number of receptors) will result in dosing consequences whereby higher doses of buprenorphine (a MAT) may be needed to prevent relapse to street heroin [58,59].

1.11. Resource allocations

Stepped care models focus on matching treatment defined by the needs of the patient. This may avoid misplacements by making the best use of available treatment resources. In principle, treatment planning for new patients starts with the least intensive care, progressing to more intensive regimes for non-responders. These models were

introduced in the medical field, including psychiatry. These models, specifically stepwise patient placement within addiction treatment, are well known from North America [60] and employed in both adolescents and adults, regarding patients with dual-diagnoses [61]. Another model comes from Europe (the Dutch model for triage and evaluation in addiction treatment MATE; a unique model for judicial patients). Since placement in either Home 1 compared to Home 2 (more intense) requires feasibility, validity, reliability, effectiveness, and cost-effectiveness, GARS testing will negate guessing and provide a genetically based method of real resource allocation methodology.

1.12. Opioid pain compound avoidance

Understanding the role of neurogenetics of opioids and its role in pain mechanisms has been extensively studied. Results indicated that both sensitivity and tolerance to morphine were found to be dependent on genotype, with inheritance characterized by dominance or partial-dominance and involves many published works.

Differences in human responses to opioids have been well known for some time, for example, a particular type of opioid may provide better analgesia than other opioids for any one individual. Differences in individual responses are not unique to an analgesic effect; they can also be seen with other opioid effects such as interactions, side effects, and toxicities. As research gained from databases on knockout rodents, pharmacogenetics, and gene polymorphisms unravels various genetic receptor interactions, and biochemical differences of opioid responses in humans, some of the differences may be exploited to provide better care. Testing will become more readily available and cost-effective as an aid to clinicians. Instead of having to rely solely on patient feedback, clinical judgment and trial and error, clinicians will be able to predict patient responses to doses of specific opioids, individualize opioid analgesic therapy, and devise optimal opioid rotation strategies. In the future, information of this type may translate into improved patient care, as clinicians become adept at tailoring appropriate opioid therapy. Although presently perfect candidate genes for gene-directed opioid therapy are not obvious, specific candidate genes have been studied [62], and associations with analgesic requirements for acute and chronic pain states, as well as with sensitivity to the pain, have been found including genes in the GARS.

These associations with analgesia and chronic pain were a consequence of an intense investigation of the candidate genes for the catechol-O-methyl-transferase, melanocortin-1 receptor, guanosine triphosphate glycohydrolase, and the mu-opioid receptor [63,64].The genetic variants of drug-metabolizing enzymes, in contrast, have well known and described impacts on responses to pharmacotherapy. The analgesic efficacy of codeine, tramadol, nonsteroidal anti-inflammatory drugs and tricyclic antidepressants are influenced by polymorphisms of the cytochrome P450 enzymes. For example, genetically caused cytochrome P450 (CYP) 2D6 inactivity, renders codeine ineffective due to lack of morphine formation, slightly decreases the clearance of methadone and the efficacy of tramadol due to lack of formation of the active O-desmethyl-tramadol [65].

In an animal genetic experiment Mogil *et al*.[66] investigated sensitivity and tolerance to morphine. They used two strains of mice and C57BL/6By and BALB/cBy, and seven recombinant inbred strains of their reciprocal F1 hybrids. Following the administration of 20 mg/kg of morphine hydrochloride or saline, sensitivity was measured using a locomotive activity. The 'hot plate' method was used to measure tolerance following the single or repeated administration of 20 mg/kg of morphine hydrochloride or saline. Results indicated that both sensitivity and tolerance to morphine were found to be dependent on genotype, with inheritance characterized by dominance or partial dominance. Ongoing research (GARS testing) will target other candidate gene polymorphisms and drug metabolizing enzyme genetic variants searching for associations between drug response and an individual's genetic profile (pharmacogenetics).

The mu opioid receptor gene encodes the receptor targets for some endogenous opioids and studies of mu-opioid receptor polymorphisms have contributed substantially to knowledge about genetic influences on cocaine and opiate addiction (including heroin, morphine, and synthetic opioids) [67]. Monoaminergic system genes and other genes of the endogenous opioid system, particularly genes encoding the dopamine, serotonin, and norepinephrine transporters, and dopamine β-hydroxylase, have also been studied [68].

It is clear that we are in the midst of an opioid epidemic in the U.S. The primary gateway to opioid addictions appears to be the over-prescription of painkillers. Using GARS might assist in teasing apart the risk for opioid dependence and force those with such risk to seek out alternative therapies like electrotherapies [69] and non-steroid analgesics [70].

1.13. Pro-dopamine regulation

"Gene Guided Precision Nutrition™" and KB220 variants (a complex mixture of amino acids, herbals, and trace metals) are the pioneers and standard-bearers for a state of the art DNA customization [71]. Findings by both, Kenneth Blum, Ph.D. and Ernest Noble, Ph.D. and others demonstrated the genetic role of shaping our cravings and pleasure-seeking, has opened the doors to the comprehension of how genetics control our actions and affect our mental and

physical health. Moreover, the technology that is related to KB220 variants to decrease or ameliorate extreme cravings via genetic influencing may be the cornerstone of the practical applications of neurogenetics/nutrigenomics [72]. Continuing research discoveries are a principle catalyst for the expansion, evolution and the scientific recognition for the significance of nutrigenomics. There are potentially remarkable contributions to medicine and human health. Neuro-Nutrigenomics is now a vital field of scientific investigation that offers great promise to improve the flawed human condition. This is at the forefront of the development of the GARS™ which has noted predictive value for the severity of drug and alcohol abuse as well as other non-substance related addictive behaviors. While individual customization of neuronutrients hasn't yet been commercialized, other than in obesity [73] we have significant evidence that in the future such a concept will be developed. This could have a profound impact on addiction medicine referred to as "Precision Addiction Management".

1.14. Evidence-based studies on KB220 variants

Dopamine along with other chemical messengers like serotonin, cannabinoids, endorphins, and glutamine, play significant roles in brain reward processing. There is a devastating opiate/opioid epidemic in the U.S. According to the Centers for Disease Control and Prevention (CDC), at least 127 people, young and old, are dying every day due to narcotic overdose and alarmingly heroin overdose is on the rise. The U.S. Food and Drug Administration (USFDA) have authorized some Medication-Assisted Treatments (MATs) for alcoholism, opiate and nicotine dependence, but nothing for psychostimulant and cannabis abuse. While these pharmaceuticals are essential for the short-term induction of "psychological extinction," in the long-term caution is necessary because their use favors blocking dopaminergic function indispensable for achieving normal satisfaction in life [54]. The two institutions devoted to alcoholism and drug dependence (NIAAA & NIDA) realize that MATs are not optimal and continue to seek better treatment options. Based upon greater than fifty years of research by Blum's group is the development of a glutaminergic-dopaminergic optimization complex called KB220 to provide for the possible eventual balancing of the brain reward system and the induction of "dopamine homeostasis."[74] This complex may provide substantial clinical benefit to the victims of Reward Deficiency Syndrome (RDS) and assist in recovery from iatrogenically induced addiction to unwanted opioids and other addictive behaviors (see table 2).

Table 2: Precision Addiction Medicine™ and KB220 variants

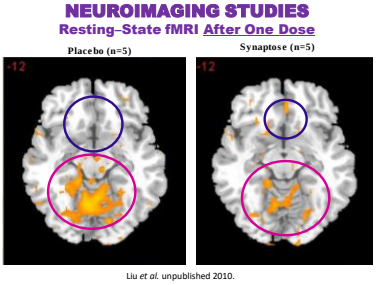
Phase 1		
Year	**Reference**	**Key points**
1973	Blum K, Calhoun W, Merritt J, et al., L-DOPA: effect on ethanol narcosis and brain biogenic amines in mice. *Nature*. 242: 407-409.	Increased brain L-DOPA increases brain dopamine in mice and causes inebriated mice to sleep. Dopamine, 1-tryptophan and alcohol work similarly in the brain.
1974	Blum K, Wallace JE, Calhoun W, et al., Ethanol narcosis in mice: serotonergic involvement. *Experientia* 30:1053-1054.	When mice were given alcohol and 1-tryptophan or saline, the mice given 1-tryptophan went to sleep. The mice given saline did not. 1-tryptophan and alcohol work similarly in the brain.
1987	Blum K, Wallace JE, Trachtenberg MC, et al., Enkephalinase inhibition: Regulation of ethanol intake in mice. *Alcohol*: 4; 449-456.	Mice genetically predisposed to like alcohol have a measured deficiency in enkephalin. D-phenylalanine and hydrocinnamic acid are substances known to stop the breakdown of enkephalin in the brain -the amount of enkephalin available in the brain increases. When the amount of enkephalin available in the brain increases, both voluntary and forced intake of alcohol decreases. D-phenylalanine is one of the ingredients in NAAT.
Phase 2		
Year	**Reference**	**Key points**
1988	Blum K, Trachtenberg MC, Elliott CE, et al., Improvement of inpatient treatment of the alcoholic as a function of neurotransmitter restoration: a pilot study. *The International journal of the addictions* 23: 991-8.	First small clinical trial of SAAVE (precursor amino acid loading and enkephalinase inhibition -earliest version of NAAT). Designed to elevate levels of enkephalin(s), serotonin, catecholamines, and GABA, thought to be deficient in alcoholics. Compared to controls those who took SAAVE had lower building up to drink score, required no PRN benzodiazepines, ceased having tremors 24 hours earlier, and had less depression.
	Blum K, Trachtenberg MC, Elliott CE, et al., Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE. *Alcohol.* 5(6): 481-93.	Double blind placebo controlled clinical trial of SAAVE of 62 people with Substance Use Disorder (SUD). Results reduced stress as measured by skin conductance, improved Physical and BESS (behavioral, emotional, social and spiritual) Scores, and had a six-fold decrease in leaving Against Medical Advice (AMA) rates.
	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.	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 dec reased 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.	Relapse prevention using neuronutrients SAAVE and Tropamine in DUI offenders; either alcohol or cocaine. Reduced relapse rates and enhanced recovery in a 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.	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,	Small preliminary study of efficacy of NeuRecover-SATM (formerly Tropamine) 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.	Cognitive processing speeds in normal young adult volunteers were measured before and after 28-30 days of supplementation with a combination of amino acids (NAAT), vitamins and minerals. Cognitive processing speeds were enhanced by a statistically significant amplitude of the P300 component of the Event Related Potentials (ERPs). FOCUS IMPROVED
	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.	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	Preliminary evaluation of six randomly selected former eating disordered female clients (three were also chemically dependent), contacted at nine months and three years of treatment with amino-acid

	emphasis on eating disorders. Mol Psychiatry. Feb; 6(1 Suppl 1):S1-8.	precursor and enkephalinase inhibition therapy. All 6 reported initial benefit, one relapsed at six months the other five all sustained, and in some cases exceeded expectations. 98% of 100 patients similarly treated and evaluated reported significant improvement in both mood and reduced substance craving.
2004	Chen TJ; Blum K, Payte, JT, et al., Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors, and enkephalinase inhibition therapy. *Medical Hypotheses* 63 (3): 538-48.	A combination of Trexan (a narcotic antagonist) and amino-acids was used to detoxify either methadone or heroin addicts. Results were dramatic regarding 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 Nov-Dec;23(6):1040-51.	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 in 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 leads to improved sleep, enhanced energy, and improved focus and performance, reduced appetite, loss of unwanted weight, decreased body inches, and enhanced well-being.
2007	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.	This one-year prospective study that evaluated the effects of taking Haveos (Synaptamine) on 61 compliant patients in a comprehensive outpatient clinical program. Results after 12 weeks include significant decrease in craving. Results after 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%
	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 in 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.	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 concerning weight loss and change in body fat.
	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 Therapy and Molecular Biology* Vol 12, page 371-382.	The preliminary investigational study that evaluated 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. *Advances in Therapy* 25 (9): 894-913.	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 of 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 Therapy Molecular Biology* 12, 129-140.	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 Therapy Molecular Biology* 13, 214-230.	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 alcoholics and in polydrug 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, 2010.	The case study was evaluating sustained weight loss with Synaptamine complex in conjunction with Diethylpropion (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*. Nov; 122(6):188-213.	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 D_2 agonist therapy: part 2. *Postgrad. Med*. Nov; 122(6):214-26.	Protracted Abstinence in Psychostimulant abusers. qEEG analysis in DRD2 A1 allele carriers. Compared to placebo -Synaptose Complex KB220Z induced positive regulation of the dysregulated electrical activity of the brain in these addicts.
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.	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 proliferation of D2 receptors leading to enhanced "dopamine sensitivity" and an increased sense of happiness. Oral KB220 showed an increase in 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):422-427,2012	This study examined the effects of combined administration of tyrosine, lecithin, L-glutamine, and L-5-hydroxytryptophan (5-HTP) on heroin withdrawal syndromes and mental symptoms in detoxified heroin addicts. The results showed that 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 six in the intervention group than in the control placebo group
	Miller M, Chen ALC, Stokes SD, et al., Early Intervention of Intravenous KB220IV-Neuroadaptagen Amino-Acid Therapy (NAAT)™ Improves Behavioral Outcomes in a Residential Addiction Treatment Program: A Pilot Study. *Journal of Psychoactive Drugs* (in press December issue 2012).	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-years post-treatment with 16 (70%) having no relapse. Note: these results of cause do not reflect any other recovery skills utilized by the patients including 12 steps program and Fellowship.
	Blum K, Miller M, Miller D, et al., Neurogenetics and Nutrigenomics of Neuro-Nutrient Therapy for Reward Deficiency Syndrome: Clinical Ramifications and Pitfalls. *Nutrients*. 2012 Nov 27. doi: 10.4172/2155-6105.1000139	New Definition of Addiction by American Society of Addiction Medicine (ASAM) is based on concepts related to Reward Deficiency Syndrome (RDS). Brain 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 critical 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*. 2013 Apr 23;4(2). doi: 10.4172/2155-6105.1000146.	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*. 2015 Jun;4(2):106-15. doi: 10.1556/2006.4.2015.008.	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.
	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.	Lucid dreams could be unpleasant or terrifying, at least in the context of patients, who also exhibit characteristics of Reward Deficiency Syndrome (RDS) and Posttraumatic Stress Disorder (PTSD). We presented eight clinical cases, with known substance abuse, childhood abuse and diagnosed PTSD/RDS. 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 Mar;27(2):232-41.	Willuhn et al. reported that cocaine use and even non-substance-related addictive behavior increases as dopaminergic function is reduced. Chronic cocaine exposure has been associated with decreases in D2/D3 receptors and was also associated with lower activation of cues in occipital cortex and cerebellum, in a recent PET study by Volkow et al., 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. Results suggest a putative anti-craving/anti-relapse role of KB220Z in addiction by direct or indirect dopaminergic interaction.

Based on all of the reviewed research presented in this paper, it has apparently been established that inducing a "dopamine homeostasis (balance)" across the brain reward cascade circuitry may be the best way to treat all addictive-like behaviors (Figure 3).

Moreover, utilizing fMRI in abstinent heroin addicts in China (see figure 3) one hour after administration of KB220Z compared to placebo showed profound activation of dopamine pathways of the caudate-accumbens region of the brain and reduction in dopaminergic activation of cerebellum [56]. This suggests that through this now known mechanism, craving behavior, as well as stress, will be reduced.



Thus, GARS testing of the already dependent person provides an exact mirror into the brain's chemical messenger function (receptor number and chemical production) and can lead to personalized addiction medicine based on Pro–dopamine regulation

2. CONCLUSION

It is now known that concerning nature (genes) combined with nurture (environment), and resulting behavioral outcomes within *Homo sapiens*, that the contribution is approximately 50% genes and 50% epigenetics (environmental influence on genetic expression) [75]. Thus, molecular genetics or DNA testing is fundamental, especially linking aberrant behaviors to any individual.

Blum's laboratory proposed that any disturbance along the reward cascade that might be due to either gene variations (polymorphisms) and/or environmental influences

(epigenetics) can result in various aberrant and addictive behaviors (i.e., RDS). In spite of a continued global-wide search to divulge specific candidate genes or clusters characterized by high-density SNP arrays, it is common knowledge that many attempts have failed to replicate or been inconclusive. However, Palmer et al. [76] recently showed that between 25–36% of the genetic variance in the generalized vulnerability to substance dependence might be attributable to common single nucleotide polymorphisms. Moreover, the additive effect of common single nucleotide polymorphisms is shared across leading indicators of various comorbidities. Furthermore, as a result of such research studies, even more, recent evidence has shown that specific gene variants may account for risk-prediction.

Adopting a new approach, a Bayesian one from earlier studies from Blum's laboratory [22] concluded that a Positive Predictive Value (PPV) of 74%, specifically for the DRD2A1 allele appeared to be an indication that if a child is born with this polymorphism, will have a much higher risk of future addictions (i.e., drugs, food, or aberrant behaviors) at some point in their lives. Over the many years since the 1990 finding of the DRD2 gene association of the *Taq A1* allele and severe alcoholism, laboratories all across the globe including NIDA and NIAAA not only confirmed this early work but also extended the importance of various candidate genes, specifically for genes for second messengers in the reward system.

An example is Moeller et al.[77] who suggested that drug cues contribute to relapse, and their neurogenetic results have identified the DAT1R 9R allele as a vulnerability allele for relapse, especially during early abstinence (e.g., detoxification). The DAT1R 9R allele influences the fast acting transport of dopamine, sequestered from the synapse, leading to a hypodopaminergic trait.

It is essential to use genetic testing to uncover reward circuitry gene polymorphisms, particularly those linked to dopaminergic pathways including opioid receptor(s) as a method of obtaining better treatment results. Comprehending the relationship between the reward circuitry's participation in buprenorphine outcomes and corresponding genotypes delivers an innovative model to enhance a patient's clinical experience and improved relapse prevention during opioid replacement therapy.

While there are other genetic proposed panels especially linked to OUD none has provided evidence for a genetic addiction risk score (GARS) of known risk polymorphisms of reward genes associated with an increased genetic risk for addiction and other RDS behaviors based on analytic evidence such as ASI prediction of drug and alcohol severity. We encourage the field of addiction medicine to take heed of these presented concepts and its adaptation following required research.

LIST OF ABBREVIATIONS

A1	a specific genetic variant of the D2 dopamine receptor
A2	the wild type genetic variant of the D2 dopamine receptor
AMA	against medical advice
ASAM	American Society of Addiction Medicine
ASI	Addiction Severity Index
BESS	behavioral, emotional, social and spiritual
BMT	Buprenorphine Maintenance Treatment
BRC	Brain Reward Cascade
CASS	Chronic Abstinence Symptom Severity
CI	confidence interval
COMT	Catechol-O-methyl transferase
CrP	chromium picolinate
CYP	Cytochrome
D1	a specific dopamine receptor
D2	a specific dopamine receptor
D5	a specific dopamine receptor
DA	Dopamine
DAT1	dopamine transporter gene
DBH	dopamine beta-hydroxylase gene
DEXA	Dual Energy X-Ray Absorptiometry
DNA	Deoxyribonucleic acid
DRD2	dopamine receptor D2
DUI	driving under the influence (of an intoxicant)
fMRI	functional magnetic resonance imaging
GABA	gamma-Aminobutyric acid (γ-Aminobutyric acid)
GARS™	Genetic Addiction Risk Score™
HWE	Hardy-Weinberg Equilibrium
IBG	Institute for Behavioral Genetics
Kg	Kilogram
L-DOPA	Levodopa
MAT	medication-assisted treatment
MATE	Dutch model for triage/evaluation in addiction treatment
MATS	medication-assisted treatments
Mg	Milligram
N. Accumbens	nucleus accumbens
NAAT	Neuro-nutrient Amino Acid Therapy
NAc	nucleus accumbens
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
OPRK1	kappa opioid receptor
OUD	opioid use disorder
PAM™	Precision Addiction Medicine
PRN	Latin for pro re nata, take a medication as needed

PTSD	posttraumatic stress disorder
PV	predictive value
qEEG	quantitative electroencephalogram
RDDS	Reward Deficiency Solution System
RDS	Reward Deficiency Syndrome
ROC	Receiver Operating Characteristic
SAAVE	a compound consisting of a combination of amino acids
SCL	skin conductance level
SD	standard deviation
SE	standard error
SNP	single-nucleotide polymorphism
SUD	substance abuse disorder
Taq1	a polymorphism of the D2 dopamine receptor
U.S.	United States
U.S.A.	United States of America
VMS	ventromedial striatum

CONFLICT OF INTEREST

Kenneth Blum Ph.D. is Chief Scientific Advisor and a paid a consultant for Dominion Diagnostics LLC., listed as one of his affiliates. Dr. Blum through his company Synaptamine Inc., owns a number of US and Foreign patents concerning genetic testing and KB220 variants. He is currently Chairman of the Board and Chief Scientific Officer of Geneus Health and Restoregen. ; These companies had no input to the design or interpretation of the present study. The contents of the manuscript are solely the responsibility of the authors and do not represent the official views of the funding agencies. Mary Hauser and David Siwicki have interest in Dominion Diagnostics. David Siwicki is President of Genus Health and Jennifer Neary is the Chief Scientific Advisor for Geneus Health.

ACKNOWLEDGEMENTS

The authors appreciate the expert edits of Margaret A. Madigan and the superb assistance of Justin Jones and Erin Gallagherof Geneus Health, LLC and James Heaney of Electronic Waveform Labs. Additionally, we would like to thank Danielle Jean Kradin for formatting the references in the reference list.

FUNDING

Rajendra D. Badgaiyan is supported by the National Institutes of Health grants www.ncbi.nlm.nih.gov/ 1R01NS073884 and 1R21MH073624. Panayotis Thanos is the recipient of R01HD70888-01A1. Kenneth Blum serves as Scientific Director of Path Foundation NY is the recipient of a grant from LifeExtension Foundation, Ft. Lauderdale, Florida awarded to Path Foundation NY www.pathfoundationny.org. Dr. Marjorie C., Gondré–Lewis is the recipient of R01 AA021262/AA/NIAAA NIH HHS/United States. Drs. Blum and Gondré–Lewis are the recipients of R41 MD012318/MD/NIMHD NIH HHS/United States. The work of Igor Elman is supported byXXXX. The work of D. Borsook is supported byXXXX. The authors appreciate the support of Electronic Waveform Labs, Huntington, Beach, California.

These funders provided support for authors [RDB, IE, MCGL, DB, PT, KB], but did not have any additional role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript. All authors approved the manuscript and equally contributed.

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Received: March 20, 2014 Revised: April 16, 2014 Accepted: April 20, 2014